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Aims and Scope

The Journal of Crohn's and Colitis is the official journal of the European Crohn's and Colitis Organisation (ECCO) and is concerned with the dissemination of knowledge on clinical, basic science and innovative methods related to Inflammatory Bowel Diseases. The journal publishes original articles, review papers, editorials, leading articles, ECCO Guidelines, viewpoints, short reports and letters to the editor. All submitted material is subject to a peer-review process.

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Oral presentations

OP01
In-depth characterisation of host genetics and gut microbiome unravels novel host–microbiome interactions in inflammatory bowel disease

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Background: A large number of host genetic factors, as well as changes in the gut microbiota, are known to determine aetiology and pathogenesis of inflammatory bowel disease (IBD). The knowledge on the interaction between these two factors is, however, still limited. To characterise these interactions, in-depth determination of the host genetics and gut microbiota is necessary. Here we aimed to identify genetic factors relevant for maintenance of the gut microbiome in the context of IBD.
Methods: We performed whole-exome sequencing of the host genome, and whole-genome shotgun sequencing of faecal samples of 524 IBD patients and 939 controls from population-based cohort. The interaction between exonic variants, microbial taxa, and metabolic pathways was explored using a four-step approach: (1) Bidirectional meta-analysis between the two cohorts to identify common variants, (2) a targeted meta-analysis of IBD risk loci and protein-truncating variants (PTVs), (3) a gene-based burden test to detect rare mutations that affect microbial features, and (4) an interaction analysis to identify IBD-specific microbial quantitative trait loci (mbQTLs).
Results: We tested 170 000 protein-coding variants and 641 microbial features, and identified 26 associations between genetic variants and gut microbial features (FDR < 0.05). Among common variants, a strong mbQTL was observed for deletion near the IBD-risk IL17REL gene that was correlated to Alistipes indistinctus abundance, which is known to be decreased in IBD patients. The gene-based burden test revealed that mutations in an IBD-related gene CYP2D6, a major component of Phase I drug metabolism, were associated with a decreased level of bacterial biosynthesis of vitamin K (PWY-5838). Moreover, GPR151 gene, known to be protective against obesity and Type II diabetes, was found to be associated with a decrease in bacterial degradation of glucose. The interaction analysis revealed another association between BTNL2 and bacteroides specific to IBD.
Conclusions: We performed the largest, high-resolution, genome–microbiome association study to date, which utilises whole-exome sequencing and metagenomics sequencing methods. Disease-specific interactions were explored in the context of IBD, including the effect of risk loci and protein-truncating variants. These results highlight the importance of host genetics in the maintenance of gut microbiome homeostasis critical for prevention of IBD.

OP02
The role of PTPN2 SNP in the pathogenesis of fibrosis in Crohn's disease

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Background: We identified altered IL-6-induced Jak1-dependent STAT3 phosphorylation in human ileal subepithelial myofibroblasts (SEMF) of patients with stricturing Crohn's disease. This resulted in co-localisation of pSTAT3(Y705) to Rab5+ signalling endosomes along with pIGF-I receptors that jointly mediated excess collagen I production and proliferation in SEMF of strictures. PTPN2 gene variants occur in patients with Crohn's disease with rs7234029 associated with apparent 'loss-of-function' and with stricturing disease. In other cells, PTPN2 targets Jak and STAT3. However, whether expression of rs7234029 in fibrostenotic Crohn's disease is associated with altered phosphatase activity, increased STAT3 phosphorylation, and excess extracellular matrix deposition has not been studied yet.
Methods: Primary cultures of SEMF isolated from ileum of patients with Montreal B2 Crohn's disease were naïve, transfected with wtPTPN2, or were used for CRISPR/Cas9-mediated PTPN2 gene deletion. Rs7234029 haplotype was determined in each subject by genotyping assay.
Results: Increased basal pSTAT3, pErk1/2, collagen I production and proliferation in SEMF of strictured ileum were normalised by inhibition of STAT3 phosphorylation or expression of dominant negative STAT3 (Y705F). Despite a 3-fold increase in PTPN2 protein in strictured SEMF in these cells, levels of STAT3 phosphorylation were also increased suggesting a loss-of-phosphatase function had occurred. Phosphatase function was restored by expression of wtPTPN2 and resulted in lowered levels of pSTAT3 (Y705). This

notion regarding PTPN2 was also confirmed in normal SEMF where CRISP/Cas9 mediated PTPN2 gene deletion resulted in a 4-fold increase in pSTAT3 (Y705) levels. The haplotype rs7234029 was significantly detected in Montreal B2 Crohn's disease compared with other phenotypes.
Conclusions: A loss of PTPN2 function associated with rs7234029 in SEMF of patients with fibrostenotic Crohn's disease leads to increased phosphorylation of pSTAT3 (Y705), and results in the excess collagen I production and proliferation that occur in these patients' strictures.

OP03

Inhibition of autophagy exacerbates intestinal fibrosis and EMT

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Background: Intestinal fibrosis is a common complication of Crohn's disease (CD) patients and it requires surgery. GWAS studies have identified several polymorphisms in genes involved in autophagy, which predispose to CD. It has been reported that this process is impaired in IBD patients, but the relevance of autophagy in intestinal fibrosis remains unclear. We aim to analyse the effect of pharmacological inhibition of autophagy in the development of murine intestinal fibrosis.
Methods: Intestinal fibrosis was induced *in vivo* using the heterotopic transplant model. Segments of 1 cm colon from mice were subcutaneously transplanted into the neck of a recipient mice and collected after 7 days. Recipient mice were treated with a daily injection of 3-MA (10 mg/kg). Expression of intestinal inflammation, fibrosis, and EMT markers were analysed by qPCR and protein levels of autophagy markers by western blot. Collagen layer was evaluated by Sirius Red Staining. Intestinal resections from CD patients were obtained and expression of p62, Col1a1, α-SMA, Snail1, and Snail2 was analysed by qPCR. Results are expressed as fold induction (mean ± SEM, $n \geq 5$). Statistical analysis was performed with one-way ANOVA followed by Newman–Keuls test. Correlations were analysed with the Spearman coefficient.
Results: Grafts obtained 7 days after surgery from 3-MA treated mice vs. vehicle-treated mice exhibited: (a) a significant increase in the expression of proinflammatory genes such as TNF-α (102.90 ± 22.94 vs. 50.46 ± 7.47), IL-1β (425.4 ± 84.92 vs. 243.70 ± 35.85), IL-6 (735.7 ± 235.0 vs. 339.90 ± 137.5) and INOS (325.7 ± 75.85 vs. 166.2 ± 23.64); (b) an increase in the expression of profibrotic genes such as Col1a1 (74.21 ± 9.18 vs. 41.27 ± 9.34), Vimentin (9.98 ± 4.54 vs. 6.73 ± 0.64) and TGF-β (6.69 ± 1.91 vs. 6.62 ± 0.60); (c) a significant increase in the expression of EMT genes such as Snail1 (21.10 ± 4.60 vs. 11.61 ± 1.49), Snail2 (7.32 ± 1.87 vs. 3.70 ± 0.73) and Itgb6 (7.70 ± 1.89 vs. 2.65 ± 0.43); (d) a significant thicker collagen layer after Sirius Red Staining. Autophagy inhibition by 3-MA was confirmed by western blot showing an increase of p62 and phospho-mTOR and a reduction in LC3. In intestinal resections from CD patients, the expression of p62 positively correlates with the expression of Col1a1 ($r_{Spearman} = 0.6098$, $p = 0.004$), α-sma ($r_{Spearman} = 0.5168$, $p = 0.041$), Snail1 ($r_{Spearman} = 0.4112$, $p = 0.0003$) and Snail2 ($r_{Spearman} = 0.4410$, $p = 0.0009$).
Conclusions: Pharmacological inhibition of autophagy exacerbates murine intestinal inflammation, fibrosis, and EMT. In intestinal resections from CD patients the expression of autophagy markers correlates with the expression of pro-fibrotic and pro-EMT genes, which led us to suggest that pharmacological modulation of autophagy might be a new therapeutic option for intestinal fibrosis.

OP04

Turning sweet in inflammatory bowel disease: glycans as novel immunomodulators of T-cell-mediated immune response

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Background: Mucosal T lymphocytes from patients with ulcerative colitis (UC) were previously shown to display a deficiency in branched N-glycans that was associated with disease severity.[1,2] However, whether this altered glycosylation pathway shapes the course of the T-cell response constituting a targeted-specific mechanism in UC remains largely unknown. Moreover, the predictive capacity of this colonic glycosignature in terms of disease course and therapy response was investigated.
Methods: We used a multi-disciplinary approach that gathers in vitro, ex vivo, mouse models of disease and clinical validation in human samples. Human ex vivo CD3+ T cells (from intestinal lamina propria) were purified from fresh colonic biopsies and blood of 75 UC patients with active disease and with different Mayo endoscopic subscores. T cells were cultured and supplemented with increasing doses of the simple glycan *N*-acetylglucosamine (GlcNAc). The impact on T-cell-mediated immune response was analysed by assessing: T-cell proliferation; T-cell activation and differentiation; cytokine profile; TCR signalling and the glycophenotype of T-cells were also determined. Additionally, colitis were induced (with DSS) in null/heterozygous mouse models displaying a deficiency in the branched N-glycosylation pathway (MGAT5–/–; MGAT5+/–); treatment with GlcNAc orally and/or with enemas was performed and the immunomodulatory effects of GlcNAc were evaluated.
Results: We demonstrated that metabolic supplementation of *ex vivo* mucosal T cells from active UC patients with GlcNAc resulted in enhancement of branched N-glycosylation in the T-cell receptor (TCR), leading to suppression of T-cell growth, inhibition of the Th1/Th17 immune response, and controlled T-cell activity. We further demonstrated that mouse models displaying a deficiency in the branched N-glycosylation pathway (MGAT5–/–, MGAT5+/–) exhibited increased susceptibility to severe forms of colitis and

early-onset disease. The treatment of these mice with GlcNAc significantly reduced disease severity and suppressed disease progression due to a controlled T-cell-mediated immune response at the intestinal mucosa.[3] Furthermore, we also showed that the levels of expression of branched N-glycans analysed in colonic biopsies of UC patients close to diagnosis predicts the failure to standard therapy.[4]

Conclusions: We propose glycans as novel immunomodulators in IBD, further disclosing a promising predictive glycobiomarker associated with therapy response.

Note: This work was sponsored by ECCO grant 2017.

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OP05

Crohn's disease exclusion diet is equally effective but better tolerated than exclusive enteral nutrition for induction of remission in mild-to-moderate active paediatric Crohn's disease: a prospective randomised controlled trial

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Background: Exclusive enteral nutrition (EEN; consumption of a liquid formula without other food for 6–8 weeks) is the recommended first-line therapy for induction of remission in children with mild-to-moderate Crohn's disease (CD). The CD exclusion diet (CDED) is a whole food diet coupled with partial enteral nutrition (PEN), designed to reduce exposure to dietary components hypothesised to negatively affect the microbiome, intestinal barrier, and innate immunity.

Methods: The CDED study was a 12-week prospective, international, multi-centre RCT in children with mild-to-moderate luminal CD <3 years comparing CDED to EEN. Children aged 6–18 years with a paediatric CD activity index (PCDAI) ≥10, + elevated inflammatory markers, were randomised to one of the two groups: Group 1, CDED Stage 1 diet + 50% calories from PEN (Modulen, Nestle) for 6 weeks, followed by CDED Stage 2 + 25% PEN for the next 6 weeks; Group 2 EEN for 6 weeks (Modulen) followed by 6 weeks of free diet with 25% supplemental calories from PEN. The primary endpoint was tolerance to diet, measured by withdrawals for refusal to continue diet and poor adherence (measured by a modified MARS questionnaire and physician's assessment). Secondary endpoints included Week 6 intention to treat (ITT) remission defined by PCDAI ≤10 but also with the more stringent definition (PCDAI < 10), and corticosteroid (CS) free ITT sustained remission Week 12.

Results: Seventy-eight patients meeting inclusion exclusion criteria were randomised to CDED+PEN (40)or to EEN (38), four withdrew because of intolerance to diet by 48 h (all EEN). Seventy-four remaining patients (mean age 14.2 ± 2.7 years) were included in the remission analysis. Median PCDAI at baseline was 25 (IQR 20–35) for CDED and 27.5 (IQR 18.75–32.5) in EEN; $p = 0.89$. Tolerance was present in 39/40 (97.5%) CDED and in 28/38(73.7%) EEN ($p = 0.003$). Poor compliance was similar [7/40 (17.5%) vs. 8/34 (23.5%); $p = 0.52$]. Week 6 ITT CS-free remission PCDAI ≤10 occurred in 32/40 (80%) in CDED vs. 25/34 (73.5%) with EEN ($p = 0.51$). Using the more stringent PCDAI < 10, remission was 30/40(75%) CDED and 20/34 (59%) EEN $p = 0.38$. Median CRP decreased from Week 0 to 6 in both groups (23.6 to 5 g/l with CDED; $p < 0.001$; 24 to 4 g/l with EEN; $p < 0.001$). Sustained CS free remission at Week 12 PCDAI ≤10 was 28/40 (70%) with CDED+PEN and 14/34 (41.2%), in the EEN followed by PEN +free diet $p = 0.01$.

Conclusions: Both diets result in high rates of ITT CS free remission with a significant decrease in inflammation. CDED with PEN has superior tolerance and sustained remission by Week 12. These data support the use of CDED+PEN as a first-line therapy for children with luminal mild-to-moderate active CD. They also support the concept that diet plays a role in inflammation in CD

OP06

Gut–brain axis revisited: Shedding light on the mucosa-associated microbial composition in IBD patients with psychological distress, anxiety, and depression

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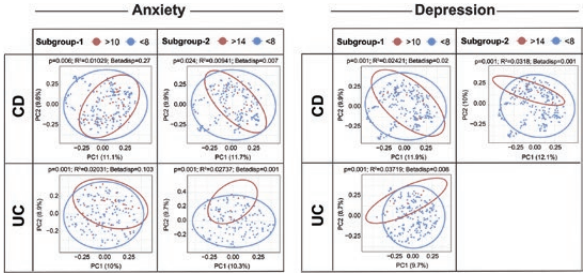
Background: The diversity and compositional stability of the gut microbiota over time has repetitively shown to be reduced in patients with IBD. Furthermore, distinctive alterations in microbial composition are not only considered a key pathogenic factor promoting intestinal inflammation, but might also affect the gut–brain axis, thereby ultimately impacting psychological well-being. In IBD patients, depressive symptoms and anxiety are frequent co-morbidities. Therefore, we aimed to elucidate a potential interplay between

microbial composition and validated psychological outcome measurements in Swiss IBD patients.

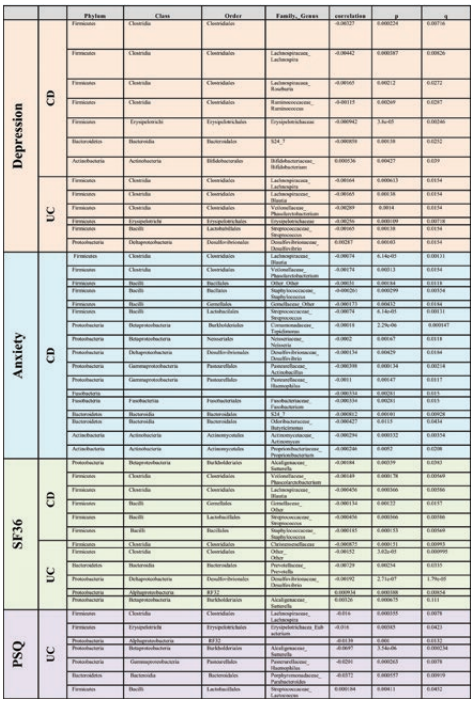
Methods: Study participants were 171 patients with available microbial sampling of the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS) who were in clinical remission (to exclude a potential impact of disease activity). All patients completed the Hospitality Anxiety and Depression Scale (HADS), the Perceived Stress Questionnaire (PSQ), the 36-item Short Form Health Survey (SF-36) and the Inflammatory Bowel Disease Questionnaire (IBDQ). Mucosa-associated intestinal microbiota composition from intestinal biopsies were sequenced via 16S rRNA high-throughput sequencing.

Results: Regarding α diversity, we found significantly lower diversity in patients with higher perceived stress and no substantial differences in patients with high vs. low levels of anxiety and depressive symptoms, respectively. Beta diversity was significantly different in IBD patients with vs. without depression or anxiety (Figure 1).



Principal component analysis of microbial β diversity according to severity (1 = moderately increased, 2 = severe vs. normal anxiety and depression) of psychological alteration (no UC patients with severe depression in our sample).

Looking at specific OTUs, we found several alterations across groups (overview in Figure 2),



Significant results of the quantitative abundance of specific microbes in correlation with extent of psychological distress (– indicating a negative correlation; *q*-values: corrected; *p* value, according to Benjamini and Hochberg false discovery rate).

Including, for instance, significant increases in represents of Proteobacteria, such as Desulfovibrio ($p = 0.001$) in UC and decreases in numerous genus of Firmicutes, such Lachnospiraceae ($p < 0.001$) in CD and UC patients with depression or decreases in Lactobacillales (Streptopcoccaceae) in CD patients with anxiety ($p < 0.001$).

Conclusions: We found significant alterations in the intestinal mucosa-associated microbiome composition in IBD patients in remission in relation to psychological well-being and quality of life. Further studies are warranted to gain more insight into the direction of this link and to investigate whether intestinal inflammation subsequent to microbial alterations or microbial metabolites itself may impair psychological well-being.

OP07

Analysing intestinal organoids in a multi-omics, systems biology framework to investigate functional processes affected in Crohn's disease due to autophagy impairment

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Background: Autophagy is a highly conserved catabolic pathway that eliminates damaged organelles, invading pathogens and specifically degrades proteins. Mutation in autophagy genes and deregulated autophagy are related to various human diseases including Crohn's disease (CD) where autophagy impairment was shown to affect Paneth cells. Previously, we developed the Autophagy Regulatory Network resource (http://autophagyregulation.org) to better understand the mechanism and regulation of autophagy in disease pathomechanisms. To investigate autophagy-related processes in Paneth cells, we combined ARN with multi-omics data from intestinal organoids. In particular, we investigated how autophagy impairment, often observed in CD, could affect the key cell functions of Paneth cells.

Methods: We generated a mouse model lacking Atg16l1 specifically in intestinal epithelial cells making these cells impaired in autophagy. Using a 3D intestinal organoid culture model that we enriched for Paneth cells, we compared the proteomic profiles of organoids derived from the wild-type (WT) and Atg16l1 KO mice. We developed an integrated computational approach combining protein–protein interaction networks, autophagy-targeted proteins

and functional information to identify the mechanistic link between autophagy-impairment and disrupted cellular processes.

Results: We detected 284 proteins with altered protein levels by comparing the proteomic profiles of organoids derived from normal mice or mice with impaired autophagy. Our integrated analysis—combination of proteomics and network biology approaches—revealed autophagy-mediated mechanisms which degrade essential proteins belonging to key Paneth cell functions such as exocytosis, apoptosis, and DNA damage repair. We performed validation experiments by generating full transcriptomics profiles of both organoid types, and by specifically focussing on Paneth cell-derived lysozyme to confirm our inferred observation of down-regulated exocytosis.

Conclusions: We used both experimental and computational approaches to analyse and uncover the systems-level regulation of cellular processes dependent on autophagy in Paneth cells enriched organoids. Strikingly, the analysis revealed that when autophagy is impaired, nearly 300 proteins display increased or decreased abundance, encompassing at least 18 functional processes. Our observations could explain how protein-level alterations in CD as a result of autophagy-impairment could affect Paneth cell functions. The established workflow enables assessing the potential intestinal effect of autophagy-related mutations in CD patients, and prioritise the key affected processes.

OP08

Long-term efficacy and pharmacodynamics of the anti-mucosal addressin cell adhesion molecule-1 (MAdCAM-1) monoclonal antibody SHP647 in Crohn's disease: the OPERA II study

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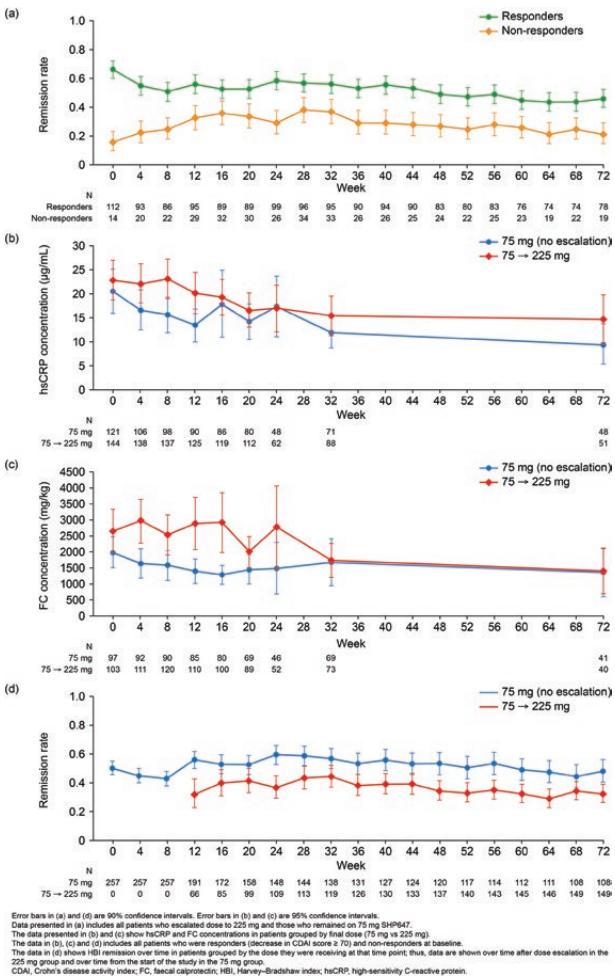
Background: SHP647 is a fully human IgG_2 anti-mucosal addressin cell adhesion molecule (MAdCAM-1) antibody in development for the treatment of Crohn's disease (CD). OPERA II, a multi-centre, open-label, Phase 2 extension study (NCT01298492), aimed to assess the long-term safety and efficacy of SHP647 in moderate-to-severe CD.

Methods: Patients enrolled in OPERA II completed either 12 weeks' induction treatment (placebo or SHP647 22.5, 75, or 225 mg sc) in OPERA (NCT01276509) regardless of response, or had a clinical response (≥3-point Harvey–Bradshaw Index [HBI] score decrease) to SHP647 225 mg in TOSCA (NCT01387594). In OPERA II, patients received SHP647 (75 mg sc) every 4 weeks from Week 0–72 and were followed up monthly for safety for a further 24 weeks. Dose reduction to 22.5 mg owing to intolerance/adverse events or escalation to 225 mg owing to clinical deterioration/poor response was allowed from Week 8 as judged by the investigator. High-sensitivity C-reactive protein (hsCRP), faecal calprotectin (FC), and HBI score were assessed as exploratory efficacy endpoints.

Results: Overall, 268 patients entered OPERA II and 149 completed; at baseline 169 patients from both OPERA and TOSCA were classed as responders (≥70-point decrease in Crohn's Disease Activity Index in OPERA or ≥3-point decrease in HBI in TOSCA) and 89 from OPERA were non-responders. Remission rate (HBI <5) initially decreased in responders and increased in non-responders from baseline to Week 8; it was then maintained in both groups to Week 72 (Figure 1a). No patients de-escalated dose, but 157 patients escalated to 225 mg. Those who escalated had slightly higher hsCRP and FC concentrations at baseline than those who remained on 75 mg (mean [95% CI] hsCRP, 22.8 [18.6, 27.0] vs. 20.5 [15.9, 25.1] µg/ml; mean [95% CI] FC, 2662.7 [1977.9, 3347.5] vs. 1988.8 [1501.0, 2476.7] mg/kg). Concentrations of hsCRP and FC decreased from



Abstract OP08 – Figure 1. Change over time in OPERA II in (a) mean remission rate (HBI score < 5) for responders and non-responders to treatment with SHP647 from OPERA (NCT01276509) and TOSCA (NCT01387594); (b) mean hsCRP concentrations (c) mean FC concentrations and (d) mean remission rate (HBI score < 5) over time in OPERA II for patients who dose-escalated to 225 mg vs. those who remained on 75 mg SHP647.

baseline to Week 72 in both groups, but remained higher in those who escalated; the decline in hsCRP and FC was slower in those who escalated (Figure 1b and c). Mean changes over time in remission rates (Figure 1d) were similar in both groups after an initial decrease in those who remained on 75 mg and an initial increase in those who escalated.

Conclusions: In this extension study, remission rates were sustained over 72 weeks with SHP647, regardless of initial response to induction treatment or dose-escalation status. hsCRP and FC levels were higher in patients who dose-escalated than those who remained on 75 mg. This adds to the evidence for long-term efficacy of SHP647.

OP09

Histological remission and mucosal healing in a randomised, placebo-controlled, Phase 2 study of etrasimod in patients with moderately to severely active ulcerative colitis

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Background: Etrasimod (APD334), an oral, selective sphingosine-1-phosphate receptor modulator, was evaluated in the randomised, double-blind, placebo-controlled, parallel-group, Phase 2 OASIS study (ClinicalTrials.gov identifier: NCT02447302) in patients with moderately to severely active ulcerative colitis (UC). Etrasimod demonstrated dose-dependent improvements in clinical response, clinical remission, and endoscopic appearance and decreased circulating lymphocytes. Here, we describe histological remission and mucosal healing results at Week 12.

Methods: Patients were randomised to receive once-daily etrasimod 1 mg (n = 52) or 2 mg (n = 50), with no dose titration, or placebo (n = 54). At baseline and Week 12, endoscopic severity was assessed by sigmoidoscopy with central readings using the Mayo endoscopic subscore. Biopsies were taken, and histology results were scored by a blinded central pathologist using the Geboes index. Prespecified endpoint definitions were endoscopic improvement (Mayo endoscopic subscore of 0 or 1); histological improvement (Geboes score <3.1); and histological remission (Geboes score <2.0). Mucosal healing (a post hoc analysis) was defined as both endoscopic improvement and histological remission. Differences between groups were estimated using the Mantel–Haenszel analysis adjusted for current corticosteroid use at baseline and prior anti-tumour necrosis factor α use.

Results: Of 156 patients randomised, 90% completed the study. Etrasimod 2 mg, compared with placebo, resulted in significantly more patients who achieved endoscopic improvement (43.2% vs. 16.3%, respectively; p = 0.003), histological improvement (31.7% vs. 10.2%; p = 0.006), and histological remission (19.5% vs. 6.1%; p = 0.027) at Week 12 (Table). Mucosal healing was seen in 19.5% and 4.1% of patients treated with etrasimod 2 mg and placebo, respectively (p = 0.010). More patients receiving etrasimod 1 mg also achieved each endpoint compared with placebo; however, results did not reach statistical significance.

Conclusions: Etrasimod 2 mg induced significantly higher rates of endoscopic improvement, histological improvement and remission, and mucosal healing in patients with moderately to severely active UC when compared with placebo. Mucosal healing may prove to be an achievable and objective measure of drug efficacy in UC induction studies.

Abstract OP09 – Table. Endoscopic, histological, mucosal measures at Week 12.

Efficacy Measure	Etrasimod 1 mg (n=49)	Etrasimod 2 mg (n=41)	Placebo (n=49)
Endoscopic improvement (Mayo endoscopic subscore ≤1)			
Patients achieving, %	22.0[a]	43.2[b]	16.3
Difference from placebo[c] (90% CI)	5.1 (−7.7 to 18.0) *P*=0.261	25.9 (11.0 to 40.8) *P*=0.003	
Histological improvement (Geboes score <3.1)			
Patients achieving, %	20.4	31.7	10.2
Difference from placebo[c] (90% CI)	9.9 (−1.8 to 21.7) *P*=0.090	21.2 (7.5 to 35.0) *P*=0.006	
Histological remission (Geboes score <2.0)			
Patients achieving, %	10.2	19.5	6.1
Difference from placebo[c] (90% CI)	3.4 (−5.7 to 12.5) *P*=0.271	13.3 (1.9 to 24.8) *P*=0.027	
Mucosal healing[d] (Both endoscopic improvement and histological remission)			
Patients achieving, %	8.2	19.5	4.1
Difference from placebo[c] (90% CI)	3.6 (−4.3 to 11.5) *P*=0.231	15.4 (4.3 to 26.4) *P*=0.010	

CI, confidence interval. Modified intention-to-treat population. All *P* values are 1-sided. [a]n=50; [b]n=44; [c]Mantel–Haenszel estimate, adjusted for current corticosteroid use at baseline and prior anti-tumour necrosis factor alpha use; [d]Post hoc analysis.

OP10

Systems genomics of ulcerative colitis: combining GWAS and signalling networks for patient stratification and individualised drug targeting in ulcerative colitis

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Background: The pathogenic signalling pathways of ulcerative colitis (UC) are complex, making patient stratification for optimal therapeutic choices challenging. Disease associated single-nucleotide polymorphisms (SNPs) make the prospect of personalised disease stratification and therapeutics tantalisingly plausible, but forward movement has been difficult. Using systems genomics, we propose

a method to identify cohort-specific pathogenic and patient-specific targetable therapeutic pathways.

Methods: Using UC-associated SNPs from the UKIBD Genetics Consortium and the Broad Institute publicly available datasets, we identified the regulatory effects of UC-associated SNPs by identifying those which were localised in transcription factor-binding sites or miRNA target sites. We developed a workflow, iSNP, to identify these regulatory SNPs and build a UC-interactome network (UC-ome). UC-ome contains the regulatory SNP affected genes, the physical interactors of their encoded proteins, the transcription factor and miRNA regulators of the affected gene. The interaction information was integrated from databases containing curated, experimentally validated interactions. We extracted the individual SNP profile from 377 UC patients, and put them through iSNP creating a UC-ome. We used the UC-ome to cluster the patients in cohorts based on their genomic footprint, and compared the clustering with patient-specific clinical parameters with random forest machine learning and enrichment analysis. We validated the workflow on a larger cohort of 941 UC patients from the IBD Biobank in Leuven.

Results: The constructed UC-ome consists of 276 molecules and 1965 physical or regulatory interactions. Analysing the genomic footprints of the patients, we identified 4 patient clusters, and identified common and differing pathogenic pathways between them. We showed that clusters were related to gender and age of onset of disease, but unrelated to therapeutic upscaling of therapy. With machine learning, we identified a subset of patients from within one of the cohorts, for whom the presence of a regulatory MAML2 SNP was a marker for therapeutic upscaling. MAML2 is a Notch pathway activator. This raises the possibility of cohorts of UC patients whose pathway to disease differs to the general UC population, making the MAML2 SNP a potential marker of severity, and the downstream Notch pathway a potential target for personalised therapeutics.

Conclusions: Using a novel systems biology workflow, iSNP, we have been able to analyse the regulatory effects of UC-associated SNPs both on a large cohort level and individual level. We have used this workflow to identify cohorts of patients who may benefit from a therapeutic approach based on their genomic footprint.

OP11

Organoids derived from inflamed intestinal biopsies of patients with ulcerative colitis lose their inflammatory phenotype during *ex vivo* culture

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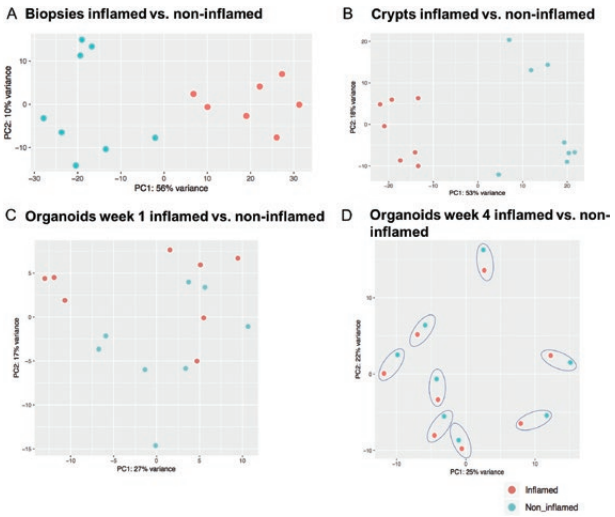
Background: Patient-derived intestinal organoids provide an excellent tool to unravel the multi-factorial mechanisms underlying ulcerative colitis (UC). Organoids develop from stem cell-containing intestinal crypts and recapitulate many features of the source tissue. However, it remains unclear whether *ex vivo* organoids retain the inflammatory character of their origin. To address this, we isolated crypts from both inflamed and non-inflamed regions of the colon, created organoids, and compared the transcriptome of whole biopsies, crypts and *ex vivo* cultured organoids.

Methods: Fresh biopsies from both inflamed and non-inflamed segments were obtained during endoscopy from eight patients with active UC (endoscopic Mayo sub-score of ≥2) and an accessible border of inflammation. Crypts were isolated and cultured as organoids for 4 weeks with weekly mechanical splitting. RNA was extracted from biopsies, crypts, and 1- and 4-week-old organoids. RNA sequencing was performed by Lexogen QuantSeq for Illumina. Differential gene expression and pathways were studied through DESeq2 and Ingenuity Pathway Analysis (FDR < 0.05).

Results: Biopsies and crypts from inflamed regions showed separate clustering on principal component analysis (PCA, Figure) and significantly higher activation of inflammatory pathways, including antigen presentation ($p < 0.01$ and $p < 0.001$), interferon signalling ($p < 0.05$ and $p < 0.001$) and granulocyte adhesion (both $p < 0.001$) compared with non-inflamed biopsies and crypts. However, organoids derived from inflamed crypts lost part of their inflammatory character after 1 week in culture. Several inflammatory markers (IFN-γ [$p = 0.01$], IL-1β [$p < 0.001$], JAK1 [$p < 0.001$]), and pathways involved in antigen presentation ($p < 0.005$) and interferon signalling ($p < 0.001$) were significantly decreased after 1 week *ex vivo* culture compared with inflamed crypts. After 4 weeks in culture, organoids derived from inflamed and non-inflamed regions were indistinguishable in PCA clustering, and expression levels of inflammatory signalling pathways were not significant.

Conclusions: We conclude that *ex vivo* organoids lose their inflammatory transcriptional signature in culture. After 4 weeks in culture, organoids derived from inflamed and non-inflamed biopsies were no longer distinguishable. Therefore, it is not essential to obtain biopsies from inflamed regions to culture organoids from UC patients. We hypothesise that to mimic the inflammatory phenotype and create a physiological representative model, inflammatory components, and/or immune cells should be added to the *ex vivo* culture system.



Principal component analysis (PCA) shows separate clustering of biopsies and crypts from inflamed regions vs. non-inflamed regions. After 1 and 4 weeks, organoids of inflamed and non-inflamed origin cluster together and are no longer distinguishable.

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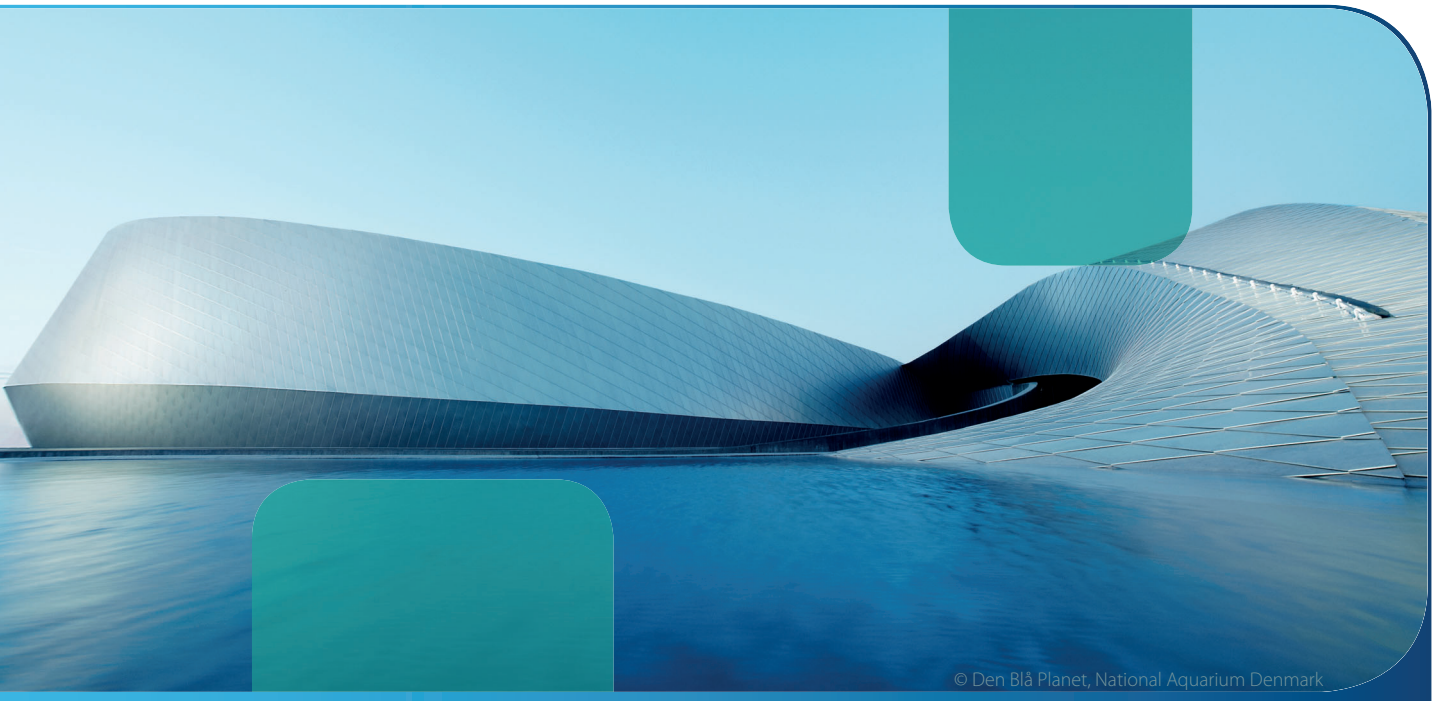

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OP12

Targeting inflammation in ulcerative colitis by inhibiting glucose uptake

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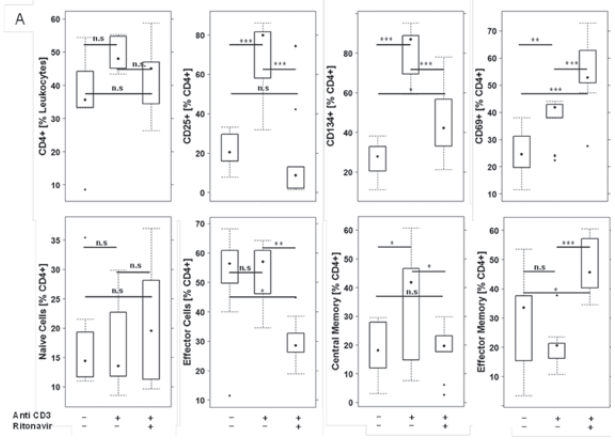
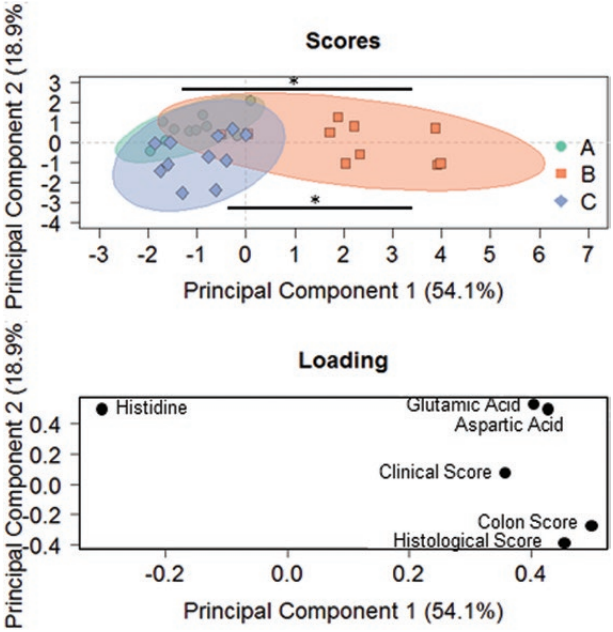
Background: The energy supply of inflammatory cells relies on three sources: Glycolysis, oxidation of lipids, and amino acid (AS) metabolism. In homeostasis, when the major task of inflammatory cells is the maintenance of tolerance, lipids are the preferred source as lipid oxidation is the most efficient albeit slowest pathway to generate ATP: The response to an assault, however, requires the immediate activation, proliferation, differentiation of inflammatory cells, their migration to sites of inflammation and expression of cytokines, growth factors and chemokines. These processes demand prompt energy supply which is met by a metabolic switch from lipid oxidation to glycolysis to ensure swift ATP generation and the synthesis of biosynthetic intermediates albeit at the expense of efficiency. Therefore, the dependence on glycolysis might offer an Achilles' heel of inflammatory cells. Glucose uptake into the cell is regulated by the PI3K/AKT/mTOR pathway and glucose uptake transporters (GLUT). Therefore, we tested the PI3K inhibitor copanlisib and the glucose uptake inhibitor ritonavir *in vitro* and *in vivo*.
Methods: Peripheral blood mononuclear cells (PBMC) were activated with anti CD3/CD28 in the presence of ritonavir. Cells were analysed by flow cytometric analysis. A seahorse analysis was performed. To examine the effect of ritonavir in vivo, the NSG-UC mouse model was used which is based on immunocompromised NOD-scid IL-2R null mice reconstituted with (PBMC) from patients with ulcerative colitis (UC). Dependent variables were clinical and histological score, frequencies of human leucocytes isolated from spleen and colon and levels of amino acids (AS) in sera of mice.
Results: Frequencies of activated CD4+ cells (CD4+ CD69+, CD4+ CD134+) were significantly affected by ritonavir and copanlisib.



Ritonavir affects frequencies of CD4+ T-cell subtypes.

Copanlisib predominantly inhibited glycolysis induced by activation of CD4+ cells with anti CD3+ / CD28 antibodies and activation of monocytes induced by LPS. Mice benefited from treatment with ritonavir as indicated by decreased clinical (p = 0.05) and histological (p = 7e–0.5) scores and Glu levels (p = 0.02). PCA analysis revealed a clustering of ritonavir treated mice with control mice.



Principal component analysis discriminates between the control group, ethanol-challenged group and ritonavir-treated group.

Conclusions: Targeting metabolic pathways might open up new avenues for therapeutic interventions. Patients might benefit from FDA-approved drugs as copanlisib or ritonavir.

OP13

Molecular response to ustekinumab in moderate-to-severe ulcerative colitis by serum protein and biopsy gene expression analysis: Results from the UNIFI Phase 3 induction study

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Background: The cytokines IL-12 and IL-23 are elevated in ulcerative colitis (UC) and genetic association suggests that they play causative roles in the disease. Ustekinumab (UST), an anti-IL-12p40 monoclonal antibody that blocks both cytokines, is an effective therapy for moderate-to-severe UC, but its molecular effects in UC patients remain unknown.
Methods: Colonic biopsy mRNA and serum samples from the first ~60% of patients who were randomised in the UNIFI Phase 3 induction study of UST in UC[1] were analysed, with equal representation of patients with a history of biological therapy failure (BF) and those without (BN) (Table 1). Biopsy and serum samples from healthy subjects were analysed as controls.
Results: Colon biopsies from UC patients had a gene expression disease profile of 4095 probe sets, including genes involved in inflammatory response, tissue remodelling and wound healing, host–microbe interaction, intestinal permeability, and solute transport. BF and BN UC patients shared almost identical disease profiles. At Week 8 after UST induction therapy, the disease profile and top canonical pathways were significantly normalised in responders to UST. A smaller

Abstract OP13 – Table 1. Biopsy mRNA and serum protein assessments in UNIFI

	Biopsy mRNA (550 UC and 18 healthy controls)	Serum Protein (574 UC and 50 healthy controls)
Time points	Screening, Week 8, Week 16	Screening, Week 4, Week 8, Week 16
Methods	Generalized linear model (GLM) & Gene Set Variation Analysis	GLM
Significance cutoffs	|fold change| > 1.5x and $p < 0.05$	|fold change| > 1.5x and $p < 0.05$
Analytes	Affymetrix HG U133 PM arrays	12 serum markers: • Matrix metalloproteinases: MMP-1,3,9 • Cytokines and cytokine receptors: IFNγ, IL-17A, IL-22, IL-10, IL-2R, TNFα, TNFR1 • Acute Phase Reactant: SAA • Inflammatory marker: NGAL

magnitude of normalisation was observed in responders to PBO. No significant change in disease signature occurred in non-responders. At baseline, BF and BN UC patients had similar serum profiles, with significantly elevated levels of IFN γ, IL-17A, IL-22, SAA, NGAL, MMPs, and TNF vs. healthy controls. Normalisation of IFN γ, SAA, IL-17A, and IL-22 was first detected in responders to UST at Week 4, the earliest time point in our assessment, and continued to improve through Week 8. A trend of normalisation of MMPs, IL-10, and NGAL was observed in UST responders; this trend was weaker or absent in UST non-responders and PBO-treated patients. TNF was elevated in UC prior to treatment and was not normalised by UST induction therapy.

Conclusions: Transcriptomic and protein analyses in this subset of patients from the Phase 3 UC induction study demonstrated the suppression of IL-12 (IFN γ) and Il-23 (IL-17A) pathways and normalisation of the UC disease gene expression profile in response to UST. These results provide insight into the molecular mechanisms of UST efficacy.

Reference

1. Sands BE, Sandborn WJ, Panaccione R, *et al.* Safety and efficacy of ustekinumab induction therapy in patients with moderate to severe ulcerative colitis: Results from the phase 3 UNIFI study. Oral Presentation at ACG, October 9, 2018, Philadelphia, PA.

OP14

Improved endoscopic outcomes and mucosal healing of upadacitinib as an induction therapy in adults with moderately to severely active ulcerative colitis: data from the U-ACHIEVE study

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Background: The efficacy and safety of upadacitinib, an oral, selective Janus Kinase 1 inhibitor, was assessed in an 8-week Phase 2 induction study of patients with moderately to severely active ulcerative colitis who had inadequate response, loss of response or intolerance to corticosteroids, immunosuppressants, or biologic therapies.[1] This analysis evaluated the endoscopic improvement, endoscopic remission, histological improvement, histological remission, and mucosal healing rates at Week 8 of the U-ACHIEVE study.

Methods: Adult patients with Adapted Mayo Score (Mayo score without Physician Global Assessment) of 5–9 points and centrally read endoscopy subscore of 2–3 were randomised to receive extended-release upadacitinib 7.5, 15, 30, 45 mg once daily (QD) or placebo for 8 weeks. Patient randomisation was stratified by previous biologic use, baseline corticosteroid use, and baseline Adapted Mayo score (≤7/>7). The proportion of patients who achieved endoscopic improvement (endoscopic subscore ≤1), endoscopic remission (endoscopic subscore of 0), histological improvement (any decrease from baseline in Geboes score), histological remission (Geboes score <2), and mucosal healing (endoscopic subscore of 0 AND Geboes score <2) were analysed and pairwise comparisons between upadacitinib doses and placebo were conducted using the Cochran–Mantel–Haenszel test stratified by randomisation factors. Non-responder imputation was utilised for missing values.

Results: A total of 250 patients were randomised with a mean (SD) age of 42.3 (14.2) years and a mean (SD) disease duration of 8.2 (2.5) years. At baseline, 77.6% had prior use of biologics, 36% had an Adapted Mayo Score >7, and 79% had an endoscopic subscore of 3. At Week 8, a dose–response relationship was observed for all efficacy endpoints. The proportion of patients achieving endoscopic improvement, endoscopic remission, histological improvement, histological remission, and mucosal healing was statistically significantly higher ($p < 0.05$) in the upadacitinib 30 and 45 mg QD groups vs. the placebo group (Table).

Conclusions: In this dose-ranging 8-week induction study, upadacitinib 30 and 45 mg QD consistently demonstrated significant improvement in endoscopic outcomes, histological outcomes, and mucosal healing compared with placebo in patients with moderately-to-severely active ulcerative colitis.

Reference

1. Sandborn WJ. Efficacy and safety of upadacitinib as an induction therapy for patients with moderately-to-severely active ulcerative colitis: data from the phase 2b study U-ACHIEVE, United European Gastroenterology (UEG) Week, Presentation #OP195, 2018.

Abstract OP14 – Table. Proportion of patients achieving endoscopic improvement, endoscopic remission, histological improvement, histological remission, and mucosal healing at Week 8.

Endpoints, n (%)	Placebo n=46	UPA 7.5 mg QD n=47	UPA 15 mg QD n=49	UPA 30 mg QD n=52	UPA 45 mg QD n=56
Endoscopic improvement	1 (2.2)	7 (14.9)*	15 (30.6)***	14 (26.9)***	20 (35.7)***
Endoscopic remission	0	3 (6.4)	2 (4.1)	5 (9.6)*	10 (17.9)**
Histologic improvement	3 (8.1)	15 (35.7)**	25 (55.6)***	23 (52.3) ***	27 (56.3) ***
Histologic remission	1 (2.6)	6 (13.6)*	11 (24.4)**	16 (35.6)***	23 (45.1)***
Mucosal healing	0	1 (2.1)	1 (2.0)	3 (5.8)*	8 (14.3)*

***, **, *, * statistically significant at 0.001, 0.01, 0.05, and 0.1 levels, respectively.
UPA: upadacitinib; QD: once daily.

OP15

Cost analysis in a prospective European population-based inception cohort: is there a cost-saving effect of biological therapy?

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P. Ellul[22], R. Salupere[23], A. Goldis[24], I. Kaimakliotis[25], N. Pedersen[26], V. Andersen[27], J. Halfvarson[28], S. Sebastian[29], J. F. Dahlerup[30], P. Munkholm[1], S. Odes[3], Epi-IBD

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Background: No prospective long-term analysis of healthcare costs in patients with inflammatory bowel disease (IBD) in the era of biological treatments exists in Europe. The aim of this study was to perform a cost analysis of a pan-European inception cohort with 5 years of follow-up.

Methods: The Epi-IBD cohort is a population-based inception cohort of IBD patients diagnosed from 31 centres in 20 European countries in 2010. Data were collected prospectively. Patient management was left to the discretion of the treating gastroenterologists. Data are expressed as mean costs (€/patient-year).

Results: The cohort included 1362 IBD patients (Western Europe: 1,104; Eastern Europe: 258); of which, 52% had ulcerative colitis (UC), 37% Crohn's disease (CD), and 11% IBD unclassified. Mean total expenditures per patient-year (PY) and the proportion of expenditure spent on different cost categories are shown in Tables 1 and 2. In both Eastern and Western Europe, total annual costs were highest in PY1 and then decreased (Table 1). Expenditure on biological therapy increased in this time period in both Western (PY1 €338, PY2 €410, PY3 €440, PY4 €504, and PY5 €516) and Eastern Europe (PY1 €31, PY2 €233, PY3 €355, PY4 €308, and PY5 €292). In both regions, this was paralleled by a steady decrease of costs of non-biological treatment, hospitalisation, and surgery. In a regression analysis, patients with worse disease phenotype (Figure 1) as well patients aged ≥40 years engendered higher costs. The overall outlay on biological therapy, expressed as a percentage of total expenditure, varied by age group: ≥40 years, 29%; 41–60 years, 21%; and ≥61 years, 11%.

	PY1	PY2	PY3	PY4	PY5
Total expenditure	5579€	1820€	1714€	1907€	1669€
Biological therapy (%)	11	46	51	48	55
Other IBD-related medication (%)	5	13	11	11	12
Hospitalisation (%)	20	14	11	11	6
Diagnostic procedures (%)	34	17	11	12	10
Surgery (%)	30	9	16	18	17

Mean total expenditure (€/patient) as well as the proportion of expenditure spent on different categories of direct costs in patients with Crohn's disease.

	PY1	PY2	PY3	PY4	PY5
Total expenditure	3612€	1421€	810€	983€	674€
Biological therapy (%)	2	7	20	19	25
Other IBD-related medication (%)	15	23	29	21	26
Hospitalisation (%)	35	29	21	33	17
Diagnostic procedures (%)	38	20	20	19	19
Surgery (%)	10	21	10	8	13

Mean total expenditure (€/patient) as well as the proportion of expenditure spent on different categories of direct costs in patients with ulcerative colitis.

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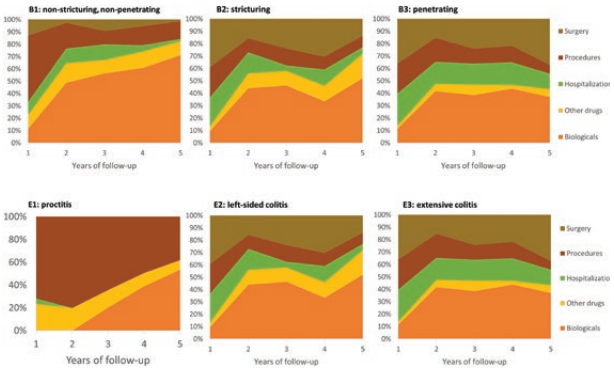

Distrubition of costs according to phenotype

Conclusions: In this population-based inception cohort of unselected IBD patients, overall direct expenditure on healthcare decreased over a 5-year follow-up period in parallel with remarkably increasing expenditure on biologics, particularly in CD patients, and decreasing expenditure on standard medical treatments, surgery, and hospitalisation. Despite their known high-acquisition charges, these data indicate a cost-saving effect of biological medications.

OP16

A randomised, multi-centre, double-blind, placebo-controlled study of a targeted release oral cyclosporine formulation in the treatment of mild-to-moderate ulcerative colitis: efficacy results

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Background: Cyclosporine (CsA) is an effective treatment for patients with acute severe ulcerative colitis (UC), and studies have shown that it has an impact on disease activity comparable to the anti-TNF agent, infliximab.[1,2] Concerns regarding systemic toxicities have limited its role to short-term induction therapy and as a bridge to other therapies. ST-0529 is a novel low dose, controlled release formulation of CsA. A Phase 1 dose-ranging study demonstrated that tissue concentrations improved when it is given twice daily (BID).[3]

Methods: A total of 118 subjects with mild (baseline DAI < 6) or moderate (baseline DAI ≥ 6) UC were randomised 1:1 to receive 75 mg ST-0529 once daily or placebo (53 and 65 patients, respectively) for 4 weeks in a multi-centre, randomised, double-blind, placebo-controlled, Phase IIa study. Patients using UC medications (eg low-dose steroids, 5-aminosalicylates, and immunomodulatory agents) on screening could continue them if agreed to maintain a stable dosing regimen during the study. The primary objective was to evaluate the efficacy of ST-0529 in inducing clinical remission (DAI score ≤2, with no individual score >1 and rectal bleeding subscore of 0 or 1). The secondary objectives included clinical response, mucosal and histological healing, safety, and tolerability.

Results: A numerical although not statistically significant advantage of ST-0529 over placebo was found for rates of clinical remission (ST-0529: 13.2%; placebo: 6.3%, $p = 0.2211$) and clinical response (ST-0529: 30.2%; placebo: 18.8%, $p = 0.1923$). There were no differences between the treatment groups for mucosal and histological healing. ST-0529 was safe and well-tolerated. A post hoc subgroup analysis was performed to evaluate effects by disease severity.

Category Disease Severity	n/N (%)		Fisher's Exact p-value	Odds Ratio	95% CI	p-value[a]
	ST-0529	Placebo				
Clinical Remission Rate						
Moderate	3/40 (7.5)	1/53 (1.9)	0.3109	4.216	0.422 – 42.142	0.2205
Mild	4/13 (30.8)	3/12 (25.0)	1.0000	1.333	0.230 – 7.743	0.7486
Clinical Response Rate						
Moderate	14/40 (35.0)	9/53 (17.0)	0.0552	2.632	1.000 – 6.928	0.0499
Mild	2/13 (15.4)	3/12 (25.0)	0.6447	0.545	0.074 – 4.008	0.5514

[a]Logistic regression model including treatment as a covariate

Clinical remission and clinical response rates in subjects with moderate (baseline DAI ≥6) and mild (baseline DAI <6) disease (ITT, $N = 118$)

Conclusions: In this pilot study, ST-0529 given once daily, was safe, well tolerated, and showed a numerically higher, but not statistically significant difference in remission rate in patients with mild-to-moderate UC compared with placebo after 4 weeks of treatment. In the post hoc analysis, differences in the clinical response between treatment subgroups achieved statistical significance in some subgroups, the largest clinical response rate in moderate UC patients taking 5-aminosalicylates and/or steroids. These preliminary data, added to the data from a Phase 1 study, support further development of ST-0529 as a treatment for the induction and maintenance of remission in UC patients with moderate to severe disease.

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OP17

A molecular measure of inflammation in IBD patients based on transcriptional profiles from 2495 intestinal biopsies

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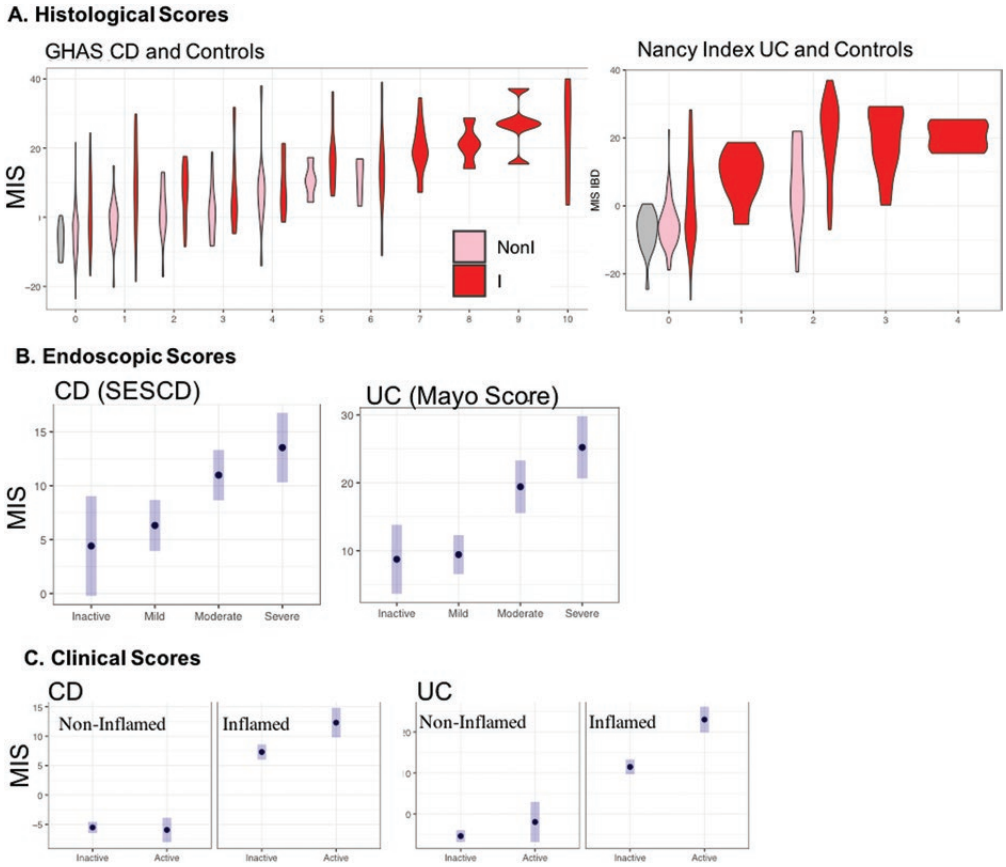
Background: Endoscopy, histology, and biomarker measures of inflammation have limitations of sensitivity, specificity, reproducibility, and range in evaluating inflammatory bowel disease (IBD). We explored whole transcriptome gene expression to define molecular scores of gut inflammation. These scores are applicable to both Crohn's disease (CD) and ulcerative colitis (UC), enabling more granular, continuous measures across multiple states and location of disease.

Methods: We present a molecular characterisation of IBD based on the transcription profiles of 719 endoscopically defined inflamed (Inf) and 1776 non-inflamed (NInf) intestinal biopsies from 498 CD, 419 UC patients in the Mount Sinai Crohn's and Colitis Registry (MSCCR) during endoscopy. Genes differentially expressed between

Abstract OP17



Association of MIS with histological (A), endoscopic (B) and clinical (C) IBD severity. Means (black dots) and CI (blue)

Inf and NInf biopsies were used to generate a biopsy-level molecular inflammation score (MIS) via gene set variation analysis.[1]

Results: MIS was strongly associated with histological biopsy scores for CD (GHAS[2]) and UC (Nancy Index[3]) and independent of inflammatory status (Inf B = 3.1, NInf B = 2.73; $p > 0.05$) (Figure 1A), MIS of Inf biopsies was higher than NInf within the same histological score, indicating that MIS describes a broader range of inflammation signal than histologic assessment. MIS was also associated with endoscopically defined severity (SES-CD and Mayo-endo for UC); capturing the gradient from mild, moderate, to severe disease (Figure 1B). Association of MIS with clinical disease severity was significant for Inf biopsies for continuous measures (HBI for CD B = 0.65, $p < 0.01$; SCCAI for UC B = 1.94, $p < 0.01$) and could also differentiate between HBI and SCCAI defined active and inactive subsets (UC d = 11.5, $p < 0.01$; CD d = 5, $p < 0.01$). This was not the case for NInf biopsies (Figure 1C), indicating that the clinical scores track with inflammation but not with homeostatic features of the gut.

Conclusions: We generated a transcriptionally based intestinal inflammation score in IBD patients, which provides an objective quantification of disease state in IBD-relevant tissues. MIS scores are associated with features captured by histological, endoscopic, and clinical evaluations, but do so with a greater dynamic range, and as a common metric for CD and UC. Further work will explore whether MIS may improve patients subsetting, identify sub-clinical disease, predict flares or therapeutic response. Furthermore, MIS can be used to regress the inflammation component, revealing novel non-inflammatory mechanisms.

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OP18

Proactive adalimumab trough measurements increase corticosteroid-free clinical remission in paediatric patients with Crohn's disease: the paediatric Crohn's disease adalimumab-level-based optimisation treatment (PAILOT) trial

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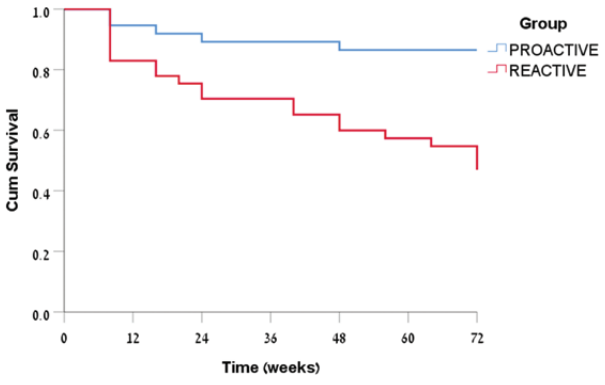
Background: The clinical benefit of proactive therapeutic drug measurement of anti-TNF agents for maintaining a pre-defined trough level compared with reactive measurement performed during exacerbations of Crohn's disease is debated. We performed the first paediatric randomised controlled trial to determine whether proactive therapeutic drug monitoring to maintain serum levels of adalimumab above 5 µg/ml is associated with higher rates of clinical remission than the reactive approach which is based on drug measurement when clinically indicated.

Methods: This was a multi-centre non-blinded randomised controlled trial, in which biological-naïve children (6–18 years) with luminal Crohn's disease who responded to adalimumab induction (Week 4), were randomly assigned into proactive and reactive groups. In the proactive group trough concentrations were measured at Week 4, 8, and every 8 weeks thereafter until Week 72, and dose (when lower than 40 mg) or intervals were adjusted in-order to maintain levels higher than 5 µg/ml. In the reactive group, physicians were informed of the trough levels only when clinically indicated (based on symptoms or elevated CRP or faecal calprotectin) and dose/intervals adjusted based upon the levels. The primary endpoint was sustained corticosteroid-free clinical remission from Week 8 to Week 72 (defined as Pediatric Crohn's Disease Activity Index [PCDAI] <10) using non-responder imputation.

Results: Eighty patients (54 males, mean age 14.1 ± 2.6 years, 43% with combination therapy with immunomodulators) were randomised, 39 in the proactive, and 41 in the reactive groups. Baseline variables were similar between groups. The primary endpoint was met by 34 children (87%) in the proactive group and 21 (49%) in the reactive group ($p < 0.001$, Figure). At Week 72, steroid-free clinical remission on adalimumab was noted in 32 (82%) in the proactive group and 19 (46%) in the reactive group ($p < 0.001$). Clinical indices, CRP, and faecal calprotectin correlated with adalimumab trough concentrations. Faecal calprotectin reduction rate was significantly higher in the proactive group. There were more patients undergoing dose/interval adjustments in the proactive group (32, 82% vs. 18, 44%, $p < 0.001$).



Kaplan–Meyer curve representing time to disease exacerbation.

Conclusions: Repeated proactive trough measurements together with tight control based on clinical indices, CRP, and faecal calprotectin were superior to tight control alone combined with reactive trough measurements resulting in higher corticosteroid-free sustained remission rates. ClinicalTrials.gov Identifier: NCT02256462.

OP19

Corticosteroid response rectal gene signature and associated microbial variation in treatment naïve ulcerative colitis

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Background: Molecular mechanisms driving disease course and response to initial therapy in ulcerative colitis (UC) are poorly understood. In the full PROTECT cohort, the strongest predictor of corticosteroids (CS)-free remission by Weeks 12 or 52 was Week 4 (WK4) remission. We used pre-treatment rectal biopsies in new-onset UC, and defined key pathways linked to WK4 response to standardised induction with CS in the largest prospective paediatric UC cohort to date.

Methods: PROTECT enrolled 428 newly diagnosed paediatric UC patients at 29 North American sites. mRNA-Seq and 16S rRNA defined pre-treatment rectal gene expression and microbial communities in 206 participants. Independent group of 50 participants were used to validate the CS response gene signature. WK4 remission was defined as PUCAI < 10 without additional therapy/colectomy.

Results: Moderate–severe UC patients (152/206) from the discovery cohort and all 50 from the validation cohort received standardised induction therapy with CS. WK4 remission was achieved in 75/152 (49%) and 21/50 (42%) of the discovery and validation groups respectively. 115 genes were differentially expressed (FDR<0.05 and FC ≥1.5) between moderate–severe UC patients who did or did not achieve WK4 remission in the discovery cohort. The corticosteroid response gene signature is highly associated with CXCR chemokines ($p < 7.12E{-}12$), innate myeloid immune signatures ($p < 1.62E{-}15$), and response to bacteria ($p < 2.16E{-}13$). Principle component analyses (PCA) PC1 that summarise the variation of the CS response signature, was significantly different between those that achieved WK4 clinical remission ($p < 0.001$) and mucosal healing ($p = 0.002$) defined as faecal calprotectin < 250 µg/g in the discovery cohort. This was replicated in the independent validation cohort, and was also associated with response to anti-TNFα and anti-α4β7 integrin induction in adults. The response gene signature was associated with shifts in microbes previously implicated in mucosal homeostasis; positive association with taxa such as Campylobacter, Veillonella, and Enterococcus implicated in mucosal inflammation, and a negative association with taxa from the Clostridiales order that are considered beneficial. Finally, the addition of the pre-treatment rectal gene signature PC1 [OR = 0.4 (0.2–0.8 95% CI)] improved WK4 clinical prediction model of remission with CS [AUC = 77.7 (70.0–85.4 95% CI)].

Conclusions: We identified a gene signature linked to WK4 CS response, which was validated in independent UC patients, and showed associations with response to anti-TNFα and anti-α4β7 integrin in adults, and with specific microbial taxa. Our data may prioritise future therapies for non-responders to current approaches.

OP20

Mucosal micoRNA profiles predict response to autologous stem-cell transplantation in Crohn's disease

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Background: The Autologous Stem Cell Transplantation for Crohn's Disease (ASTIC) trial did not achieve its ambitious primary endpoint, but reported meaningful benefits in some CD patients previously refractory or intolerant to conventional therapies. However, the haematopoietic stem cell transplantation (HSCT) regimen used was associated with a high burden of adverse events. Consequently, there is a clear need to target this therapy to patients with the greatest chance of benefit. MicroRNAs (miRNAs) regulate cell signalling and their potential as biomarkers of disease is recognised. Here, we explore the ability of miRNAs to predict response to HSCT in CD patients.
Methods: miRNA profiles were analysed in RNA extracted from mucosal biopsies taken prior to HSCT from 14 CD patients enrolled in ASTIC. Clinical response to therapy was defined as CDAI <150 at 1 year; the cohort included seven 'responders' and seven 'non-responders'. miRNA profiling was conducted using the miRCURY LNA microRNA Array (7th Gen). Natural groupings were explored using principal component analysis (PCA) and differences in miRNAs between groups determined by a two-tailed Student's *t*-test assuming equal variance.
Results: PCA identified two natural groupings; Group 1 contained 6/7 of the responders and Group 2 contained 6/7 non-responders. Significant separation of responders and non-responders was identified along principal component 2 ($p = 0.007$, Figure 1). Inspection of the loadings for PC 2 identified miR-155-5p as a significant contributor to the separation of the groups. Levels of miR-155-5p were significantly higher in non-responders relative to responders ($p = 0.033$). Furthermore, the area under the receiver-operating characteristic curve for miR-155-5p was 0.877, indicating that response to therapy could be accurately predicted in 87.7% of patients from their basal miR-155-5p levels.
Conclusions: The data indicate that miRNAs may act as predictive biomarkers of clinical response following HSCT. In particular, miR-155-5p, a well-characterised pro-inflammatory miRNA, was identified as a putative candidate biomarker. The results of the array now require independent validation.

OP21

ABX464 is safe and efficacious in a proof-of-concept study in ulcerative colitis patients

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Background: Despite the availability of new drugs in IBD, there is still a high unmet medical need for patients suffering from ulcerative colitis. ABX464 has potent anti-inflammatory properties impacting the expression of miR124 as shown in HIV studies. We performed a first-in-disease Phase 2a study with ABX464 in patients with moderate-to-severe ulcerative colitis intolerant and/or refractory to existing treatments.
Methods: The study was performed in 15 European centres. A total of 32 patients were randomised (2:1) to ABX464 50 mg QD orally or placebo for 8 weeks. The primary endpoint was safety of ABX464 and key secondary endpoints included remission (assessed a rectal bleeding sub-score = 0 and an Endoscopy sub-score ≤1 and at least one-point decrease in stool frequency sub-score from baseline to achieve a stool frequency sub-score ≤1), endoscopic improvement (Mayo endoscopic score of 0 or 1), and clinical response and histological healing. Centrally-read endoscopy with histopathology were performed at Day 0 and Day 56. After the blinded induction phase, patients had the option to roll over into a 52-week open-label 50 mg QD ABX464 study.
Results: Total of 29 (90.6%) patients (20 randomised to ABX464 and 9 to placebo) completed the induction study. Baseline demographics and characteristics showed well-balanced groups. The overall safety profile of ABX464 was overall very good with no serious adverse events (SAE). Safety profile was similar to the one seen in the clinical development in the HIV reservoir reduction indication. Main efficacy results are presented below.

	ABX464 ($n = 20$)	Placebo ($n = 9$)	p value
Clinical remission	35%	11%	0.16
Endoscopic improvement	50%	11%	0.03
Clinical response	70%	33%	0.06
Total Mayo score reduction	–53%	–27%	0.03
Partial Mayo score reduction	–62%	–32%	0.02
Faecal calprotectin decrease >50%	75%	50%	
miRNA124-fold expression	7.69	1.46	0.004

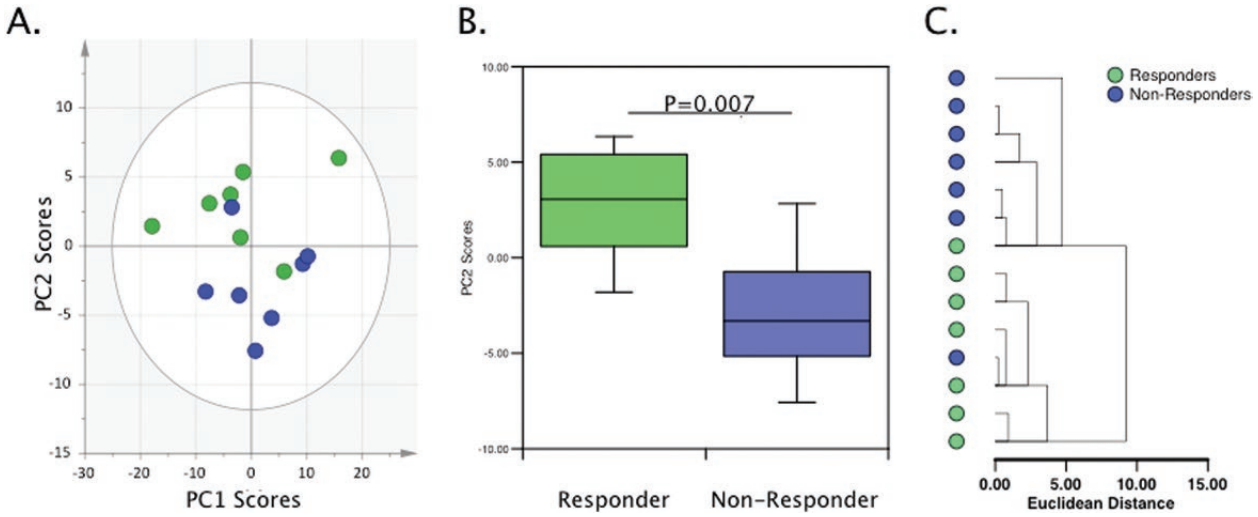
ABX464-101 study endpoints results at Day 56.

The interim data from the 52-week maintenance study show further improvement of Partial Mayo Score and reduction in faecal calprotectin.

Twenty-two patients were included in the 52 weeks maintenance study. The interim analysis with a mean maintenance treatment duration of 5.1 months (max: 9.0 months; min: 3.5 months) showed further improvement in both Partial Mayo score and faecal calprotectin levels.

Conclusions: In this Phase 2a study in patients with moderate-to-severe UC, ABX464 50 mg QD orally for 8 weeks was safe and well

Abstract OP20



PCA separates responders and non-responders to HSCT in CD based on baseline miRNA profiles (A), along principal component 2 (B), which divides patients into two natural groupings (C).

tolerated. Clinical, endoscopy, histopathology, and biomarker analysis all changed in a consistent way and all in favour of ABX464. These data support a Phase 2b multi-centre placebo-controlled dose-ranging study in UC and a Phase 2a study in Crohn's disease.

OP22

Mesenchymal stromal cell-derived exosomes stimulate epithelial regeneration in vitro and reduce experimental colitis

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Background: Local injection of mesenchymal stromal cells (MSCs) stimulates the closure of perianal fistulas in inflammatory bowel disease (IBD) and was therefore recently approved for clinical use in Europe. MSCs are generally believed to work by modulation of immune responses and stimulation of tissue regeneration. MSCs are thought to communicate with neighbour cells through secreted proteins and via direct cell-to-cell contact. However, recent literature shows that they can also communicate via MSC-derived exosomes. In this project, we investigated the effect of MSC–exosomes on epithelial regeneration and whether local MSC therapy in experimental colitis could be mediated by MSC-derived exosomes. Simultaneously, we explored MSC–exosome therapy as a cell-free alternative for MSC therapy.
Methods: Exosomes were isolated from bone marrow-derived murine MSCs using ultracentrifugation. The presence of exosomes was verified using electron microscopy and western blotting for the exosome markers flotillin-1 and alix. To evaluate the epithelial regenerative capacity of exosomes in vitro, a dextran sodium sulphate (DSS)-induced cell death assay in CT26 epithelial cells was used, as well as a scratch cell migration assay. The damaged epithelial cells were treated with low (2 ng/ml) and high (20 ng/ml) concentrations of exosomes, MSC-conditioned medium (CM) with/without exosomes and non-CM. An MTS assay was used to evaluate the effects of exosomes on proliferation of non-damaged epithelial cells. To examine the therapeutic effects of MSC-derived exosomes in vivo, exosomes, MSCs, or PBS were locally applied to the distal colon in DSS-treated mice.
Results: Exosomes were successfully isolated from the CM of MSCs, as shown by high flottilin-1 and alix expression, and could be visualised using electron microscopy. PKH-labelled exosomes showed fusion with epithelial cells in vitro after 24 h. MSC–CM and a high-exosome concentration were found to increase epithelial cell survival/proliferation in the in vitro DSS assay and cell migration in the scratch assay, and also enhanced the proliferation of non-damaged epithelial cells compared with non-CM and a low concentration of exosomes. Furthermore, in vivo experiments showed that endoscopic injections with a high dose of exosomes partially reduced DSS-induced colitis, demonstrated by a higher relative body weight and lower endoscopic disease score compared with PBS-treated mice. Yet, the MSC–exosomes were not as effective as the MSC therapy in vivo.
Conclusions: We showed that a high dose of MSC-derived exosomes is able to counteract epithelial damage in vitro and partially reduce colitis in vivo. These results pave the way for further exploring cell-free MSC-related therapy by using MSC–exosomes in the treatment of IBD.

OP23

CKD-506, a novel histone deacetylase (HDAC) 6 inhibitor, ameliorates colitis in various animal models

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Background: Inhibition of HDAC6 has been proposed beneficial and therapeutic effects in inflammatory bowel disease. CKD-506, an oral selective HDAC6 inhibitor, had completed phase I clinical study and is being investigated for rheumatoid arthritis in phase II clinical study. Herein, we verified the therapeutic effect of CKD-506 in various colitis animal models and identified its underlying molecular mechanisms.
Methods: HDAC6 expression was assessed in colon tissue of healthy individual and patients with Crohn's disease and ulcerative colitis by real-time RT-PCR and immunohistochemistry. Macrophages with HDAC6 overexpression were used for mechanism studies. DSS-, TNBS-, Piroxicam (IL-10$^{-/-}$)-, and adaptive T-cell transfer (RAG1$^{-/-}$)-mediated colitis animal models were used to check the efficacy of CKD-506. Colitis animals were treated with 1 to 100 mg/kg of CKD-506 and analysed disease activity indexes such as body weight, and colon length, and cytokines in serum, colon tissue, and lamina propria mononuclear cells (LPMC).
Results: HDAC6 was overexpressed in colon tissue of patients with Crohn's disease and ulcerative colitis. *In vitro*, HDAC6 overexpression by pDNA strongly induced the production of various inflammatory mediators, especially TNFa, IL-6, IP-10, and ROS production from macrophages. However, CKD-506 inhibited HDAC6-mediated inflammatory responses in macrophages through NF-kB and AP-1. In vivo, CKD-506 strongly inhibited disease activity indexes in DSS-, TNBS-, Piroxicam- (IL-10$^{-/-}$)-, and adaptive T-cell transfer-mediated colitis. In acute colitis models, CKD-506 inhibited IL-6 and TNFa expression in colon tissue of DSS-induced colitis and also inhibited ICAM-1, VCAM-1, and IP-10 expression in colon tissue of TNBS-induced colitis model. In addition, CKD-506 inhibited Ik-B phosphorylation, IL-6, and TNFa expression in colon tissue and mononuclear cells of lamina propria in Piroxicam-induced colitis of IL-10$^{-/-}$ mice. Moreover, CKD-506 inhibited various inflammatory cytokines in serum as well as in colon tissue of T-cell adaptive transfer colitis of RAG$^{-/-}$ mice.
Conclusions: These data provide insight that inhibition of HDAC6 by CKD-506 has therapeutic effect in colitis animal models. Therefore, CKD-506 may beneficial effect in patients with Crohn's disease and ulcerative colitis.

OP24

Effectiveness and safety of ustekinumab 90 mg every 4 weeks in Crohn's disease

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Background: The most commonly drug regimen for ustekinumab in Crohn's disease (CD) is 90 mg every 8 weeks. Some patients will partially respond to ustekinumab or will experience a secondary loss of response. These patients might benefit from shortening the interval between injections. The efficacy and safety of ustekinumab 90 mg every 4 weeks (90 mg q4W) is unknown.
Methods: All patients with active CD, as defined by CDAI > 150 and one objective sign of inflammation (CRP > 5 mg/l and/or faecal calprotectin > 250 µg/g and/or radiologic and/or endoscopic evidence of disease activity) who required ustekinumab dose escalation to 90 mg q4W for loss of response or inadequate response to ustekinumab 90 mg q8W were included in this retrospective multi-centre cohort study.
Results: Seventy-six patients, with a median age of 33 years (interquartile range [IQR], 27–42) and median disease duration of 12 years (IQR, 7–16), were included. Optimisation was performed after a median of 4.5 months (IQR, 2.2–7.2) of ustekinumab treatment initiation. Ustekinumab was associated with corticosteroids and immunosuppressants in, respectively, 32% (n = 25/76) and 32% (n = 25/76) of cases. Clinical response was observed in 57% (n = 43/69) after a median of 2.1 months (IQR, 1.0–3.0). After a median follow-up of 8.2 months (IQR, 5.2–12.0), 47% (n = 36/76) were still treated with ustekinumab, and 26% (n = 20/76) were in steroid-free clinical remission. Among the 29 patients with colonoscopy during follow-up, 10 had mucosal healing (no ulcers). At the end of follow-up, 35% (n = 27/76) were hospitalised, and 22% (n = 17/76) underwent surgery. Adverse events were reported in 9% (n = 7/76) of patients, including two serious adverse events (pneumonitis, infectious colitis). In multivariate analysis, colonic location (L2) (hazard ratio (HR), 4.6 (95% CI, 1.8–8.4); p = 0.047), inflammatory behaviour (B1) (HR, 9.1 (95CI%, 1.2–16.5); p = 0.015) and duration of ustekinumab therapy before optimisation (HR, 3.2 (95% CI, 1.2–5.4); p = 0.043) were associated with clinical response at 2 months.
Conclusions: This is the first study that evaluates the efficacy and safety of ustekinumab optimisation 90 mg q4W in CD. Two-thirds of patients recaptured response following treatment optimisation. Colonic location, inflammatory behaviour, and duration of ustekinumab therapy before optimisation were associated with clinical response at 2 months

OP25

Targeting endoscopic outcomes through combined pharmacokinetic and pharmacodynamic monitoring of infliximab therapy in patients with Crohn's disease

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Background: In TAILORIX, infliximab (IFX) trough concentrations (TC) >23.1 mg/l at Week 2 and >10.0 mg/l at Week 6 predicted endoscopic remission (Crohn's disease (CD) endoscopic index of severity <3) at Week 12.[1] During maintenance therapy, no exposure–response relation was observed, but faecal calprotectin (FC) was lower in patients achieving the endoscopic outcomes compared with patients who did not.[1]

Methods: A two-compartment population PK (popPK) model was developed based on data from 1329 samples from 116 patients in TAILORIX (NONMEM 7.4).[2]

Results: In line with the previously observed higher IFX TC,[1] also the estimated IFX clearance (CL) during induction therapy was lower in patients achieving endoscopic remission at Week 12 (–0.067 ± 0.020 l/day, p = 0.001), but this was not observed during maintenance therapy (P > 0.05). During maintenance therapy, an exposure–response relationship was observed only after dose escalation, with a TC >10.8 mg/l after dose escalation predicting the absence of ulcers at Week 54 (Figure 1A). However, this exposure–response relation only appeared after three infusions at the elevated dose (Figure 1B). Furthermore, in patients with elevated FC (>250 mg/kg), a significant drop was observed right upon dose escalation, resulting in FC concentrations that were lower in patients without ulcers compared with patients with ulcers (p = 0.033) (Figure 1C). Antibodies to IFX (ATI), measured using a drug-tolerant assay, increased IFX CL with ~48%, resulting in a reduction of the terminal half-life from 9.4 to 6.4 days (Table 1). Even when dose escalations masked the detection of ATI, the popPK model still estimated an effect of ATI on IFX CL. In addition, IFX exposure reduced when albumin was lower and FC and fat-free mass were higher.

Conclusions: We recommend proactive and reactive monitoring of FC during IFX maintenance therapy, but when FC does not normalise upon dose escalation, the IFX TC provides information on the mechanism of failure and can thus guide clinical decision-making (Figure 2). Future prospective trials are needed to evaluate this proposed TDM algorithm.

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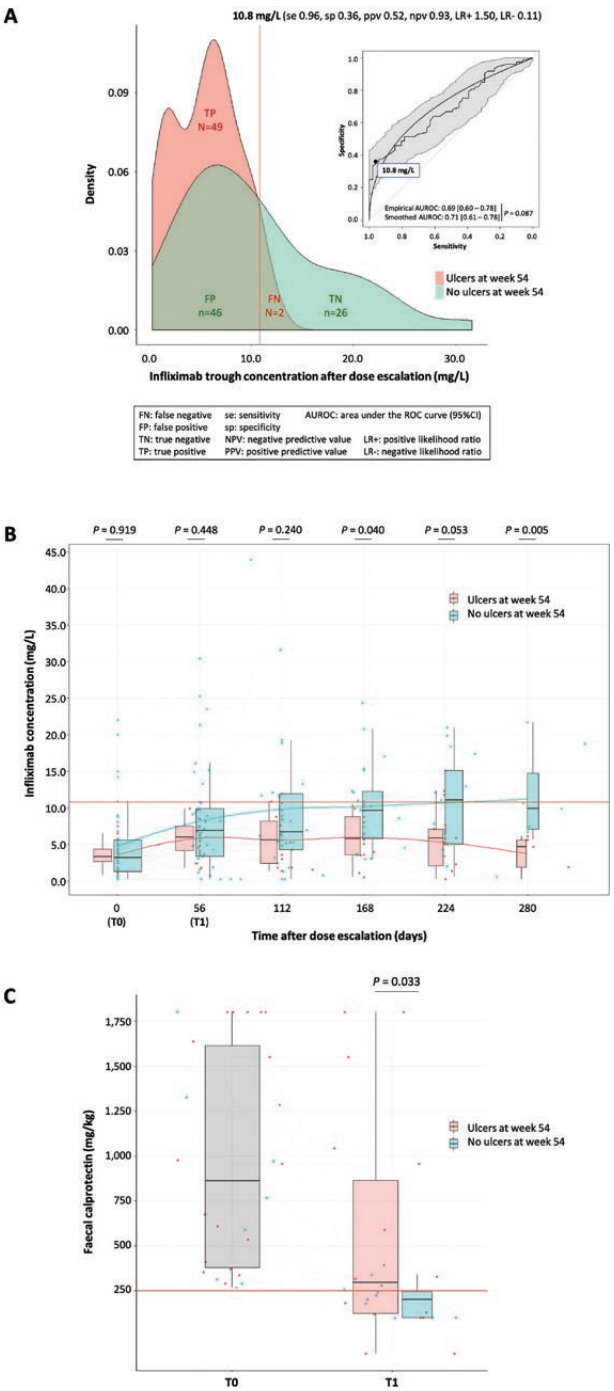

(A) Density plot and ROC curve and (B) boxplots representing the relation between IFX TC after dose escalation and the absence/presence of ulcers at Week 54. (C) The difference in FC upon dose escalation (T1) between patients with/without ulcers at Week 54.

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Parameter	Estimate	% relative standard error	Interindividual variability (%)	Interoccasion variability (%)	Bootstrap estimate	Bootstrap 95% confidence interval	Bootstrap deviation (%)
Clearance (CL), l/day	0.279	3.8	27.7	12.0	0.278	[0.257 to 0.300]	–0.36
Antibodies to infliximab on CL	0.475	18.3	–	–	0.477	[0.297 to 0.648]	+0.42
Albumin on CL	–0.766	30.9	–	–	–0.798	[–1.323 to –0.439]	–4.18
Faecal calprotectin on CL	0.0554	24.4	–	–	0.0553	[0.0280 to 0.0813]	–0.18
Fat-free mass on CL	0.391	30.2	–	–	0.396	[0.138 to 0.615]	+1.28
Volume of distribution in the central compartment (Vc), l	3.79	7.0	18.2	–	3.76	[3.26 to 4.18]	–0.79
Volume of distribution in the peripheral compartment (Vp), l	1.14	5.7	–	–	1.14	[1.06 to 1.21]	0.00
Intercompartmental clearance (Q), l/day	0.156	7.9	–	–	0.157	[0.143 to 0.169]	+0.64

Parameter estimates from the final population pharmacokinetic model for infliximab (extract).

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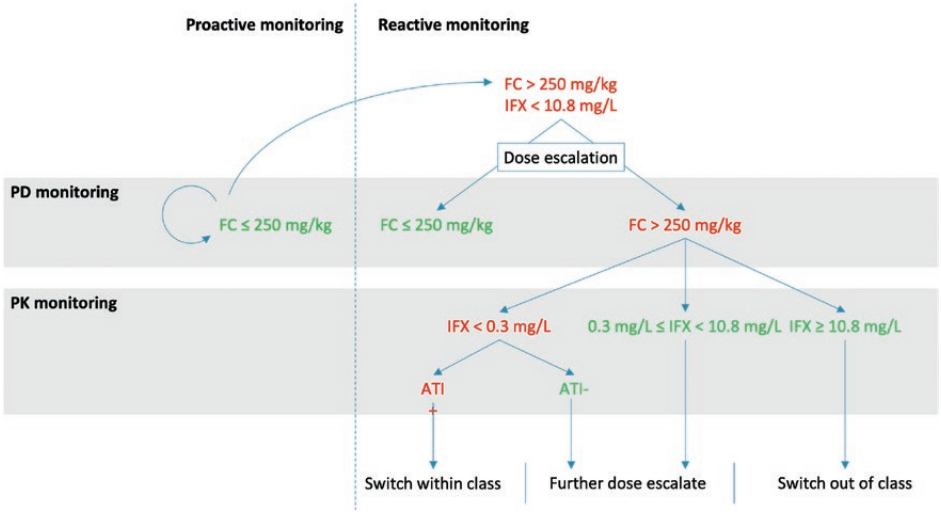

Algorithm implementing proactive PD monitoring (left) and a tiered approach for reactive PD and PK monitoring (right) during infliximab maintenance therapy.

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OP26

Long-term safety of vedolizumab in ulcerative colitis and Crohn's disease: final results from the GEMINI LTS study

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Background: Vedolizumab (VDZ), a gut-selective, humanised, $\alpha_4\beta_7$ integrin monoclonal antibody, was approved in 2014 in the USA and EU to treat moderately to severely active ulcerative colitis (UC) and Crohn's disease (CD). GEMINI long-term safety (LTS) is the longest VDZ continuous treatment study to date and provides unique data for VDZ therapeutic profiling. We report the final GEMINI LTS safety and efficacy findings.

Methods: GEMINI LTS was a multi-national, multi-centre, open-label, Phase 3 study (NCT00790933/EudraCT 2015-000480-14). Patients with UC or CD received VDZ 300 mg IV every 4 weeks after they completed or withdrew from a Phase 2 study or one of the GEMINI Phase 3 studies or enrolled as VDZ-naïve de novo patients. Treatment continued until study completion or loss to follow-up (eg, after VDZ approval or expanded-access programme availability at the local site). Long-term safety was the primary endpoint and efficacy was an exploratory endpoint.

Results: A total of 894 patients with UC and 1349 with CD enrolled in GEMINI LTS for a planned treatment duration of 9 years. All patients had received ≥1 prior conventional therapy (Table 1). Adverse events (AEs) occurred in 93% of UC patients and 96% of CD patients; most frequent were UC (36%) and CD (35%) exacerbations and nasopharyngitis (UC, 28%; CD, 25%; Table 2). No new trends were observed for infections, malignancies, infusion-related reactions, or hepatic events. Serious AEs (SAEs) were reported in 31% of UC patients and 41% of CD patients; disease exacerbation was the most frequent SAE in both cohorts (UC, 13%; CD, 17%). VDZ was discontinued due to AEs

Abstract OP26 –Table 1. Baseline demographics and clinical characteristics.

Parameter	Ulcerative colitis N = 894	Crohn's disease N = 1,349
Age[b], mean ± SD, years	41.2 ± 13.6	37.8 ± 12.7
Vedolizumab exposure, median (range), months	43.0 (1 day-113.7 months)	31.9 (1 day-101.7 months)
Disease duration, mean ± SD, years	8.1 ± 7.0	10.1 ± 8.3
Partial Mayo score, mean ± SD	6.0 ± 1.5	NA
Harvey Bradshaw Index score, mean ± SD	NA	10.9 ± 3.4
Crohn's disease activity index score, mean ± SD	NA	314.0 ± 63.2
Prior or ongoing therapy, n (%)		
Corticosteroids	862 (96)	1,233 (91)
Immunomodulators	666 (74)	1,158 (86)
Anti-tumour necrosis factor alpha agents	415 (46)	898 (67)

NA, not available; SD, standard deviation.
[a]Baseline for rollover patients was defined as the last assessment before the first dose of vedolizumab in the previous studies. Baseline for *de novo* patients was defined as the last assessment before the first dose of vedolizumab in GEMINI LTS.
[b]Age was defined as (1 + first dose date in GEMINI LTS – birth date)/365.25.

Abstract OP26 – Table 2. Safety overview.

Parameter	Ulcerative colitis N = 894 n (%)	Ulcerative colitis N = 894 Incident rate per 1,000 pt-years[a]	Crohn's disease N = 1,349 n (%)	Crohn's disease N = 1,349 Incident rate per 1,000 pt-years[a]
Any AE	829 (93)	1220.460	1,296 (96)	1799.186
Disease exacerbation	321 (36)	105.203	476 (35)	121.355
Nasopharyngitis	252 (28)	93.854	342 (25)	94.073
Arthralgia	155 (17)	51.640	329 (24)	90.259
Abdominal pain	111 (12)	34.381	309 (23)	79.997
Headache	164 (18)	55.450	290 (21)	76.442
Upper respiratory tract infection	166 (19)	55.661	213 (16)	53.244
AEs of specific interest				
Total infections	591 (66)	388.898	937 (69)	492.128
Serious infections	61 (7)	18.029	146 (11)	33.625
Malignancies	58 (6)	17.171	92 (7)	20.846
Infusion reactions	36 (4)	NA	67 (5)	NA
Hepatic events	29 (3)	8.435	63 (5)	14.119
PML	0	0	0	0
Severity of AE				
Mild	163 (18)	NA	223 (17)	NA
Moderate	451 (50)	NA	656 (49)	NA
Severe	215 (24)	NA	415 (31)	NA
SAEs	277 (31)	90.944	548 (41)	146.535
Disease exacerbation	119 (13)	34.756	224 (17)	50.314
Abdominal pain	9 (1)	2.584	41 (3)	9.027
Anal abscess	0	0	33 (2)	7.278
Small intestinal obstruction	4 (<1)	1.146	25 (2)	5.474
Treatment-related AEs	355 (40)	NA	623 (46)	NA
Treatment-related SAEs	37 (4)	NA	79 (6)	NA
Deaths	4 (0.4)[b]	NA	6 (0.4)[c]	NA
Treatment-related death	1 (0.1)[d]	NA	1 (0.1)[e]	NA
AE outcome				
Treatment withdrawn	137 (15)	NA	229 (17)	NA

AE, adverse event; SAE, serious adverse event; NA, not available; PML, progressive multifocal leukoencephalopathy.
[a]Time-adjusted incidence rate per 1,000 patient-years = (Number of patients experiencing an AE of interest / Total Person Time in Years) × 1000.
[b]Respiratory failure, acute stroke, West Nile virus encephalitis, pulmonary embolism.
[c]Traumatic intracranial haemorrhage, hepatocellular carcinoma, suicide, pneumonia, septicaemia, leiomyosarcoma.
[d]West Nile virus encephalitis.
[e]Hepatocellular carcinoma.

in 15% of UC patients and 17% of CD patients, with UC or CD exacerbation (9% and 8%, respectively) the most frequent reason for discontinuation. There were no cases of progressive multi-focal leukoencephalopathy and 10 (UC, 4; CD, 6) deaths during the study. Clinical response was maintained long-term in patients who continued to receive VDZ throughout the entire study; however, the efficacy analysis was limited due to the expected, protocol-defined, patient loss to follow-up.

Conclusions: The final GEMINI LTS results provide evidence that VDZ has a safety profile suitable for long-term treatment of UC and CD. In this carefully monitored population receiving VDZ in a clinical trial setting, there continue to be no unexpected or new safety concerns.

OP27

High-dimensional mass cytometry reveals the immune cell landscape in inflammatory bowel disease

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Background: Inflammatory bowel disease (IBD) is characterised by chronic inflammation of the intestine. Studies on individual immune lineages have shown alterations in the innate and adaptive intestinal immune system implicated in IBD. However, a comprehensive analysis of the cell composition in intestinal biopsies from IBD patients across all major immune lineages simultaneously was lacking.

Methods: In patients aged 10–40 years with a clinical suspicion of IBD, we took paired biopsies (N = 104) from ileum and colon (both inflamed and uninflamed mucosa if available) and blood samples in 23 IBD patients and in 15 controls with a normal colonoscopy. Single-cell suspensions were stained with a 36-antibody panel and analysed with mass cytometry. The generated dataset was analysed with Hierarchical t-SNE (HSNE) in the Cytosplore analysis and visualisation tool.

Results: In total, we identified 309 distinct cell clusters from the collective intestinal dataset containing 3.4 million cells in a data-driven manner. Here, controls clustered separate from patients, ileum samples separate from colon samples, and affected segments separate from unaffected segments (Figure 1A). However, affected samples from the different subgroups of IBD (Crohn's disease, ulcerative colitis, undeterminate colitis) were mostly intermixed, suggesting similarities in the immune profiles. Moreover, we observed a large interindividual variation in the immune cell composition, indicative of unique individual 'immune fingerprints' in the intestinal tract. In addition, 19 subsets were significantly different between affected-IBD samples and unaffected-IBD samples/controls. Finally, in a correlation analysis, several CD4+ T-cell clusters correlated with ILC and myeloid cell clusters and were up-regulated in IBD-affected segments (Figure 1B, top-left network), while in particular TCRgd cell clusters (Figure 1B, top-right network) and a group of ILC clusters (Figure 1B, bottom network) were up-regulated in unaffected samples of patients and controls.

Conclusions: Our study provides evidence that a coordinated cellular network of both innate and adaptive immune cell types are implicated in IBD. Together with the evidence for the unique individual-specific composition of the intestinal immune system, this may aid in the development of more (cost-)effective and personalised patient care.

OP28

Host–microbial crosstalk in the pathogenesis of inflammation and cancer in primary sclerosing cholangitis

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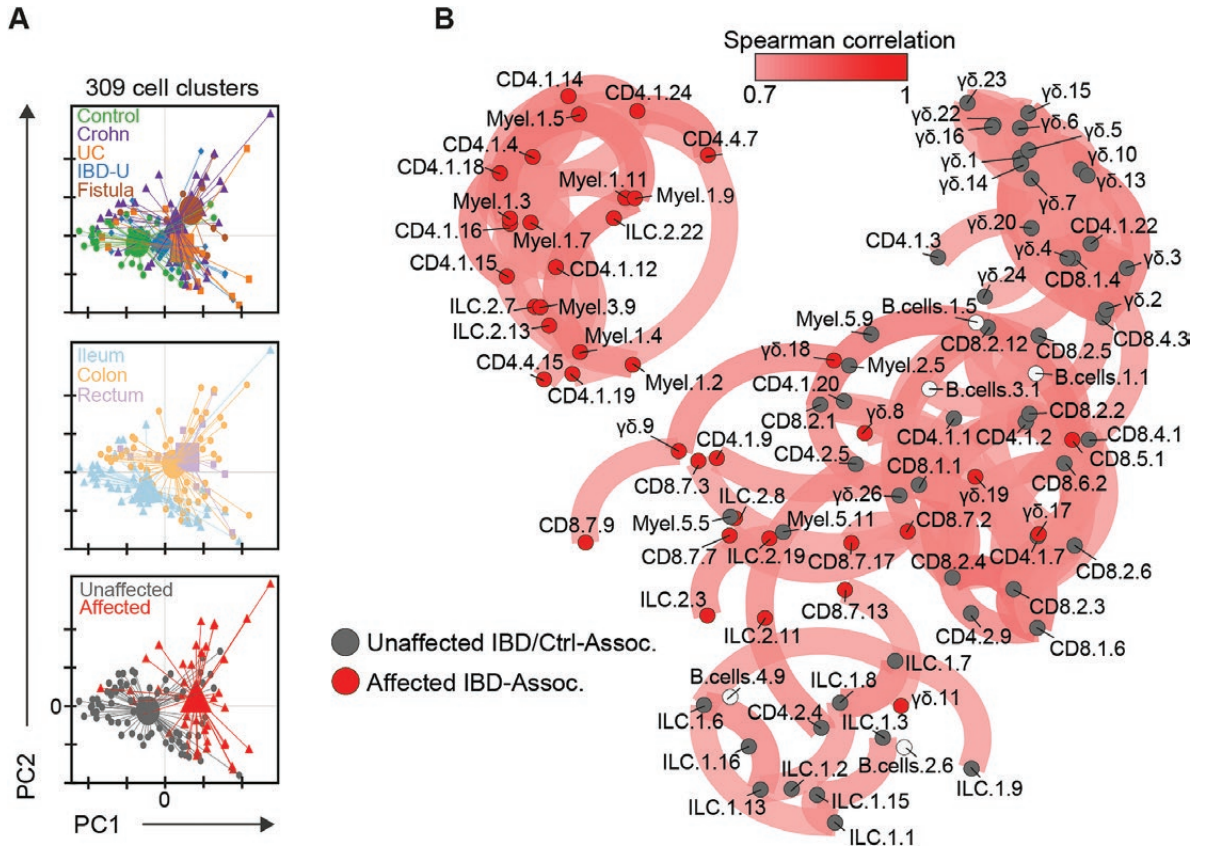
Background: Distinct inflammatory responses have been involved in primary sclerosing cholangitis-inflammatory bowel disease (PSC-IBD) and dysbiosis has been observed supporting a role for the microbiome in the pathogenesis of disease. We aimed to: (1) assess host–microbial functions in PSC-IBD (2) evaluate whether PSC-IBD-associated pathways affect epithelial transformation.

Methods: Biopsies and mucosal brushings from colon and terminal ileum were collected from patients with PSC-IBD, ulcerative colitis without PSC (UC), and healthy controls (HC). 3′RNA sequencing was performed to analyse intestinal transcriptomes and 16S rRNA sequencing to characterise the adherent microbiome. Colonic crypts were isolated from biopsies, seeded onto basement membrane extract, and cultured in media containing growth factors to develop organoids. Organoids were stimulated with different cytokines for 24 h and markers of cytokine downstream pathways, stemness, and pluripotency were analysed by qPCR.

Results: A distinct transcriptomic profile in the caecal biopsies of patients with PSC-IBD compared with UC and HC was identified (Figure 1, A left panel), with 890 genes being regulated in PSC-IBD (DESeq2 likelihood ratio test, adjusted $p < 0.05$). Amongst differentially regulated genes, we found an enrichment of pathways associated with cytokine signalling including IL22 and TGFβ (fold enrichment >2 and adjusted $p < 0.05$) (Figure 1A, right panel). We successfully cultured primary intestinal organoids from both groups of patients and HC (Figure 1B). Stimulation with IL22 or



Abstract OP27 – Figure 1. Integrated immune system analysis of immune cell infiltrates. (A) PCA-visualisation of samples clustered for 309 cell cluster frequencies. Coloured for clinical info. (B) Network representation of immune cell cluster correlations.

IFNγ resulted in *STAT1* induction, and higher *STAT3* induction was observed in PSC-IBD-derived organoids. Interestingly, expression of the IL22 receptor, *IL22RA1*, was induced by IFNγ stimulation in PSC-IBD-derived organoids that also over-expressed *OLFM4* and *POU5F1*, both associated with pluripotency and early stages of neoplastic transformation (Figure 1C).

Conclusions: The transcriptomic profile in the colonic mucosa of patients with PSC-IBD shows altered regulation of pathways previously associated with IL22 and TGF signalling. Both cytokines have been implicated in cancer pathogenesis. PSC-IBD-associated Th1 responses may result in increased epithelial IL22 responsiveness. Higher expression of the cancer stemness genes *OLFM4* and *POU5F1*, triggered by bacteria and IL22 via STAT3 activation, suggest that microbial-driven IL22 responses may contribute to epithelial transformation.

OP29

ST2+/IL-33 responsive cells promote tumorigenesis in colitis-associated colorectal cancer

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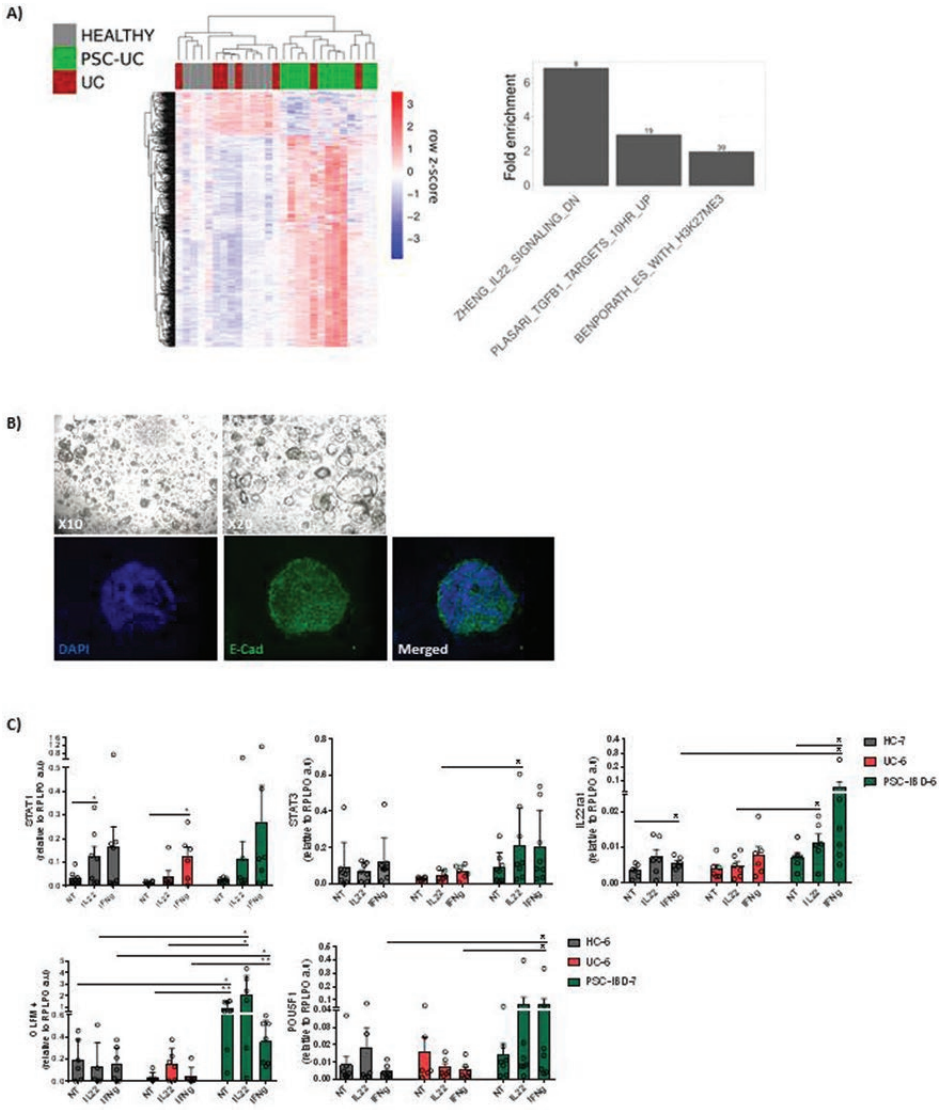
Background: IL-33 and its receptor, ST2, are important factors in the pathogenesis of IBD. Emerging evidence suggests its critical role the potential contribution to inflammation-driven tumorigenesis that can lead to colorectal cancer (CRC). The aim of our study was to characterise the precise contribution of IL-33/ST2 axis in the azoxymethane (AOM)/dextran sodium sulphate (DSS) model of colitis-associated CRC.

Methods: C57/BL6 wild-type (WT), IL-33 KO, ST2 KO, and CD73 KO mice were given a single dose of AOM (7.4 mg/kg) followed by two cycles of 3% DSS for 7 days in drinking water. Disease activity index (DAI), as well as endoscopic and histological evaluation of colons, were performed. IHC, immunofluorescence (IF), and qPCR were done on full-thickness colons for IL-33 and ST2 localisation and identification, as well as mRNA expression, respectively. FACS analysis was performed on cell suspensions from resected, isolated polyps and qPCR for Vimentin, Desmin, αSMA, CD34, CD31, CD73 was completed on sorted cells in order to functionally characterise ST2+/IL-33 responsive cells.



Abstract OP28 – Figure 1.

Results: IL-33, ST2L, and sST2 mRNA transcripts were dramatically elevated in AOM/DSS-treated WT mice vs. controls. IHC of treated WT mice revealed localisation of IL-33 to the colonic epithelium and to cells within the LP morphologically consistent with tissue macrophages. ST2 staining was localised to the intestinal epithelium in tissues immediately adjacent to tumours, while within the tumours themselves, ST2+ cells displayed a spindle/fibroblast-like morphology with a unique distribution throughout the polyps. Little to no staining for both IL-33 and ST2 was present in controls. Using IF, ST2 co-localised with αSMA in polyps; however, ST2 staining was not exclusive for αSMA+ cells. FACS analysis showed a distinct population of CD45+ haematopoietic cells consisting of CD3/CD8+ cytotoxic T cells (CTLs), CD19+ B-lymphocytes, CD11b+CD11c- and CD11b+CD11c+ myeloid cells. ST2 was mainly expressed by CTLs, and CD11b+CD11c- and CD11b+CD11c+ myeloid cells. Non-haematopoietic cells (CD45-) also expressed ST2. At qPCR, CD45-ST2+ and CD45+ST2+ expressed significantly elevated levels of CD73 vs. ST2- cells. AOM/DSS treatment in IL-33, ST2 KO, and CD73KO mice resulted in a significant decreased polyp number and size vs. WT, with colonoscopy revealing the development of protruding lesions with abnormal vascular patterns, suggesting pre-tumorous lesions in WT mice, while all KO mice showed their absence with a more impressive mucosal inflammation, likely due to reduced epithelial proliferation and repair caused by the deficiency of IL-33 signalling.

Conclusions: Our results suggest that the IL-33/ST2 axis promotes tumorigenesis in colitis-associated CRC through the activation of CD73.

OP30

Serum proteomic profiling predicts and diagnoses pouchitis in ulcerative colitis patients undergoing ileal pouch-anal anastomosis

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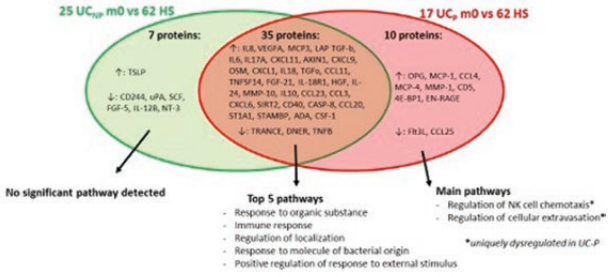
Background: Pouchitis is the most common complication in patients with ulcerative colitis (UC) requiring ileal pouch anal anastomosis (IPAA). Pouchoscopy remains the gold standard to diagnose pouchitis in the absence of other surrogate biomarkers. We performed serum proteomic profiling to identify biomarkers that could be predictive and discriminative for development of pouchitis following IPAA.

Methods: This was a prospective cohort study in 51 patients undergoing IPAA at our centre (46 UC and 5 familial adenomatous polyposis patients). Serum was collected before colectomy and at predefined clinical visits at month 1, 3, 6, and 12 after IPAA. At every clinical visit, patients had endoscopic evaluation of the pouch. Pouchitis was defined by the presence of endoscopic inflammation. Serum samples from 62 age- and sex-matched healthy subjects (HS) served as controls. A panel of 91 inflammation-related proteins was measured using Proximity Extension Assay (Olink). Logistic regression and receiver-operating characteristic curve analysis were used to evaluate the predictive and discriminative power of significant biomarkers and clinical variables (cut-off $p < 0.1$). Pathway analyses was conducted using STRING database.

Results: A total of 17 (37%) UC patients were diagnosed with pouchitis during the first year after IPAA. Younger age at colectomy (OR = 1.11, 95% CI = 1.03–1.21; $p = 0.008$) and backwash ileitis (OR = 8.37, 95% CI = 1.06–65.9; $p = 0.04$) were associated with pouchitis. When comparing the protein profiles prior to colectomy in UC patients developing pouchitis (UC-P) and UC patients with normal pouches (UC-NP), we observed respectively 42 and 45 proteins significant from the profiles in HS (FDR < 0.05) (Figure 1).

Combination of HGF, TNFRSF9, and age at colectomy was the most accurate to predict development of pouchitis within 1 year (AUC = 0.875). A panel of four proteins (IL17A, CXCL1, CCL25, and TRAIL) showed a good discriminative power (AUC = 0.984) to diagnose pouchitis at month 12 post-IPAA.

Conclusions: Before colectomy, there is a great overlap in serum protein profiles between patients who do or do not develop pouchitis. We found that proteins involved in NK cell chemotaxis and cellular extravasation were dysregulated solely in patients developing pouchitis. HGF and TNFRSF9 in combination with age at colectomy were predictive for pouchitis, and we identified a combination of four biomarkers with diagnostic potential. Further validation in a larger cohort is required.



Abstract OP30 – Figure 1. Venn diagram of significantly dysregulated proteins (FDR < 0.05) and corresponding pathways prior to colectomy, when comparing UC-NP and UC-P with HS.

OP31

TP53 mutation in human colonic organoids acquires resistance to *in vitro* long-term inflammation

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Background: In colitis-associated cancer (CAC), tumour protein p53 (TP53) mutation often occurs in the early phase of colon carcinogenesis known as dysplasia–carcinoma sequence. Although there are some reports about the relation between TP53 mutation and colon carcinogenesis in mice model, the function of TP53 mutation on colonic epithelial cells in the patients with inflammatory bowel disease (IBD) has remained unknown. We therefore aimed to assess the influence of TP53 mutation by using a CRISPR Cas9 system on human colon epithelial organoids under long-term inflammation model which we originally generated.

Methods: TP53 was mutated by using CRISPR Cas9 system (LentiCRISPR v2®) in human colonic epithelial organoids derived from normal mucosa. Written informed consent was obtained and this study was approved by the Ethics Committee of Tokyo Medical and Dental University. The guide RNA was designed to bind exon 10 of TP53 according to previous report (Matano et al. Nat Med. 2015). The long-term inflammation model was established by culturing organoids with inflammatory factors (TNF-α, Flagellin, and IL-1β) for 60 weeks. Inflammatory response in the organoids was assessed by gene expression of inflammatory-related genes and the level of reactive oxygen species (ROS). Phenotypes of each organoids were assessed by MTS Assay, sphere formation assay for cell proliferation and stemness, respectively.

Results: We successfully established TP53 mutation in three different human colon epithelial organoids. Mutant TP53 was strongly expressed in nuclei as often shown in dysplastic lesion of IBD, whereas wild type (WT)–TP53 was not expressed in naive organoids. We assessed the effect of mutant TP53 with or without inflammatory stimulation for 60 weeks. Long-term inflammation impaired cell proliferation and sphere formation of the organoids with WT-TP53. Mutant TP53, however, enhanced cell growth and stemness with increased gene expression of c-myc and Lgr5 compared with WT–TP53 under the inflammatory situation; nevertheless, inflammatory response in the organoids with mutant TP53 was equal to that in the organoids with WT-TP53.

Conclusions: We, for the first time, showed TP53 mutation maintains cell proliferation and stemness of human colonic organoids even under *in vitro* long-term inflammation. Mutant TP53 acquired resistance to cell damage by chronic inflammation, suggesting that these results might mimic cell phenotype at the early step of colitis associated carcinogenesis.

OP32

A novel mechanism of colonic epithelial-T-cell cross-talk is dysregulated in IBD

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Background: Epithelial dysfunction is an early initiating factor of inflammatory bowel disease (IBD), yet the immunological consequences of this remain enigmatic. Juxtaposed to epithelial cells are specialised intraepithelial γδ T cells, implicated in maintaining tissue integrity. We have shown that specific members of the Butyrophilin-like (BTNL) protein family are restricted to intestine epithelial cells and are profound γδ T-cell regulators. Thus, Btnl1$^{-/-}$ mice show selective depletion of a signature intestinal γδ subset.[1] This axis is conserved in humans, where signature colon-resident, Vγ4^{+} γδ T cells are selectively regulated by direct interactions between their TCRs and a BTNL3/8 heteromer.[2] Here we investigated whether such selective regulation of human colonic γδ cells by BTNL3 + 8 is perturbed in IBD and have examined factors which may modulate this.

Methods: We used a short-term whole gut explant culture to isolate γδ T cells from colonic biopsies obtained at endoscopy from healthy donors, facilitating flow-cytometric phenotyping and functional studies.

Results: In most non-IBD controls, co-culture of colonic lymphocytes with HEK293T cells co-transduced with BTNL3 + 8 resulted in profound TCR down-regulation in T cells reactive to an antibody specific for Vγ2/3/4 chains. In non-IBD controls, expression of $\alpha_E\beta7$, a marker of epithelial residence, by Vγ2/3/4^{+} cells, was associated with TCR down-regulation responses to BTNL3 + 8, whereas Vγ2/3/4$^{+}\alpha_E\beta7^{-}$ cells, which were generally the minority, had markedly attenuated or absent assay responses. In many patients with IBD, we found significantly reduced $\alpha_E\beta7$ expression by Vγ2/3/4^{+} cells, and a severe attenuation or loss of BTNL-dependent Vγ2/3/4 TCR down-regulation. Phenocopying the situation in disease; addition to the organ culture of pro-inflammatory cytokines IL-12 and IL-18 (but not IL-1β and IL-23) lead to down regulation of $\alpha_E\beta7$ on γδ T cells and a consequent attenuation of response to BTNLs. This clearly implicates specific cytokines in the disruption of the functional γδ-BTNL axis evident in disease. Further characterisation of $\alpha_E\beta7^{-}$ γδ T cells demonstrated an activated pro-inflammatory phenotype in comparison to quiescent $\alpha_E\beta7^{+}$ γδ T cells.

Conclusions: We describe a novel and important axis by which epithelial cells maintain homeostasis of the γδ T cell compartment, and which is frequently dysregulated in IBD. Our data may support the use of IL-12 blockade in restoring this axis whilst IL-23 may be redundant in this setting, with implications for future therapeutic strategies. Furthermore, therapeutic blockade of $\alpha_E\beta7$ has the potential to disrupt an important axis in the human colon, which may exacerbate disease given the precociously active, pro-inflammatory nature of $\alpha_E\beta7^{-}$ γδ T cells.

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OP33 and OP34

OP33 & OP34 are late-breaking abstracts and are published on www.ecco-ibd.eu/publications and www.academic.oup.com/ecco-jcc

OP35

Endoscopic and deep remission at 1 year prevents disease progression in early Crohn's disease: long-term data from CALM

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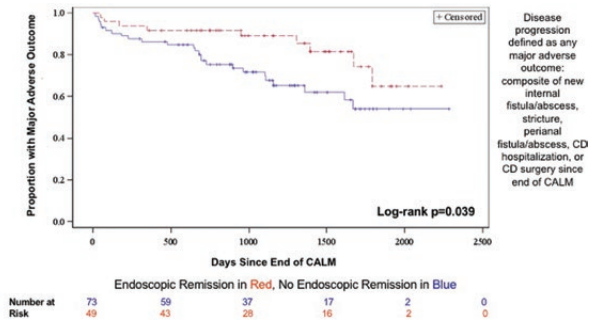
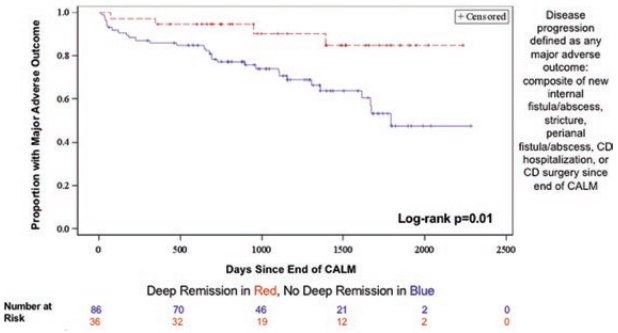
Background: We aimed to describe the long-term impact of achieving endoscopic and deep remission among participants in the effect of tight control management on CD (CALM) trial.



Abstract OP35 – Figure 1. Kaplan–Meier estimates of CD disease progression based on endoscopic remission at 1 year



Abstract OP35 – Figure 2. Kaplan–Meier estimates of CD disease progression based on deep remission at 1 year.

Methods: We analysed medical records from patients with follow-up data since end of CALM. Patients were stratified by outcomes in CALM at 1 year: clinical remission (Crohn's disease activity index, CDAI <150), endoscopic remission (Crohn's disease endoscopic index of severity, CDEIS <4 with no deep ulcerations), and deep remission (CDAI <150, CDEIS <4 with no deep ulcerations, and no steroids for ≥8 weeks). The primary outcome was a composite of major adverse outcomes reflecting CD progression: new internal fistula/abscess, stricture, perianal fistula/abscess, CD hospitalisation, or CD surgery since end of CALM. Kaplan–Meier and Cox regression methods were used to compare composite rates between patients who achieved or did not achieve remission at 1 year. Adjusted hazard ratios (aHR) with 95% confidence intervals (CI) are reported, controlling for randomisation arm and baseline variables significant at $p < 0.2$ level.
Results: One hundred twenty-two patients with median age 29 years (IQR 22.5–37) and median disease duration 0.2 years (IQR 0.1–0.8) were included. Median follow-up time from end of CALM was 3.02 years (range 0.05–6.26 years). Fifty per cent were randomised to the tight control arm. There were no significant differences in baseline characteristics in patients with follow-up data and those lost to follow-up with the exception of a slightly higher CDEIS score in patients lost to follow-up (14.6 vs. 12.9, $p = 0.04$). Thirty-four patients (27.9%) had a major adverse outcome during follow-up. Patients in clinical remission at 1 year did not have significantly lower rates of the composite endpoint (log-rank $p = 0.15$). Patients in endoscopic and deep remission at the end of CALM were significantly less likely to have a major adverse event over time (Figures 1 and 2). After adjusting for age, disease duration, prior surgery, prior stricture, and randomisation arm, endoscopic remission (aHR 0.44, 95% CI 0.20–0.96, $p = 0.038$) and deep remission (aHR 0.25, 95% CI 0.09–0.72, $p = 0.01$) were significantly associated with lower risk of major adverse events.
Conclusions: Early CD patients who achieve endoscopic or deep remission after 1 year of intensive treatment are less likely to have disease progression over a median of 3 years.

OP36

A colonic gene expression signature predicts non-response to anti-inflammatory therapies in inflammatory bowel disease

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Background: The ability to predict response to therapy in inflammatory bowel disease (IBD) is a significant unmet need. We previously described PROgECT, a Phase 2a open-label study of patients with moderate-to-severe ulcerative colitis (UC), which prospectively validated the ability of a molecular profile score (MPS) consisting of a colonic 13-gene expression panel to predict response to TNF-antagonist therapy. Although the MPS had low specificity in predicting responders to therapy, we evaluated whether the MPS could be a useful tool in accurately identifying a subset of non-responder patients to therapy.
Methods: We evaluated the sensitivity and specificity of the MPS in identifying non-responders to therapy in four independent TNF-antagonist trials (ACT1, PURSUIT-SC, PROgECT, PURSUIT-J) and an anti-IL12/23 trial (UNITI). We also characterised the gene expression and microbiome profiles of predicted non-responders by the MPS using microarray and 16S sequencing in the PROgECT cohort.
Results: We report that the MPS can accurately predict non-responders, as defined by lack of mucosal improvement, to TNF-antagonist therapy in UC in four independent clinical trials, with a high negative predictive value (NPV) of 0.78 in ACT1, 0.79 in PURSUIT-SC, 0.89 in PROgECT, and 0.73 in PURSUIT-J. In addition, the MPS could predict non-responders, as defined by lack of endoscopic response, to anti-IL12/23 therapy in Crohn's disease (CD) with an NPV of 0.85. The predicted non-responders by MPS did not differ compared with predicted responders in baseline disease severity as measured by Mayo Score, or baseline inflammatory markers including CRP, faecal calprotectin, or faecal lactoferrin levels. Transcriptomics and microbiome analysis revealed insights into potential ways to treat this predicted non-responder population, as predicted non-responders had 268 differentially expressed genes enriched in inflammatory pathways and also demonstrated significant microbial dysbiosis.
Conclusions: The MPS consistently predicts non-responders to therapy in IBD regardless of ethnicity or whether the therapy targeted TNF or IL12/23 pathways. Clinical parameters and inflammatory markers by themselves lack the granularity to identify this subset of non-responder patients. The MPS is the first prospectively validated predictive biomarker that can accurately identify a discrete subset of non-responder patients to two different anti-inflammatory therapies and may be valuable in identifying subsets of patients in need of treatment with alternative therapies or for patient stratification in clinical trials.

OP37

Efficacy and safety of ustekinumab as maintenance therapy in ulcerative colitis: Week 44 results from UNIFI

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Background: The study objective was to evaluate the safety and efficacy of SC ustekinumab (UST) as maintenance therapy in UC patients who were in clinical response to a single IV induction dose of UST.

Methods: This was a Ph3, double-blind, randomised withdrawal study in patients with moderate–severe active UC who failed conventional or biologic therapy (including anti-TNF and/or vedolizumab) and were in clinical response 8 weeks after receiving a single UST IV induction dose. The primary study population included 523 patients randomised 1:1:1 to placebo (PBO) SC, UST 90 mg SC q8w or q12w at Week 0. Primary endpoint was clinical remission at Week 44 (52 weeks after IV induction); key secondary endpoints were maintenance of clinical response, endoscopic healing, corticosteroid-free clinical remission, and maintenance of clinical remission among patients who achieved clinical remission at baseline.

Results: Baseline (induction Week 0) demographics, UC disease characteristics, concomitant UC medications, and medication history were generally similar among treatment groups. Significantly greater proportions of UST q8w and q12w patients were in clinical remission at Week 44 (43.8% and 38.4%, respectively) vs. PBO patients (24.0%; $p < 0.001$ and $p = 0.002$, respectively). Significantly greater proportions of UST q8w and q12w patients maintained clinical response through Week 44 and achieved endoscopic healing and corticosteroid-free clinical remission vs. PBO patients. Clinical remission through Week 44 was maintained for a significantly greater proportion of q12w patients and a numerically greater proportion of q8w vs. PBO patients.

The proportions of patients with AEs, serious AEs, infections, and serious infections in the UST groups were generally comparable to PBO group. The proportions of patients who discontinued study agent were lower with UST q8w and q12w vs. PBO. Among the primary population in the maintenance study: no deaths, 2 malignancies other than NMSC (1 colon cancer,q8w; 1 papillary renal cell carcinoma, q12w) were reported. One patient-reported NMSC (2 SCC events, q12w).

Conclusions: Both UST 90 mg q8w and q12w SC achieved clinical remission and maintained clinical response and were effective in achieving endoscopic healing and corticosteroid-free remission among patients with moderate–severe UC induced into clinical response with single IV dose of UST. The safety for UST in UC patients was consistent with the known safety profile of UST in CD.

Abstract OP37 – Table 1. Primary and key secondary endpoints.

	PBO SC[a]	UST 90 mg SC q12w	UST 90 mg SC q8w
Number of randomised patients	175	172	176
Patients in clinical remission at Week 44[b]	42 (24.0%)	66 (38.4%) p=0.002	77 (43.8%) p<0.001
Patients maintained clinical response through Week 44[c]	78 (44.6%)	117 (68.0%) p<0.001	125 (71.0%) p<0.001
Patients achieved endoscopic healing at Week 44[d]	50 (28.6%)	75 (43.6%) p=0.002	90 (51.1%) p<0.001
Patients in clinical remission and not receiving corticosteroids at Week 44[b]	41 (23.4%)	65 (37.8%) p=0.002	74 (42.0%) p<0.001
Patients who maintained clinical remission through Week 44 among patients in remission at maintenance baseline[b]	17/45 (37.8%)	26/40 (65.0%) p=0.011	22/38 (57.9%) p=0.069

[a] Patients who were in clinical response to ustekinumab IV induction dosing and were randomised to placebo SC on entry into this maintenance study.
[b] Mayo score ≤2 points, with no individual subscore >1.
[c] Decrease from induction baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from induction baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore = 0 or 1.
[d] Also described as endoscopic improvement in the appearance of the mucosa and defined as a Mayo endoscopy subscore = 0 or 1.

Abstract OP37 – Table 2. Summary of key safety findings through Week 44.

	PBO SC[a]	UST 90 mg SC q12w	UST 90 mg SC q8w
Randomised patients	175	172	176
Average duration of follow-up (weeks)	42.3	41.8	42.2
Average exposure (number of administrations)	7.1	7.3	7.4
Patients who died	0	0	0
Patients with 1 or more			
Adverse events	138 (78.9%)	119 (69.2%)	136 (77.3%)
Serious adverse events	17 (9.7%)	13 (7.6%)	15 (8.5%)
Infections	81 (46.3%)	58 (33.7%)	86 (48.9%)
Serious infections	4 (2.3%)	6 (3.5%)	3 (1.7%)
AEs leading to DC of study agent	20 (11.4%)	9 (5.2%)	5 (2.8%)
Malignancies (excluding NMSC)	0	1 (0.6%)	1 (0.6%)

[a] Patients who were in clinical response to ustekinumab IV induction dosing and were randomised to placebo SC on entry into this maintenance study.

OP38

Maintenance treatment with mirikizumab, a p19-directed IL-23 antibody: 52-week results in patients with moderately-to-severely active ulcerative colitis

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Background: Interleukin (IL)-23 is a critical cytokine in inflammatory bowel disease pathogenesis. Mirikizumab (miri), a p19-directed IL-23 antibody, demonstrated efficacy and was well-tolerated during 12 weeks of induction treatment in a Phase 2 randomised clinical

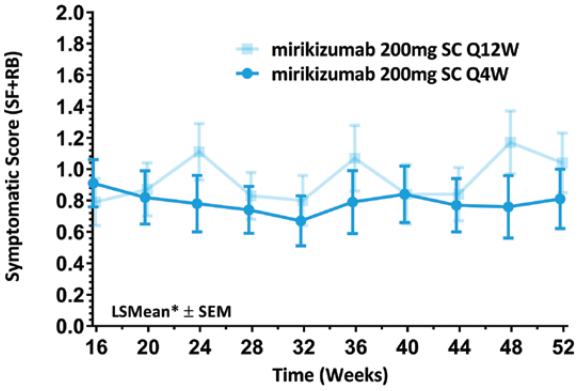
Abstract OP38 – Table 1.

	Treatment Groups (Wk-12 clinical responders)		
Mean (SD) unless otherwise specified	**Miri 200mg Q4W (N=47)**	**Miri 200mg Q12W (N=46)**	**Total miri (N=93)**
Baseline characteristics			
Age, years	41.3 (14.1)	38.9 (12.4)	40.1 (13.3
Male, n (%)	27 (57.4)	22 (47.8)	49 (52.7)
Weight, kg	74.6 (17.3)	72.5 (18.0)	73.5 (17.5)
Concomitant UC therapy, n (%)			
Corticosteroid	22 (46.8)	19 (41.3)	41 (44.1)
5-ASA	37 (78.7)	40 (87.0)	77 (82.8)
Thiopurines	15 (31.9)	9 (19.6)	24 (25.8)
Number of previous biologic therapies, n (%)			
0	21 (44.7)	23 (50.0)	44 (47.3)
1	12 (25.5)	17 (37.0)	29 (31.2)
2	10 (21.3)	5 (10.9)	15 (16.1)
≥3	4 (8.5)	1 (2.2)	5 (5.4)
Modified Mayo score	6.0 (1.4)	6.1 (1.4)	-
Wk 52 (NRI)			
Clinical remission[a], n (%)	22 (46.8)	17 (37.0)	39 (41.9)
Clinical response[b], n (%)	38 (80.9)	35 (76.1)	73 (78.5)
ES=0/1[c], n (%)	27 (57.4)	22 (47.8)	49 (52.7)
ES=0 [d], n (%)	7 (14.9)	13 (28.3)	20 (21.5)
Symptomatic remission[e], n (%)	36 (76.6)	30 (65.2)	66 (71.0)
TEAE, n (%)	36 (76.6)	31 (67.4)	67 (72.0)
SAE, n (%)	2 (4.3)	1 (2.2)	3 (3.2)
Discontinuations due to AE, n (%)	0 (0.0)	1 (2.2)	1 (1.1)

[a] **Clinical remission:** 9-point Mayo score: rectal bleeding (RB) subscore=0, stool frequency subscore=0 or 1 with ≥ 1 point decrease from baseline, and endoscopy subscore=0 or 1
[b] **Clinical response:** Decrease in 9-point Mayo score ≥ 2 points and ≥ 35% from baseline, and either a decrease in RB subscore ≥1 or RB subscore of 0 or 1
[c] **ES=0/1:** centrally read Mayo endoscopic subscore=0 or 1
[d] **ES=0:** centrally read Mayo endoscopic subscore= 0
[e] **Symptomatic remission:** Stool frequency subscore=0 or 1 and rectal bleeding subscore=0

[1]Sandborn WJ, et al. Presented at DDW 2018: 882-Efficacy and Safety of Anti-Interleukin-23 Therapy with Mirikizumab (LY3074828) in Patients with Moderate-To-Severe Ulcerative Colitis in a Phase 2 Study. Gastroenterology. 2018 May 31;154(6):S-1360.

AE=Adverse Event; Nx=number of evaluable patients; NRI=non-responder imputation; SAE=Serious Adverse Event; TEAE=treatment-emergent adverse events



***MMRM model includes baseline, geographical region, prior biologic therapy group, treatment, time, treatment*time interaction term**

Abstract OP38 – Figure 1

trial (AMAC, NCT02589665).[1] Maintenance results through Week 52 from this trial are reported.

Methods: Patients (Mayo score 6–12 with a minimum endoscopic subscore [ES] ≥2) were randomised 1:1:1:1 to receive intravenous (IV) placebo (*N* = 63), miri 50 mg (*N* = 63) or 200 mg (*N* = 62) with possibility of exposure-based (EB) dose increases, or fixed miri 600 mg (*N* = 61) every 4 weeks (Q4W), with efficacy assessment at Week 12. Patients who achieved a clinical response to miri at Week 12 were re-randomised 1:1 into a double-blind maintenance period to receive miri 200 mg subcutaneously (SC) Q4W (*N* = 47) or every 12 weeks (Q12W; *N* = 46), and were treated through Week 52. See Table 1 for definitions of secondary and exploratory outcomes. Missing data were imputed as nonresponse.

Results: Baseline (BL) characteristics of patients who entered the maintenance period were similar between groups. At BL, 52.7% had previously received a biologic. At Week 52, 46.8% (Q4W) and 37.0% (Q12W) were in clinical remission. Additionally, 80.9% (Q4W) and 76.1% (Q12W) had clinical response, and 57.4% (Q4W) and 47.8% (Q12W) had an ES = 0/1. Among those in clinical remission at Week 12, 61.1% (Q4W) and 38.5% (Q12W) remained in clinical remission at Week 52. Among those in clinical response (but not remission) at Week 12, 37.9% (Q4W) and 36.4% (Q12W) achieved clinical remission at Week 52. Symptomatic scores throughout the maintenance period are shown in Figure 1. During the maintenance period, 1 patient discontinued study due to an adverse event (AE), and similar frequencies of treatment-emergent AEs and serious AEs were reported across both treatment groups. Additional demographic, BL disease characteristics, and outcome data are reported in Table 1.

Conclusions: Miri demonstrated durable efficacy (assessed by multiple measures) with no unexpected safety signals and few discontinuations due to AEs throughout the maintenance period. These are the first data demonstrating that a p19-directed IL-23 antibody may be an effective treatment as maintenance therapy in patients with moderately-to-severely active UC.

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Digital oral presentations

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DOP Session 1 - Advances in IBD pathophysiology

DOP01

Extracellular Nicotinamide Phosphoribosyltransferase (eNAMPT): possible new target and biomarker in inflammatory bowel diseases.

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Background: Nicotinamide phosphoribosyltransferase (NAMPT) is a pleiotropic enzyme involved in cellular mammalian metabolism. It is present in two different forms: an intracellular form, called iNAMPT, which acts as an enzyme-producing nicotinamide mononucleotide, precursor of NAD (Chiarugi et al., 2012), and an extracellular form, eNAMPT. eNAMPT is a metabokine with with paracrine and autocrine effects on different cell types (e.g. immune and cancer cells). However, the mechanism of action is still unknown, only recently TLR4 as been proposed as the possible eNAMPT receptor.
eNAMPT levels are increased in inflammatory bowel diseases (IBD). It has been reported that serum eNAMPT levels correlate with the stage of the pathology: in an active state of the disease the level of eNAMPT are very high, however its levels are partially reduced in a remission stage. After 3 months of treatment, eNAMPT levels seem to be lowered, regardless of treatment class (Moschen et al., 2007). Abundant inflammatory stimuli are able to cause eNAMPT oversecretion, especially from innate immune cells.
Methods: We investigated the role of eNAMPT in murine IBD models (DNBS and DSS models) and its neutralisation through a neutralising monoclonal antibody generated by us (C269). We took into account phenotypic effect as weight loss and colon shortening, but also the reduction of inflammatory genes with RT-PCR, tissue damage with H&E and IHC analysis, reduction of eNAMPT levels and *lamina propria* immune cells through FACS analysis. Therefore, we determined serum eNAMPT levels in a cohort of 21 paediatric IBD patients, upon infliximab treatment.
Results: Exogenous administration of recombinant eNAMPT (i.p. 50 µg/mice) in DNBS model determined a worsening of IBD symptoms (increased weight loss, colon shortening and tissue damage). These symptoms are reduced after the treatment with an anti-eNAMPT monoclonal antibody (50 µg/mice/twice), also observable in a reduction of tissue damage through H&E analysis, in mRNA proinflammatory gene expression, especially IFNγ and its associated genes (e.g. IL12p40, IL23p19, IL18, IL22, and TBX21), usually up-regulated in IBD. Moreover, we observed a reduction in myeloid and T cells counterpart, through FACS analysis. Anti-eNAMPT antibody also determined a decrease of serum eNAMPT levels in DNBS model. Moreover, we performed ELISA analysis on sera of paediatric IBD patients, treated with infliximab. Responsive patients verified a reduction of initial high eNAMPT levels, while no-responsive maintained higher levels.
Conclusions: We evaluated the role of eNAMPT in IBD and its possible neutralisation as a novel therapeutic strategy, through a monoclonal antibody. eNAMPT could be considered a biomarker upon infliximab response.

DOP02

Supplementation with butyrate producing bacteria reduces tumour load in a mouse model of colitis-associated cancer

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Background: Colorectal carcinoma is still a severe complication in patients with long-standing and severe ulcerative colitis. Current guidelines suggest that surgical total proctocolectomy must be considered in patients with high-grade dysplasia. Pharmacologic treatments that could prevent the onset of carcinoma in UC patients would be a milestone in the therapy of these patients. Here, we studied how the intestinal microbiota contributes to the onset/prevention of inflammation-induced colorectal carcinoma.
Methods: Colitis associated tumours were induced in wild-type (WT) and RAG2–/– C57BL/6 mice via administration of three cycles of DSS in the drinking water (7 days DSS, 10 days recovery, each) + AOM injections at Day 1 and 8 of each DSS cycle. *Peptostreptococcus stomatis* or a mix of 4 butyrate-producing strains (*A. caccae*, *E. hallii*, *F. prausnitzii*, and *R. intestinalis*) was supplemented via daily oral gavage on Days 8–10 of each AOM/DSS cycle.
Results: We found that tumour burden in the DSS/AOM model was associated with increased levels of faecal *P. stomatis*, but overall reduced levels of butyrate producers. In DSS/AOM-treated WT

mice, supplementation with *P. stomatis* significantly enhanced tumour load when compared with PBS-treated controls ($p < 0.01$, $n = 10$, each). In contrast, only a small fraction of WT mice supplemented with butyrate producers developed tumours ($n = 10$; $p < 0.05$ vs. PBS group). Supplementation with *P. stomatis* was associated with increased intestinal inflammation as assessed in endoscopy and histology ($p < 0.05$, each) after each AOM/DSS cycle. As causative mechanisms, we found elevated numbers of PD-L1+/PD-L2+ tumour-associated macrophages ($p < 0.05$) in *P. stomatis* supplemented mice, while numbers of regulatory T cells were not affected. In mice receiving butyrate producers, DSS-induced intestinal inflammation was similar to DSS/AOM-treated control mice; however, we observed increased numbers of IFNγ+ CD8+ cytotoxic T cells and IFNγ+ NK cells specifically within the tumour tissue, indicating that supplementation with butyrate producers promoted increased anti-tumour immune responses. Furthermore, the increase in PD-L1+/PD-L2+ tumour-associated macrophages was absent in those mice. Of interest, the protective effect of supplementation with butyrate producers was completely abrogated in RAG–/– mice, indicating that T cells are crucially involved in mediating the anti-tumour effect.

Conclusions: Our results indicate that oral supplementation with selected butyrate producers protects from colitis-associated tumour development via promoting anti-tumour T-cell responses *in vivo*. Our findings suggest that manipulation of the intestinal microbiota might be a promising novel approach to promote anti-cancer immune responses.

DOP03

The correlation of regulatory miRNAs with cytokine serum levels and cytokine genes' polymorphisms

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Background: Mesenteric adipocites, fat tissue and lymphatics initiate pathologic response to the bacterial antigens and lead to chronic inflammation. The main signal tracks for the immunological response responsible for CD are NOD2 and TLR that are regulated by miRNAs. They control activity of macrophages, dendritic cells, lymphocytes, and secretion of cytokines. Most crucial for CD are TNF-α and TGF-β. MicroRNAs are endogenic non-coding, single-stranded molecule of 22 nucleotides responsible for post transcriptional gene expression. MicroRNAs regulate secretion of TNF-α, TGF-β, IFN-γ, IL-1, IL-6, IL-12, IL-22. They also regulate cell adhesion, autophagy, and neoplasia. These characteristic makes microRNAs a fascinating diagnostic target. The aim of the study is to evaluate the correlation of the expression of microRNAs with the serum level of pro-inflammatory cytokines TNF-α and TGF-β, as well as gene polymorphisms.

Methods: The pilot study consisted of 52 IBD patients. The inclusion criteria were: age over 18, diagnosed IBD, surgical treatment. The expression patterns of the circulating miRNA-21 and miRNA-210 in serum were quantitatively assayed using reverse transcription and real-time PCR. Genomic DNA quantity and quality was checked by NanoDrop ND-1000. SNPs were genotyped using TagMan allelic discrimination assay (Thermo Fisher) on the Step One Real-Time PCR System (Thermo Fisher). TNF-α and TGF-β cytokines were analysed using ELISA kits according manufacturer's instructions (Fine Test). The results were analysed using Statistica software. Study was approved by The Bioethical Committee.

Results: The level of the circulating miRNA-21 was lower in the IBD group than in the control group ($p < 0.01$) and was associated with the polymorphism of the TGFB1 rs1800470 gene ($p < 0.05$). The serum level of TGF-β was significantly higher in the IBD group and in the recessive model of IBD compared with the control group ($p < 0.001$). The AA genotype of TGFB1 was related with severe types of IBD. The TGF-β serum level was higher among patients who received thiopurines. MiRNA-210 levels were not detectable in the serum.

Conclusions: The expression of miRNA-21 in serum correlates with the severity of IBD and serum levels of pro-inflammatory cytokines. It can be easily detected from the serum and thus is a potentially beneficial diagnostic tool to distinguish IBD from other intestine inflammations.

DOP04

The ability of epithelial regeneration is reduced in the Crohn's disease patient-derived organoids, especially in TNF-α enriched condition

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Background: Recent evidence has featured 'mucosal healing' as the most significant prognostic factor for long-term remission in patients with Crohn's disease (CD), suggesting that accomplishment of epithelial regeneration is critically required to improve the treatment for CD. Recent established minigut organoid model re-enact the epithelial layer of patients and provides and is able to assess the ability of epithelial regeneration.

Methods: Intestinal crypts were isolated from jejunum and ileum using the endoscopic biopsy of normal mucosa of CD patients and healthy controls and performed the *ex vivo* 3-dimensional culture. One hundred crypts were plated on Matrigel and counted the organoid formation (CD: duodenum, $n = 15$, jejunum, $n = 18$, ileum, $n = 21$, colon, $n = 5$, controls: duodenum, $n = 16$, jejunum, $n = 16$, ileum, $n = 12$, colon, $n = 12$). The organoids maintained in culture for at least 8 passages (stable organoids, CD: jejunum, $n = 5$, ileum, $n = 3$, controls: jejunum, $n = 8$, ileum, $n = 5$). Stable enteroids derived from CD patients and controls were cultured with different concentration of TNF-α and assessed the organoid morphology. After Day 7 days of culture, viability via MTT reduction, proliferation via Edu incorporation, apoptosis via TUNEL stain, and histology of patient-derived organoids were compared with those of controls.

Results: The organoid formation rate of crypt of CD patients were significantly reduced those of controls (duodenum: 53 ± 18 vs. 62 ± 12, $p = 0.652$; jejunum: 38 ± 15% vs. 58 ± 16%, $p < 0.05$; ileum: 48 ± 15 vs. 21 ± 8%, $p < 0.01$; and colon: 24 ± 10 vs. 12 ± 8%, $p < 0.01$). When the CD patient-derived organoids maintained more than 4–6 passage, the formation rate and morphology of organoid

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were parallel in those of controls. Stable organoids passaged at least 8 times were counted before TNF-α treatment at the budding stage after 3 days of culture. With additional 7 days culture with TNF-α (0 ng/ml, 10 ng/ml, 30 ng/ml, and 100 mg/ml), the relative number of organoids and enteroid/spheroid ratio were decreased steadily as increasing concentration of TNF-α. Susceptibility of TNF-α was significantly amplified in CD patients-derived organoids compared with normal organoids and ileal organoids compared with jejunal organoids. MTT-stained organoids were decreased and Edu-positive cells and TUNEL-positive cells were increased in CD ileal organoids significantly.

Conclusions: The ability of epithelial regeneration is reduced in the CD patients, especially in TNF-α enriched condition.

DOP05

Adipose-derived stem cells from Crohn's disease patients show antigen presenting cell-like properties

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Background: Under physiological conditions, mesenchymal stem cells (MSCs) are known to modulate the function of diverse types of immune cells, both adaptive and innate. However, only recently has their role in an inflammatory microenvironment undergone scrutiny. In this sense, our group reveals that MSCs isolated from adipose tissue (called adipose-derived stem cells; ASCs) from Crohn's disease (CD) patients are immune activated (showing a high inflammatory profile, high invasive and phagocytic capacities and worse immunosupressive properties). So, our hypothesis is that in CD, ASCs within the creeping fat (*CF*) and also the mesentery (*MES*) are tightly stacked in a chronic inflammatory milieu, which may cause their enforced expression of Class II major histocompatibility complex (MHC) due to an inappropriate response to intestinal dysbiotic microbiota.

Methods: Donors are being recruited at Hospital Joan XXIII of Tarragona and Hospital Vall d'Hebron of Barcelona in accordance with the principles of the Helsinki Declaration. ASCs were isolated from adipose tissue biopsies of visceral origin: *CF* and *MES* in Crohn subjects (n = 6) and *MES* in no-Crohn subjects (n = 6). Groups were matched by age, gender, and BMI. Antigen-presenting cell properties were studied by flow cytometer, gene expression and immunofluorescence in ASCs of Crohn vs. no-Crohn subjects.

Results: Significant differences in the surface expression of human leucocyte antigen–DR isotype (HLA-DR) and the costimulatory molecule 86 (CD86) were observed between ASCs isolated from Crohn vs. no-Crohn subjects (Figure 1A and B). Interestingly, all ASCs were able to uptake ovalbumin (OVA) when we administered to the cell (Figure 1C). Furthermore, multiple genes involved in MHCII antigen processing and presentation increased in ASCs isolated from Crohn patients (Figure 1D).

A.

Surface markers	No-Crohn Mesenteric %	Crohn Mesenteric %	Crohn Creeping Fat %
HLA-DR	32,00±5,90	88,53±3,50*	85,43±5,09*
CD86	1,90±0,29	62,78±7,27*	69,25±4,53*
CD34	0,63±0,31	0,91±0,41	1,15±0,35
CD45	0,28±0,09	0,52±0,07	0,97±0,22
CD14	0,84±0,23	3,00±1,41	2,13±1,37
CD90	92,60±1,76	97,22±0,95	97,70±1,14
CD73	79,90±7,66	86,61±4,50	85,68±8,00
CD36	34,58±7,02	29,37±6,94	25,83±9,48

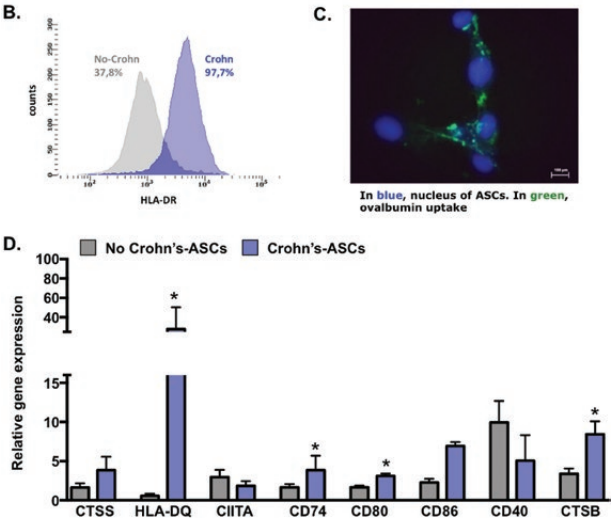

Figure 1. Adipose-derived stem cells from Crohn's disease patients function as antigen-presenting cells. (A) Adipose-derived stem cells (ASCs) obtained from 6 no-Crohn and 6 Crohn donors and stained with the panel of antibodies and analysed by flow cytometry on the FACS ARIA III cytometer (BD). (B) Representative histogram of HLA-DR in ASCs of Crohn and no-Crohn subjects. (C) Fluorescence representative image of OVA uptake by ASCs. (D) Gene expression of antigen presentation markers in ASCs isolated from Crohn and no-Crohn subjects. *$p < 0.05$ vs. no-Crohn subjects. No parametric test (U-Mann Whitney).

Conclusions: Our investigation highlights a role of ASCs as antigen-presenting cell in CD subjects promoting the immune system activation, influencing CD outcome and disease progression.

DOP06

Dynamic shifts in the balance of gut homing Treg and Th17 cells play a critical role in ulcerative colitis and may predict response to vedolizumab therapy

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Background: The balance between regulatory T cells (Treg) and Th17 cells is thought to play a key role in the development and outcomes of human autoimmune and inflammatory diseases. Therapeutic targeting of gut trafficking lymphocytes using vedolizumab, an

anti-integrin monoclonal antibody, is an effective treatment for IBD. However, little is known about the effect of vedolizumab on different effector T-cell subsets or Tregs. We analysed the profile of circulating gut homing effector memory T-cell subsets and Tregs as well as the Treg/Th17 immune balance in ulcerative colitis (UC) patients. We also evaluated the longitudinal impact of vedolizumab on a small cohort of prospectively recruited patients.

Methods: Using multi-parametric flow cytometry, we analysed the gut homing (β7+) effector T cells (CD4+CD45RA-CD45RO+CCR7-) and their functional lineages (Th1, Th2, and Th17) based on chemokine receptor expression (CXCR3, CCR4, and CCR6, respectively) as well as memory Treg (CD4+CD25+CD127-CD45RA-CCR4+) from peripheral blood of healthy controls (HC) and UC patients. Peripheral blood was taken from patients before their first dose of vedolizumab and at each subsequent infusion.

Results: The ratio of gut homing Treg to Th17 cells was significantly lower in UC (n = 21) compared with HC (1.4 in HC vs. 0.5 in UC, p = 0.01). Although there was minimal impact on gut homing Th1 and Th2 cells in vedolizumab treated (n = 15) patients (comparison between baseline [BL] and Week 14), both gut homing Th17 and Treg compartments increased over the same time period (from 17.3% at BL to 45.3% at Week 14 for Th17 and from 9.7% to 57.2% for Treg). Intriguingly, while comparing clinical response to vedolizumab (30% fall in SCCAI at Week 14 compared with BL), preliminary data indicated that the magnitude of increase in gut homing Tregs at Week 2 is much higher in responders compared with non-responders (3-fold increase in responders vs. –0.4-fold increase in non-responders). This increase was more prominent in the gut homing Treg/Th17 ratio in responders at Week 2 (6-fold increase in responders vs. –0.7-fold increase in non-responders, p = 0.02) and could distinguish between the two groups, thereby increasing the positive probability of response to 80%.

Conclusions: UC is characterised by a shift in the proportional abundance of Treg and TH17 cells, implicating a disruption of Treg/Th17 immune balance. The magnitude of increase in the gut homing Treg/Th17 ratio following vedolizumab therapy could differentiate between responders and non-responders to treatment as early as at Week 2 (following the first dose of vedolizumab infusion), raising the possibility that this test could be used as an early biomarker to aid decision-making in clinical practice.

DOP07

IMP761, a novel anti-LAG-3 agonist antibody for the treatment of auto-immune diseases.

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Background: Blockade of the immune checkpoints PD-1 and LAG-3 using antagonist antibodies is currently investigated for many indications in immuno-oncology. Deficiencies in the PD-1 and LAG-3 pathways have been linked to the development of auto-immune diseases. Auto-immune T cells chronically stimulated by the same self-peptide at site of inflammation tend to express exhaustion markers such as PD-1 or LAG-3, therefore making these two markers prime targets for treating the root cause of T-cell–based auto-immunity. To date, no therapeutic immune checkpoint agonist antibody targeting PD-1 or LAG-3 has been developed to downmodulate the activation of these self-antigen specific T cells. We here describe the first agonist anti-LAG-3 antibody (IMP761) and its immunosuppressive properties on human T cells *in vitro* and in a delayed-type hypersensitivity non-human primate model *in vivo*.

Methods: Flow cytometry staining was used to show the capacity of IMP761 to bind and to inhibit CD8 T cells activation and proliferation in response to a foreign antigen peptide pool using activation marker staining and CFSE-based dilution assay. Eighteen cynomolgus macaques received BCG vaccines before being challenged by intradermal injection of tuberculin. Twelve animals received one subcutaneous injection of IMP761 (six at 0.03 mg/kg, six at 0.3 mg/kg) and six animals received PBS as control. A second tuberculin challenge was then performed. Skin biopsies were performed to monitor T-cell infiltration by immunofluorescence staining. IMP761 circulating concentration was measured by ELISA.

Results: The 13E2 LAG-3-specific hybridoma cells were selected in functional assays for their ability to suppress human peptide-specific T-cell responses. The murine Ig sequences were then humanised, giving IMP761. IMP761 was able to bind to activated CD8 T cells with an average IC50 of 34.25 ng/ml (range: 17.7–54.6 ng/ml) and to inhibit human CD8 T-cell activation and proliferation. In the cynomolgus macaque studies, median maximum IMP761 concentrations monitored were 165.6 and 1367 ng/ml for the 0.03 and 0.3 mg/kg injected groups, respectively. There was a significant inhibition of CD3-positive T cells infiltration in the skin biopsy in both IMP761 injected groups compared with the PBS group. The 0.3 mg/kg dose was able to decrease CD8 T-cell infiltration.

Conclusions: IMP761 is the first LAG-3-specific product candidate that can inhibit antigen-specific T-cell–mediated immune responses *in vitro* and *in vivo*, for the treatment of auto-immune diseases.

DOP08

The regulatory landscape of intestinal cells—investigating the transcriptional effect of autophagy impairment observed in Crohn's disease using organoid and network biology approaches

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Background: Intestinal homeostasis is maintained through complex interactions between the epithelial cell barrier, the host immune system, and the enteric microbiota. Paneth cells of the small intestinal crypts play an important role in innate immunity through release of antimicrobial peptides (AMPs). AMP release depends on the intracellular recycling process autophagy, and dysfunction of both of these processes, in Paneth cells, has been shown to contribute to Crohn's disease. Therefore, we have developed an integrative workflow to study regulatory pathways of intestinal cells such as Paneth cells, using organoids and network biology. We have applied this pipeline to study potential master regulators of Paneth cells and to analyse the regulatory effect of autophagy impairment using an extreme Crohn's disease model.

Methods: We performed detailed transcriptomics analysis on differentiated organoids derived from normal mice and mice deficient in

the autophagy-related protein Atg16l1. These organoids were grown from isolated small intestinal crypts, where the Lgr5+ stem cells drove multi-lineage differentiation to form the *in vivo* architecture of the epithelial layer. Application of a certain cocktail of growth factors drives the differentiation towards Paneth cells, enriching for Paneth cells compared with the control organoids. Differentially expressed mRNAs, miRNAs and long non-coding RNAs were identified by comparing RNA expression between the organoids. These RNAs were contextualised by linking them together into a unified regulatory network. This network was generated using experimental information from published databases such as GTRD and TarBase.

Results: By mapping cell-type–specific marker genes to the network derived from normal mice, we were able to identify regulators potentially contributing to Paneth cell–specific functions. Among the seven putative master regulators, we identified four nuclear hormone receptors with links to inflammatory bowel disease (IBD), immunity, and autophagy: *Vdr, Rxra, Nr1d1*, and *Nr3c1*. Subsequent analysis of the autophagy impaired mouse-derived networks has enabled investigation of the effect of autophagy impairment on the regulatory landscape of Paneth cell.

Conclusions: We have developed an integrative -omics and multi-layered network approach to study regulatory landscapes of small intestinal cells using organoids. We show that application of these methods in a cell-type specific context can be used to disentangle multi-factorial mechanisms in Crohn's disease. The established workflow will enable analysing human Paneth cells from clinical biopsies as well as use to investigate the regulatory effect of microbial challenges on Paneth cells in Crohn's disease.

DOP09

Interleukin-20 subfamily cytokines in controlling intestinal inflammation and epithelial barrier integrity

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Background: Intestinal epithelial integrity plays a vital role in maintaining mucosal homeostasis. Disrupted epithelial barrier which leads to increased bacterial translocation and perturbed inflammatory immune responses are common in patients with ulcerative colitis. Our laboratory previously demonstrated that interleukin (IL)-22, a IL-20 subfamily cytokine produced by the immune cells can promote appropriate protein biosynthesis from the secretory cells. In this study, we aimed to identify the therapeutic potential of IL-20 subfamily cytokines including IL-20, IL-22, and IL-24 and determine whether they can improve the barrier integrity by promoting secretory cell function during acute and chronic intestinal inflammation in mice.

Methods: In this study, we employed the widely used dextran sodium sulphate (DSS)-induced colitis and *Winnie* mice of spontaneous colitis models. The *Winnie* mice has point mutation in the *Muc2* gene that causes misfolding of Muc2 resulting in impaired epithelial barrier function. Here, we treated the DSS-induced mice with recombinant cytokines IL-20 or IL-22 (100 ng/g/d, i.p.) for 7 days and the *Winnie* mice (100 ng/g/2d, i.p.) for 2 weeks. As IL-24 is regarded as stress inducing and pro-inflammatory cytokine, we treated mice with anti-IL-24 antibody (10 µg/mouse/7d, i.p.) and observed if targeting these cytokines can improve disease severity and other histopathological features of colitis.

Results: Among others, only IL-22 treatment improved disease severity index including body weight loss and diarrhoea score in the DSS-induced model. Together with reduced colon weight/length ratio, IL-22 also reduced macrophage and intestine-specific ($\alpha4\beta7^+$) CD4 T-cell infiltration in the mesenteric lymph nodes. Increased *Hes-1*, *Lgr5*, and antimicrobial peptides *Reg3β* and *Reg3γ* expressions were observed in mice receiving IL-22 treatment, suggesting that there is increased epithelial cell proliferation and improved epithelial function. In addition, *Winnie* mice receiving IL-22 had improved goblet cell mucin production, decreased inflammation, and reduced histological colitis score in the distal colon. The efficacy of IL-22 was then tested on primary colonic organoid culture. Among others, increased STAT3 and ERK1/2 phosphorylation were observed in the organoids with IL-22 treatment. These results indicate that the observed beneficial effects could be via direct action of IL-22 on epithelium and activation of STAT3 and ERK1/2 signalling pathways.

Conclusions: Our results indicate that IL-22 could be a potential therapy to treat ulcerative colitis. The efficacy of IL-22 in suppressing intestinal inflammation is via restoring epithelial barrier function.

DOP Session 2 - Mechanisms of intestinal inflammation

DOP10

Serum N-glycomic biomarkers predict treatment escalation in inflammatory bowel disease

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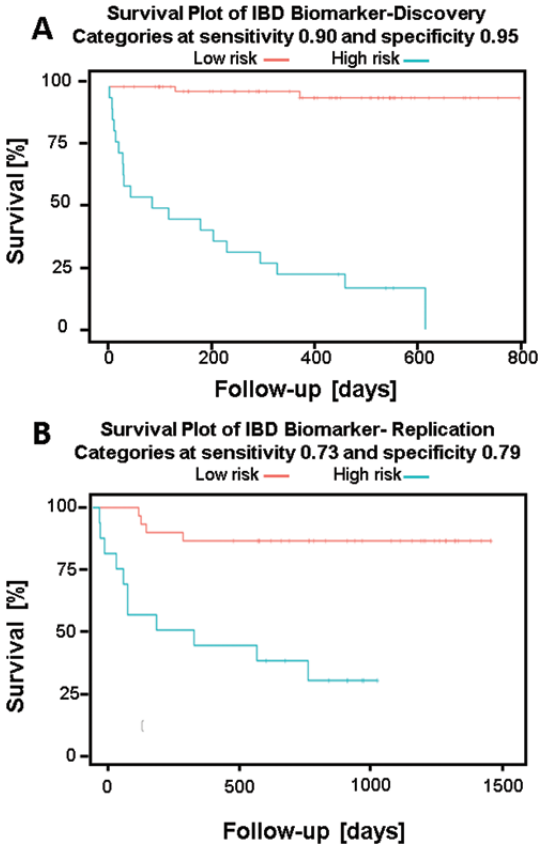
Background: Biomarkers to predict treatment response would be highly beneficial in the clinical management of inflammatory bowel disease (IBD). To that end we have investigated the validity of a composite N-glycomic biomarker from 10 µl of serum taken at diagnosis.

Methods: An automated high-throughput fluorescent labelling of total serum N-glycans (TSNG) from 227 patients and 195 controls from Edinburgh (UK) was performed using ultra-high-performance liquid chromatography (UHPLC). Forty-seven individual glycan peaks were integrated consisting of 105 glycoforms and structurally

related glycans were used to create 24 derived glycan traits. Cox proportional hazard models was used to determine prediction of treatment escalation to anti-TNF, biologics, and surgery. A replication cohort of 49 patients (15 requiring treatment escalation) was recruited in Orebro (Sweden) to validate the escalation biomarker. Additionally, logistic regression analysis was performed to determine associations of glycomics with IBD and clinical markers.

Results: The glycomics biomarkers for treatment escalation gave a hazards ratio (HR) of 23.73 ($p = 6.81 \times 10^{-06}$) for CD and an HR of 30.83 ($p = 1.88 \times 10^{-04}$) for UC. A composite marker for all IBD patients gave an HR of 25.91 ($p = 1.12 \times 10^{-12}$) using the discovery cohort (Panel A). This composite IBD biomarker was further validated in an independent replication cohort with an HR of 5.07 ($p = 1.14 \times 10^{-5}$) (Panel B). Additionally, changes (Bonferroni, $\alpha < 0.05$) in glycosylation-derived traits were associated with IBD ($n = 13$), as well as with clinical parameters ($n = 18$).



Conclusions: Serum N-glycan signatures were shown to predict the need for treatment escalation in patients with CD or UC separately or all IBD patients. Therefore, serum N-glycan biomarkers could help deliver personalised treatment of IBD.

DOP11

Lymphocyte activation gene (LAG)-3 on T cells is a potential therapeutic target in ulcerative colitis

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Background: LAG-3 is a transmembrane protein expressed on T cells following antigen-driven activation. Although it functions as a negative co-stimulatory receptor, similar to PD-1 and CTLA-4, its expression identifies lymphocytes that may contribute to initiation and persistence of inflammation in patients with inflammatory disease. We quantified LAG-3 expression in patients with ulcerative colitis before and after treatment, and characterised the sub-populations of activated T cells in the mucosa that express LAG-3, examining in particular effector cells, memory cells, and regulatory cells. Previously we presented an initial characterisation of LAG-3$^+$ T cells; here we extend our findings with RT-PCR and functionally characterise lamina propria LAG-3$^+$ T cells with intracellular cytokine staining.

Methods: High-dimensional flow cytometric analysis on blood and inflamed and non-inflamed colonic biopsy samples from patients with ulcerative colitis ($n = 42$) and non-IBD controls ($n = 9$) was performed. Immunohistochemical analysis on mucosal samples was used to determine the correlation of LAG-3$^+$ cells with endoscopic and histological scores, as well as the impact of biologic therapies. Cytokine production from mucosal LAG-3$^+$ cells was determined by flow cytometry and quantitative RT-PCR.

Results: The frequency of LAG-3$^+$ cells in peripheral blood was negligible (<0.5%), regardless of disease activity in patients. However, in the lamina propria, the frequency of LAG-3$^+$ T lymphocytes was markedly increased in active UC compared with uninflamed and non-IBD controls ($p < 0.0001$ and $p = 0.001$, respectively) and correlated positively with endoscopic score (UCEIS, $p = 0.004$, $r = 0.43$). LAG-3 expression was enriched on effector memory and CD161$^+$ T cells. *LAG3* mRNA levels were also increased in active disease ($p = 0.003$ and $p = 0.008$, respectively) and correlated with the histological Nancy score ($p < 0.001$, $r = 0.68$). Mucosal LAG-3$^+$ T cells demonstrated robust production of IFNγ ($p = 0.04$) and IL-17A ($p = 0.01$) when stimulated *ex vivo* compared with LAG-3$^-$ cells, with lower amounts of IL-10 detected ($p < 0.06$). In patients undergoing treatment for ulcerative colitis, the number of LAG-3$^+$ cells decreased in patients who responded to therapy ($p < 0.0001$, $n = 11$), but remained elevated in non-responders ($p = 0.058$, $n = 12$).

Conclusions: LAG-3 expression is not altered in circulating blood. However, mucosal expression is increased in inflammation and normalises after successful treatment. Although some reports suggest that LAG-3$^+$ cells have mainly regulatory functions, in human IBD, LAG-3$^+$ cells are mainly effector memory cells and predominantly produce IFNγ, IL-17A, and low levels of IL-10. Therefore, depleting LAG-3$^+$ cells is a promising strategy for IBD that merits further clinical investigation.

DOP12

Mutations in the X-linked inhibitor of apoptosis protein promote susceptibility to microbiota-induced intestinal inflammation

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Background: Mendelian forms of IBD have provided novel insight into the mechanisms underlying intestinal inflammation in IBD. We and others have recently described mutations in the gene encoding X-linked inhibitor of apoptosis protein (XIAP) as the basis for a novel Mendelian form of Crohn's disease (CD). However, the mechanisms through which XIAP deficiency promotes intestinal inflammation are unknown. Here, we investigated the pathways that link XIAP defects and intestinal inflammation using mice deficient in XIAP.
Methods: *Xiap*$^{-/-}$ mice and wild-type (WT) littermates were analysed under constitutive conditions as well as upon exposure to the pathobiont *Helicobacter hepaticus*.
Results: *Xiap*$^{-/-}$ mice showed a reduced number of Paneth cells (PCs) in the ileum as a consequence of increased PC death, in line with the role of XIAP as an inhibitor of effector caspases. Increased cell death was specific to PCs and not observed for other secretory or absorptive intestinal epithelial cells. The loss of PCs was associated with reduced abundance of antimicrobial peptides in the ileum and colon, impaired bacterial control, and dense colonisation of intestinal crypts by commensal bacteria as well as an increased number of mucosa-adherent bacteria. In addition, we observed alterations in the composition of the microbiota in *Xiap*$^{-/-}$ mice with an increased relative abundance of Deltaproteobacteria including increased abundance of the pathobiont *Bilophila wadsworthia*. While these alterations in PCs and bacterial control were insufficient to elicit spontaneous intestinal inflammation under specific pathogen-free (SPF) conditions, exposure to the pathobiont *Helicobacter hepaticus* led to granulomatous ileitis in *Xiap*$^{-/-}$ mice but not WT littermates.
Conclusions: Our results demonstrate that XIAP deficiency is associated with susceptibility to microbiota-induced intestinal inflammation. These findings reinforce the notion of a critical role of PC defects and altered host–microbial interactions in the pathogenesis of CD, provide a mechanistic explanation to incomplete penetrance of CD in patients with *XIAP* mutations, and highlight the microbiota as a potential therapeutic target in patients with *XIAP* mutations and CD.

DOP13

Immune profiling of adipose tissue in murine models of inflammatory bowel disease (IBD)

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Background: Crohn's disease is characterised by epithelial barrier breaches and a subsequent translocation of bacteria from the intestinal lumen into the adjacent mesenteric fat, inducing fat hyperplasia as well as the recruitment of various immune cells. Nevertheless, the functional role of mesenteric fat in intestinal auto-immunity is unknown and it remains elusive, how intestinal barrier breaches alter the immune cell composition of mesenteric fat. We therefore compared the immunological imprinting occurring upon superficial or transmural intestinal inflammation in mouse models of IBD.
Methods: To induce acute or chronic colitis, C57BL/6 mice were either fed 2.5% DSS in their drinking water for 5 days or received 4 cycles of 1.5% DSS for 7 days followed by 7 DSS-free days, respectively. Intestinal epithelial specific caspase-8 (Casp8$^{\Delta IEC}$) knockout mice were used as a model for terminal ileitis and compared with wild-type littermates. Immune cells were isolated from mesenteric fat, gonadal fat, mesenteric lymph nodes and intestinal lamina propria and subsequently analysed by mass cytometry using a panel of 36 lineage and functional markers.
Results: Our data provide for the first time a comprehensive, comparative immune cell characterisation of lamina propria, mesenteric lymph nodes, mesenteric fat and gonadal fat in DSS-induced colitis or Casp8$^{\Delta IEC}$-induced ileitis. In all 3 models, immunosuppressive CD64^{+} CD206^{+} macrophages were the most abundant myeloid cells found within adipose tissue. Interestingly, in acute DSS, colitis mesenteric fat gained pro-inflammatory characteristics as TNF-α production was induced in CD206^{+} macrophages, which could not be observed in chronic DSS-induced colitis. In contrast, we observed that CD206^{+} macrophages infiltrating mesenteric fat of mice with ileitis displayed an up-regulation of anti-inflammatory markers, including CD38 and CD103. Moreover, only the mesenteric fat of Casp8$^{\Delta IEC}$ mice and not DSS colitis models showed infiltration of Ly6G^{+} neutrophils, probably caused by transmural but not superficial inflammation. Finally, adipose tissue of all models showed an enrichment in innate lymphoid cells.
Conclusions: Our data suggest, for the first time, a dynamic immunemodulatory function of mesenteric fat in relation to location and development of intestinal inflammation driven by epithelial damage, highlighting a specific anti-inflammatory function of fat tissue upon transmural inflammation. Furthermore, functional assays have to be performed in order to assess a protective function of mesenteric wrapping fat in Crohn's disease.

DOP14

TiO_2 nanoparticles abrogate the protective effect of the autoimmunity-associated PTPN22^{R619W} variant during acute DSS colitis

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Background: Titanium dioxide (TiO_2), commonly used in comestible goods and personal care products, is omnipresent in everyone's daily life. TiO_2 nanoparticles (1–100 nm) possess high bioreactivity and aggregate in the human body. We have demonstrated that in patients suffering from inflammatory bowel disease (IBD), defects in the epithelial barrier lead to increased TiO_2 serum concentrations. *In vivo*, oral TiO_2 administration aggravates colitis via activation of the NLRP3 inflammasome. The NLRP3 complex is essential for innate immune response and is directly regulated by protein-tyrosine phosphatase 22 (PTPN22). A polymorphism within the *PTPN22* gene locus has been associated with increased risk to develop auto-inflammatory disorders, but protects from Crohn's disease (CD). Since IBD is a multi-factorial disease, investigation how genetic risk variants interact with environmental influences is essential to understand the pathogenesis of the disease.

Methods: To investigate potential interactions between TiO_2 nanoparticles and PTPN22, we induced acute colitis in *Ptpn22* wild-type, *Ptpn22* deficient and *Ptpn22R619W* transgenic mice, which express the murine ortholog to the disease-associated *PTPN22R620W* variant. Mice (n = 8/group) were exposed to 2% dextran sodium sulphate (DSS) in the drinking water with simultaneous TiO_2 administration (500 mg/kg BW; 30–50 nm rutile) per daily oral gavage.
Results: As expected *Ptpn22R619W* mice were protected from inflammation in the acute DSS colitis model. TiO_2 application during DSS treatment, however, resulted in strong inflammation within the gastrointestinal tract of *Ptpn22R619W* mice and colonoscopy revealed increased granularity, fibrin deposits and altered vascularisation of the colonic wall. Histological analysis confirmed severe colitis and lesions throughout the colon, culminating in immune cell infiltration and epithelial damage. Interestingly, *Ptpn22R619W* transgenic mice, simultaneously exposed to DSS and TiO_2, displayed significantly decreased NQO1 gene and protein expression levels. TiO_2 administration did not significantly affect the extent of colitis in the *Ptpn22*-deficient mice.
Conclusions: Our findings indicate that TiO_2 abrogates the protective effect of the CD-associated *Ptpn22R619W* polymorphism during colitis induction. Our data demonstrate that consumption of TiO_2 is able to induce colitis in mice carrying the *Ptpn22R619W* variant and therefore to render a protective into a detrimental mechanism. Since TiO_2 nanoparticles are highly abundant in daily life, our findings might contribute to a better understanding of the mechanisms contributing to the onset of IBD. Deciphering how TiO_2 directly targets the mode of action of the *Ptpn22R619W* variant might yield new therapeutic approaches for IBD treatment.

DOP15

Metabolomics coupled with pathway analysis characterise metabolic changes in treatment-naive ulcerative colitis patients

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Background: Metabolomics, defined as the large-scale assessment of small molecules, known as metabolites, is a powerful tool in understanding complex inflammatory disease. This approach has been applied to study immune-mediated diseases such as rheumatoid arthritis, psoriasis, and diabetes mellitus. However, there are few studies describing the metabolomic profile in inflammatory bowel disease (IBD) patients. Therefore, our study aims to identify the main metabolic alteration in newly diagnosed treatment-naïve ulcerative colitis (UC) patients compared with UC patients in deep remission and healthy controls.
Methods: Colon mucosa biopsies were taken from 22 treatment-naive UC patients at the debut of the disease (inflamed mucosa), 14 UC patients in deep remission, and 15 healthy subjects. The degree of inflammation and state of remission were assessed by endoscopy, histology, and by measuring TNF gene expression. Metabolomics analysis of the colon biopsies was performed by ultra-high-performance liquid chromatography coupled with tandem mass spectrometry (UPLC-MS-MS). In total, 140 metabolites from 33 metabolic pathways (Kyoto Encyclopedia of Genes and Genomes database KEGG) were identified.
Results: Mucosal levels of 17 metabolites were significantly changed in treatment-naive patients with respect to controls, whereas mucosal levels of 7 metabolites were significantly changed in deep remission patients compared with healthy controls. The most prominent changes were in Omega-6 arachidonic acid phospholipids, namely phosphatidylcholine (PC20:4) and phosphatidylethanolamine (PE20:4). Pathway enrichment analysis revealed disruption in six metabolic pathways. Pathway topology analysis revealed that UC is associated mainly with altered tryptophan and omega-6 linoleic acid metabolism pathways. Furthermore, high mucosal TNF mRNA levels were correlated with changes in the omega-6 arachidonic acid metabolism pathway.
Conclusions: To the best our knowledge, this is the first study describing metabolomic profiles in colon mucosa of untreated newly diagnosed and deep remission UC patients. We have identified main metabolic pathways that might be involved in the UC onset. These pathways may present diagnostic biomarker or monitoring tools in UC. In addition, these metabolic fingerprints may suggest potential therapeutic targets.

DOP16

Endoplasmic reticulum stress in subepithelial myofibroblasts increases the TGF-β1 activity that regulates fibrosis in Crohn's disease

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Background: Endoplasmic reticulum (ER) Stress is an essential response of epithelial and immune cells to inflammation in Crohn's disease. ER stress sensors, GRP-78, ATF-6α, and XBP1, can influence the expression and activity of the pro-fibrotic cytokine TGF-β1 in addition to initiating the unfolded protein response. In addition to the genetically mediated components that lead to fibrosis Crohn's disease, epigenetic changes also influence the development of fibrosis in susceptible patients. GRP78 is a key factor for two reasons: (1) it has an RGD-binding domain complementary to latent TGF-β1 and (2) GRP78 expression is regulated by miR-199a. Transcription of miR-199a is silenced by DNMT-1 mediated methylation. The presence and regulation of the ER stress in subepithelial myofibroblasts (SEMF), and its role in the development of fibrosis in patients with Crohn's disease have not been reported yet.
Methods: SEMF were isolated from the affected ileum and normal ileum of patients with each Montreal phenotype of Crohn's disease (B1 inflammatory, B2 fibrostenotic, and B3 penetrating) and from non-Crohn's subjects. Isolated SEMF were used to prepare RNA, cell lysates or initiate primary cell cultures. ER stress was induced by treatment with thapsigargin. Binding of GRP78 to latent TGF-β1 and it subcellular trafficking was examined using proximity ligation–hybridisation assay (PLA). The effects of GRP78, ATF-6α, XBP1 on TGF-β1 were measured using siRNA-mediated knockdown and DNA-ChIP. Transcriptional activity of TGF-β1 was measured by dual luciferase (Firefly–Renilla) assay system after transfection of

cells with TGFB1-SBE reporter. Latent-TGF-β1 activation was quantified by ELISA.

Results: In SEMF of strictured intestine from patients with B2 Crohn's disease expression of ER stress sensors GRP78 and ATF-6α increased 3.1 ± 0.2-fold and 2.5 ± 0.1-fold, respectively, compared with normal intestine in the same patient and compared with other Crohn's phenotypes. ER stress induced by thapsigargin elicited time-dependent and concentration-dependent increase in GRP78 protein levels, direct interaction with latent-TGF-β1, and translocation of the complex to the cell surface where TGF-β1 is activated. The process was abolished after siRNA-mediated knockdown of GRP78. TGF-β1 DNA-binding activity of ATF-6α and XBP1 were similarly increased by 3.2 ± 0.16- and 8.5 ± 0.43-fold, respectively, in SEMF of strictured intestine compared with normal intestine. Latent-TGF-β1 activation was significantly blocked even in the presence of tunicamycin by GRP78 siRNA. Collagen production was further reduced by 2.5 ± 0.2-fold by GRP78 siRNA compared with control.

Conclusions: ER stress-mediated pathway presents a novel therapeutic intervention for the patients with fibrostenotic Crohn's disease.

DOP17

AZD4205, a potent, GI tract-enriched, JAK1-selective inhibitor for treatment of inflammatory bowel disease (IBD)

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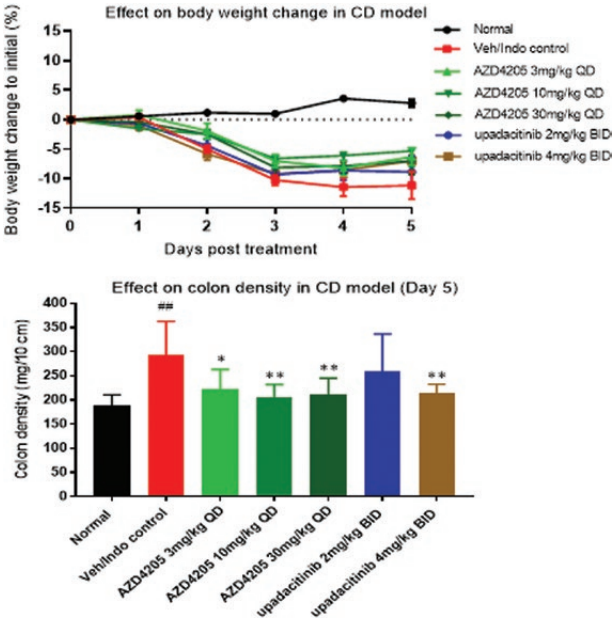
Background: AZD4205, a JAK1-selective inhibitor, is in early development as a treatment for IBD. Here we present preclinical data of AZD4205 in peripheral blood mononuclear cells (PBMCs) and IBD models, as well as human pharmacokinetics (PK) and biomarker data from an ongoing phase I study (NCT03450330).

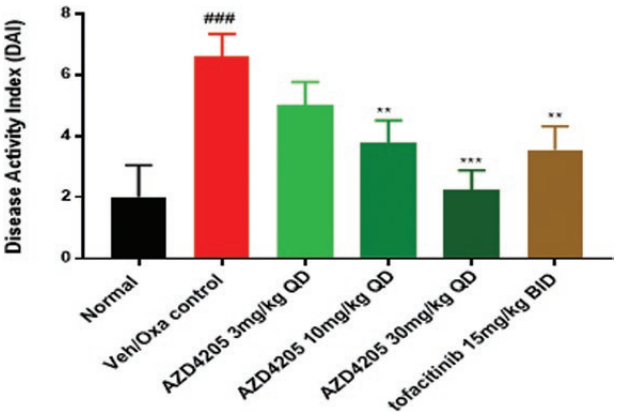
Methods: The cellular activity of AZD4205 was evaluated in human PBMCs by assessing cytokine-induced phosphoSTATs (pSTATs). Murine Crohn's disease (CD) model was induced by dosing 10 mg/kg indomethacin on Day 0 and Day 1. Ulcerative colitis (UC) model was induced by dosing 1% oxazolone on Day 1. The drug exposure, biomarker, and efficacy of AZD4205 in IBD models were assessed. pSTAT3 level in ileum and bone marrow were measured by immunohistochemistry. Human PK and biomarker data were obtained from an ongoing Phase I study.

Results: AZD4205 exhibited more than 200-fold selectivity against JAK1 over other JAK family members. Potent pSTAT inhibition in human PBMCs was elicited, comparable to tofacitinib, with IC_{50} of 50 nM, 308 nM, and 90 nM for pSTAT1, pSTAT3, and pSTAT5, respectively. The exposure of AZD4205 in murine ileum was 100-fold higher than that in plasma. Consistently, in murine CD model, there was a higher inhibition of pSTAT3 in ileum than that in bone marrow post AZD4205 dosing. In murine CD model, AZD4205 exhibited dose-dependent activity in improving body weight loss and decreasing colon density. AZD4205 at 10 mg/kg showed comparable efficacy to upadacitinib at 4 mg/kg BID (Figure 1).



Abstract DOP17 – Figure 1. The body weight change and colon density post treatment with upadacitinib and AZD4205 in indomethacin-murine CD model (n = 10/group). *p < 0.05, **p < 0.01 (vs. Veh/Indo), ##p < 0.05 (vs. normal). One-way ANOVA, Fisher's LSD post-hoc test

In murine UC model, AZD4205 demonstrated dose-dependent activity in attenuating oxazolone-induced elevation of disease activity index (Figure 2). AZD4205 at 30 mg/kg showed better efficacy than tofacitinib at 15 mg/kg BID.



Abstract DOP17 – Figure 2. The disease activity index post treatment with tofacitinib and AZD4205 in oxazolone-induced murine UC model (n = 10/group). **p < 0.01, ***p < 0.001 (vs. Veh/Oxa control), ###p < 0.001 (vs. normal). One-way ANOVA, Fisher's LSD post-hoc test.

As of 6 August 2018, four patients with malignancy were dosed with AZD4205 75 mg QD. The human $T_{1/2}$ of AZD4205 was around 40 h. The average concentration of AZD4205 was above pSTAT1 and pSTAT5 IC_{50}. An average of 61%, 47%, and 60% inhibition of pSTAT1, pSTAT3, and pSTAT5 were detected in PBMCs at 4 h post dosing, respectively. C-reactive protein (CRP) levels of all four patients were above normal range at screening, but decreased and then maintained within normal range 7 days after AZD4205 treatment.

Conclusions: With its GI tract-enriched exposure and JAK1 selectivity, AZD4205 has the potential to maximise safety and efficacy for IBD patients.

DOP18

OSM neutralisation in IBD mucosal explant cultures reduces pro-inflammatory cytokine production

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Background: Oncostatin M (OSM) is a proinflammatory and profibrotic cytokine that has been implicated in the pathogenesis of inflammatory bowel disease (IBD). This is at least partly due to an ability to induce the secretion of cytokines and chemokines from intestinal stromal cells (West et al., Nat Med 2017). However, while mRNA expression is known to be elevated in inflamed bowel tissue from IBD patients, less is known about OSM protein levels and the effect of inhibiting OSM on cytokine production. The objective of this study was to measure OSM protein levels in serum and inflamed intestinal tissue from IBD patients, and to determine the effect of OSM neutralisation on cytokine production in an IBD mucosal explant model.
Methods: Serum and involved intestinal mucosa from patients with active moderate/severe ulcerative colitis (UC) or Crohn's disease, along with corresponding samples from healthy volunteers, were obtained with patient informed consent in accordance with ICH GCP under an ethics committee-approved protocol. For the gut explant model, IBD mucosal biopsies from each individual donor were cultured *ex vivo* for 24 h with either anti-OSM antibody (10 or 40 µg/ml), isotype control antibody or prednisolone (1 µM). Cytokine concentrations were measured in serum, tissue lysates, and explant culture supernatants by ELISA.
Results: OSM protein was significantly ($p < 0.001$) increased in serum from Crohn's and UC patients compared with healthy volunteer samples and significantly ($p < 0.05$) elevated in intestinal tissue from Crohn's and UC patients compared with healthy control samples. Incubation of human IBD intestinal explants with an anti-OSM antibody reduced spontaneous pro-inflammatory cytokine production. In the UC mucosal explant assay ($n = 9$ donors), 10 and 40 µg/ml anti-OSM treatment resulted in a mean 49% and 48% inhibition of IL1β, 36% and 57% inhibition of IL6, and 27% and 43% inhibition of TNFα production, respectively. In the Crohn's mucosal explant assay ($n = 13$ donors), 10 and 40 µg/ml anti-OSM treatment resulted in a mean 51% and 64% inhibition of IL1β, 57% and 42% inhibition of IL6, and 31% and 37% inhibition of TNFα production, respectively. This degree of cytokine inhibition was greater than that shown for the isotype control.
Conclusions: OSM protein is elevated in both serum and inflamed intestinal tissue from IBD patients. OSM neutralisation in the IBD mucosal explant assay reduced spontaneous pro-inflammatory cytokine production. Together these data support targeted approaches to modulating OSM for the treatment of UC and Crohn's disease.

DOP Session 3 - Translational science in IBD

DOP19

Spermidine treatment ameliorates experimental colitis *in vivo*

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Background: Genetic variations within the gene encoding protein tyrosine phosphatase non-receptor type 2 (PTPN2) are associated with an increased risk to develop inflammatory bowel disease (IBD). In the intestine of IBD patients, cellular levels of the natural polyamine spermidine are reduced. We have recently demonstrated that spermidine activates PTPN2 and thereby supresses pro-inflammatory effects *in vitro*. These effects are even further enhanced in immune cells derived from PTPN2 variant IBD patients. Therefore, the aim of this study was to evaluate the effect and molecular mechanisms of spermidine treatment in a mouse model of colitis.
Methods: To induce intestinal inflammation, Rag2–/– immunodeficient mice were injected intraperitoneally with wild-type (WT) or PTPN2-deficient (KO) naïve T cells. Spermidine (3 mM) was administered in the drinking water throughout the experiment. Colitis severity was studied by analysis of clinical parameters, mouse endoscopy, histology of the colon, and myeloperoxidase activity. To assess T-cell subsets, flow cytometry was performed on lamina propria lymphocytes (LPL) and mesenteric lymph nodes (LN).
Results: We did not detect any toxic effects of spermidine administered in the drinking water for up to 3 months. Spermidine treatment significantly ameliorated colitis symptoms, as observed by reduced weight loss ($p < 0.001$), reduction of endoscopic colitis scores ($p < 0.001$), absence of colon shortening ($p < 0.01$), and lower signs of inflammation in histological assessment of the terminal colon ($p < 0.0001$). In addition, myeloperoxidase activity, a measurement of infiltrating myeloid cells, was also significantly reduced ($p < 0.001$) in mice receiving spermidine when compared with untreated mice. Furthermore, administration of spermidine resulted in a significant reduction of CD4+ T-cell numbers ($p < 0.01$) in LN and LPL in mice receiving WT T cells, but not in mice receiving KO T cells. In particular, IFN-γ+ T helper (Th) 1 cells and IL-17+IFN-γ+ Th1/17 were significantly reduced ($p < 0.01$) in mice receiving WT T cells, while IL-17+ Th17 cells were not affected. Of note, lack of PTPN2 in T cells abrogated the spermidine-induced reduction in Th1 cells, but did not affect the reduction of Th1/17 cells.
Conclusions: Our results demonstrate that spermidine treatment significantly ameliorates T-cell–induced colitis via reducing infiltration of pathogenic T helper cells. Interestingly, the action of spermidine is not dependent on the presence of PTPN2 in T cells, which implicates that spermidine treatment might have a local effect on the mucosa and or other stromal cells. Nevertheless, our findings indicate that spermidine administration might be a promising novel therapeutic strategy in IBD.

DOP20

Drugs that modulate histone acetylation disrupt TGF-β-signalling and reduce collagen I expression in models of stricturing Crohn's disease

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Background: Stricturing Crohn's disease (SCD) is associated with excess deposition of extracellular collagen, is not reversed by current medical therapies, and is a frequent indication for surgery. Acetylation of histone proteins is an important epigenetic mechanism that controls gene expression. We have previously shown that hypoacetylation of histone-3 lysine 27 (H3K27ac) is an important marker of transcriptionally active enhancer elements and a pathological feature of SCD. Furthermore, restoration of histone acetylation using an HDAC inhibitor (valproic acid [VPA]) limits fibroblast remodelling and supresses Collagen I expression. Here, we identify novel genes associated with SCD in patients regulated by VPA and demonstrate the impact of VPA on TGF-β-signalling.
Methods: Pathways altered by VPA were identified by illumina HT-12 gene expression array using RNA isolated from CCD-^{18}Co intestinal fibroblasts cultured with VPA (5 mM) or control media (n = 4). VPA target genes linked to collagen biosynthesis, such as TGF-β1|1 (also known as HIC5) from the TGF-β pathway, were validated by qPCR in an independent sample set. The effects of VPA on H3K27ac levels, collagen I and TGF-β1|1 expression, as well as phosphorylated SMAD3 were assessed in CCD-^{18}Co stimulated by TGF-β1 (10 ng/ml) using immunohistochemistry. Expression of TGF-β1|1 was analysed in tissue from SCD patients by qPCR.
Results: Transcriptomics identified 790 and 604 mRNA probes that were up-regulated or down-regulated, respectively in VPA treated CCD-18Co fibroblasts. Hierarchical cluster analysis identified a close association between inhibition of COL1A1 and the down-regulation of TGF-β1|1, also known as HIC5. In CCD-18Co cells, TGF-β1 decreased H3K27 acetylation (0.720 fold, p = 0.031) and increased phosphorylated SMAD3 levels (1.165 fold, p = 0.038) as well as TGF-β1|1 protein expression leading to increased cytoplasmic collagen I protein (1.10 fold, p = 0.076) and secreted pro-collagen-IαI (1.152 fold, p = 0.017). VPA reversed these changes suggesting a direct effect on TGF-β signalling. TGF-β1|1, which has not previously been implicated in SCD, was increased in the mucosa overlying strictured intestine (2.882 fold, p = 0.009, n = 7). Functional studies to elucidate the function of TGF-β1|1 in intestinal fibrosis are now ongoing.
Conclusions: Inhibition of HDACs is a potential novel therapeutic agent for SCD which reverses TGF-β-induced hypoacetylation of histone-3 and suppresses collagen I expression in intestinal fibroblasts. A role for TGF-β1|1, which has not previously been implicated in SCD, was identified.

DOP21 has been withdrawn.

DOP22

UC-related and segment-specific properties of patient-derived colonic organoids

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Background: Colonic stem cells (CSCs) play indispensable roles in the maintenance and the regeneration of the colonic epithelium. It has been reported that the inflammatory environment of ulcerative colitis (UC) or Crohn's disease (CD) can modify gene expression and functions of colonocytes and/or CSCs. Organoids generated from those patients can maintain disease-modified or segment-specific properties of colonocytes and CSCs *in vitro*. However, to what extent the patient-derived organoids generated from different colonic segments exhibit disease-specific phenotypes remain uncertain.
Methods: Colonic organoids were established by using endoscopic biopsy specimens taken from various colonic segments of UC, CD, and non-IBD patients. Colonic segment-specific gene expression was analysed by microarray analysis. CSC-specific gene expression was examined at the single-cell level by microfluid-based multiplex qPCR analysis. Proliferation/growth efficiency of patient-derived organoids were evaluated for up to 33 days by using 3D scanner-based quantification method (Sci Rep, 2012) and/or haemocytometer-based cell counting.
Results: A total of 55 colonic organoids were established from UC or CD patients in remission, and also from non-IBD patients. Organoids established from different colonic segments of the same patient successfully identified candidate segment-specific genes of the ascending colon (15 genes), transverse colon (5 genes), Sigmoid colon (3 genes), and rectum (5 genes). Single-cell gene expression data of 12 representative ISC-marker genes including LGR5, MYC, SLC12A2, LRIG1, SMOC2 revealed similar, indistinguishable expression pattern in segment-matched organoids of UC and non-IBD patients. Proliferation/growth efficiency profile of non-IBD patient-derived organoids also showed equivalent level and pattern between those from the ascending colon and the rectum. However, in sharp contrast, proliferation/growth efficiency profile of UC patient-derived organoids clearly showed a segment-specific pattern, as those from the ascending colon generally exhibited over 2-fold higher proliferation efficiency compared with those from the rectum.
Conclusions: Colonic organoids established from the ascending colon of UC patients maintain high *in vitro* proliferation potential compared to those established from the rectum. Results suggest colonic segment-specific modification of colonocyte function in UC patients, which may be further revealed by deeper gene expression analysis of our patient-derived organoid library.

DOP23

Myenteric plexitis and post-operative recurrence in Crohn's disease: the role of enteric glial cells and ICAM-1

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Background: Half of Crohn's disease (CD) patients require surgery within 20 years of diagnosis, and post-operative recurrence (POR) is frequent. Among the risk factors of POR, the presence of myenteric plexitis (≥ one immune cell in contact with myenteric ganglia) at the proximal resection margin has been incorporated in the European guidelines. However, this criterion is rarely used, as little is known about the involved mechanisms. Our objectives were to determine which cells of the enteric nervous system interact with T cells and to identify the molecules responsible for these interactions.

Methods: *In vivo*: 29 patients (20 CD, 9 cancer) who underwent an ileocolonic resection were included. Full-thickness slices of the proximal resection margin were analysed by immunohistochemistry (IHC) to identify enteric glial cells (S100β), neurons (Hu), and T cells (CD3, CD4, CD8). T cells in contact with ganglia of the myenteric plexus were counted on each slide. *In vitro*: To analyse neuro-immune interactions, human enteric glial cells (EGC) were co-cultured with T cells which were activated by anti-CD3/CD28 antibodies beforehand. To determine the impact of inflammatory conditions, EGC were pre-treated with lipopolysaccharide (LPS) or IL-1β/TNFα (IT). Immunocytochemistry (ICC) was used to analyse the adhesion of T cells to EGC. The expression of adhesion molecules was determined by qPCR, western blot and ICC.

Results: IHC showed the presence of T cells, CD4+ and CD8+, in contact with EGC of myenteric ganglia in both CD and control patients. The number of T cells per ganglion was significantly higher in CD patients (5.6 ± 0.9) when compared with controls (1.2 ± 0.2) ($p < 0.001$), with a threshold of 1.7 T cells per ganglion, and was twice higher in CD patients suffering from POR (7.1 ± 1.4) when compared with those in whom CD did not recur (3.6 ± 0.9) ($p = 0.175$). POR was systematic above 7.7 T cells per ganglion. *In vitro*, pre-treatment of EGC with LPS and IT significantly increased the number of T cells in contact with EGC, respectively, by a factor of 2.7 (± 0.7) ($p < 0.01$) and 2.1 (± 0.3) ($p < 0.01$) when compared with the control condition. These inflammatory stimuli were associated with an overexpression of ICAM-1 in EGC as measured by qPCR, while the expression of MAdCAM and NCAM was not increased. This up-regulation of ICAM-1 was confirmed at the protein level.

Conclusions: Our results indicate that T cells interact with EGC *in vitro* and *in vivo*. These interactions are increased under inflammatory conditions and are associated with an up-regulation of ICAM-1. This suggests a role of EGC in the formation of plexitis, possibly through the binding of LFA-1 to ICAM-1. Further experiments will be carried out to confirm this possibility.

DOP24

Intestinal acidification sensed by pH-sensing receptor GPR4 contributes to fibrogenesis

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Background: During active inflammation, intraluminal intestinal pH is decreased in patients with inflammatory bowel disease (IBD). Acidic pH may play a role in IBD pathophysiology. pH-sensing G-protein-coupled receptor (GPR) 4 is regulated by key inflammatory cytokines. Patients suffering from IBD express increased mucosal levels of GPR4 compared with non-IBD controls. pH-sensing may be relevant for progression of fibrosis, as extra-cellular acidification leads to fibroblast activation and extracellular matrix remodelling. We aimed to determine GPR4 expression in fibrotic lesions in the intestine of Crohn's disease (CD) patients, and the effect of Gpr4 deficiency in fibrogenesis.

Methods: Human fibrotic and non-fibrotic terminal ileum was obtained from CD patients undergoing ileocaecal resection due to stenosis. Gene expression of fibrosis markers and pH-sensing receptors was analysed. The *in vivo* murine model of DSS-induced chronic colitis and the heterotopic transplantation model of intestinal fibrosis was used. Collagen layer thickness and hydroxyproline content were determined. Primary human fibroblast cultures were obtained from surgical specimens taken from healthy areas of the mucosa of a patient undergoing surgery for colorectal carcinoma. Fibroblasts were exposed to pH 6.4, 7.4, and 7.8 for 3 and 24 h, respectively, and additionally stimulated with recombinant TGF.

Results: Increased expression of fibrosis markers was accompanied by an increase of GPR4 (3.07 ± 1.03 vs. 0.80 ± 0.12, $p = 0.035$) in fibrosis-affected human terminal ileum, compared with the non-fibrotic resection margin. Positive correlation between GPR4 expression and pro-fibrotic cytokines (TGF and CTGF) or pro-collagens was observed. Gpr4–/– mice from both the DSS-induced chronic colitis model and the heterotopic transplantation animal model for intestinal fibrosis showed a significant decrease in mRNA expression of fibrosis markers as well as a decrease in collagen layer thickness and hydroxyproline compared with wild-type mice. *In vitro*, GPR4 expression was increased at low pH (6.4) compared with normal (7.4) and high pH (7.8). Expression of pro-fibrotic TGF and collagen was increased at low pH. Last but not at least, exposure to low pH triggered nuclear translocation of p-SMAD3, pointing to the activation of the TGF signalling pathway upon low pH stimulation.

Conclusions: GPR4 expression correlates with the expression of pro-fibrotic genes and increased levels of collagen deposition. Gpr4 deficiency is associated with a decrease in fibrosis formation. Targeting GPR4 may be a potential new treatment option for IBD-associated fibrosis.

DOP25

Unravelling vedolizumab mechanism of action in ulcerative colitis

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Background: Vedolizumab (VDZ) was approved for IBD treatment in 2014. It targets the integrin α4β7, which facilitates the migration of leucocytes to the intestine. VDZ achieves clinical remission in <45% of ulcerative colitis (UC) patients, and currently there are no predictors of response to guide treatment decisions. Our aim was to unravel the mechanism of action underlying VDZ by assessing its effect in UC patients and how they correlate with response/remission to VDZ. In this regard, our specific objectives were: (1) to analyse the frequencies of leukocytes in the intestine and peripheral blood; (2) to characterise the expression of integrins α4β7, α4β1, and αEβ7 in lymphocytes before and after VDZ treatment; and (3) to determine the occupancy of α4β7 achieved by VDZ.

Methods: Intestinal biopsies were collected from healthy controls and UC patients at initiation (week 0) of VDZ treatment and at Weeks 14 and 46 of follow-up. Blood was drawn from healthy controls and UC patients treated with VDZ at weeks 0, 2, 6, 14, 30, and 46 of follow-up. Single-cell suspensions obtained from blood and biopsies were stained for flow cytometry analysis to determine lymphocyte frequencies and integrin expression. α4β7 occupancy was assessed by co-staining with fluorescently labelled Vedolizumab and the non-competing a-β7 mAb (clone FIB504). Intestinal biopsies were also processed in paraffin blocs and used for CD103 (αE) IHC staining. Flow data were analysed with FlowJo software and statistical analysis was performed in R and Prism software.

Results: Using flow cytometry, we showed that percentages of T and B cells in the intestine decreased significantly at Weeks 14 (n = 7, 2 of them in remission) and 46 (n = 8, 4 of them in remission) after VDZ initiation (week 0, n = 8) while no accumulation of these cells was detected in peripheral blood. Moreover, VDZ therapy decreased expression of α4β7 and α4β1 on most lymphocytic populations in blood and intestine, suggesting VDZ-induced internalisation. Interestingly, we observed a significant increase in the percentage of circulating αEβ7+ memory CD8+ T cells in VDZ-treated patients. Nonetheless, treatment with VDZ had no significant effect on the frequencies of αEβ7 in the intestine by flow or IHC. Finally, we showed that 100% of α4β7 was bound to VDZ in all patients who received the drug, regardless of time points, sample origin (blood or biopsy) or immune population studied.

Conclusions: Our results confirm that the current regimen of VDZ blocks the migration of T and B cells to the intestinal lamina propria. Although this effect stems from the complete blockade of a4b7, it is probably aided by the reduced presence of the integrin on the cell surface.

DOP26

Biological therapy increases NCR+ ILC3 levels in IBD patients

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Background: Innate lymphoid cells (ILCs) reside at mucosal barriers where they exhibit high cytokine producing capacity to maintain homeostasis and control infections. Natural cytotoxicity receptor (NCR) positive ILC3s, an important source of intestinal IL-22, have been shown to be decreased in the mucosa of patients with Crohn's disease (CD) and ulcerative colitis (UC) in favour of pro-inflammatory ILC1s. To study whether current biological anti-TNF, ustekinumab (UST) or vedolizumab (VDZ) therapy can restore the intestinal ILC balance, ILC frequencies were determined in serial blood and biopsies samples.

Methods: We included 26 CD patients initiating UST, 14 patients initiating VDZ (9 CD, 5 UC), 14 CD patients initiating anti-TNF (8 infliximab, 6 adalimumab) and 10 healthy controls (HC) without endoscopic abnormalities. All cohorts were matched for age, gender, and age at diagnosis. Colonic biopsies and blood were taken at baseline and during endoscopic assessment (Week 8–14 UC, 24 CD). Peripheral blood and lamina propria mononuclear cells were stained for flow cytometric analysis. Pairwise comparisons were performed on ILC numbers determined as frequency of total ILC or total leucocyte population.

Results: Intestinal NCR+ ILC3 levels before initiation of biological treatment were significantly decreased in anti-TNF and VDZ cohort (42.0, 37.5 vs. 86.8% of total ILC, both $p < 0.001$) while ILC1 levels were increased (15.7, 7.7 vs. 2.7, both $p < 0.01$) when compared with HC. In contrast, ILC subgroup levels were not different in the UST cohort (NCR+ ILC3: 74.8, ILC1:2.4, $p = 0.9$). In the anti-TNF and VDZ cohort, recovery of NCR+ ILC3s compared with start ($p = 0.04$, $p = 0.03$) was observed after first endoscopic evaluation independent of treatment response. Mucosal ILC levels could not be correlated to peripheral ILC levels ($r = 0.39$, $p = 0.27$); however, an increase of peripheral NCR+ ILC3s in the total ILC (Figure 1) and leucocyte population could be observed in both the anti-TNF ($p = 0.01$) and UST ($p = 0.001$) cohort when compared with the start of therapy. In contrast, no effect of VDZ ($p = 0.47$) was observed on peripheral ILC levels.

Conclusions: Biological therapy can restore the intestinal ILC levels towards homeostatic proportions even in absence of endoscopic response. Anti-TNF and UST treatment increased NCR+ ILC3s levels in the circulation, which are not described in physiological conditions. In contrast, no increased NCR+ ILC3s levels were not observed in VDZ-treated patients. NCR+ ILC3 level will be correlated to cytokine levels in future.

DOP27

DOP27 is a late-breaking abstract and is published on www.ecco-ibd.eu/publications and www.academic.oup.com/ecco-jcc

DOP Session 4 - Practicalities of IBD patient care

DOP28

Maternal obstetric outcomes in women with IBD compared with the general population

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Background: Pregnant women with IBD face important but complex choices on medication, delivery and breast feeding. While foetal and maternal IBD outcomes have been well studied, there is less evidence regarding maternal obstetric outcomes. Women with IBD have higher rates of Caesarean section (CS) but the reasons for this remain largely unknown. Perineal birth trauma in IBD can potentially negatively affect long-term quality of life but is so far unstudied.
Methods: In this prospective cohort study, we compared maternal and foetal outcomes in singleton pregnancies of IBD and non-IBD patients in a tertiary centre. IBD patients from the Combined IBD Antenatal Clinic delivering between 2014 and April 2018 were included. All non-IBD patients delivering between 2015 and April 2018 were comparators. Routinely collected maternal and foetal data were analysed with sub-analysis of primiparous patients. We recorded indications for CS as IBD/obstetric and absolute/relative.
Results: Of 31,707 births analysed, 179 occurred in mothers with IBD. Incidence of CS was higher in IBD patients overall (30% vs. 21%, RR 1.6, p = 0.02, CI 1.2–2.6) and in primiparous analysis of 12639 (33% vs. 21%, RR 1.9, p = 0.03, CI 1.2–2.9). CS rates between IBD subtypes in multiparous and primiparous women were similar. In IBD patients, obstetric rather than IBD indication was more common for elective CS (60% vs. 40%). IBD indications were all absolute indications (active perianal disease, ileo-anal pouch, extensive previous surgery, emergency surgery for ileal perforation). Emergency CS constituted 35% of IBD and 40% of non-IBD CS deliveries with no significant difference across all patients (p = 0.08, CI 0.9–3.8) or primiparous patients (p = 0.3, CI 0.4–1.4). There was no increased risk of perineal tears involving at least the internal anal sphincter in IBD patients compared with non-IBD (RR 0.7, p = 0.5, CI 0.3–1.9). Four IBD patients with significant perineal trauma were followed in a specialist obstetric injury clinic: None had pelvic floor dysfunction or incontinence at follow-up. Previous perianal disease was not associated with an increased risk of significant tears.
Conclusions: Data on Caesarean delivery and perineal trauma are reassuring for IBD patients. Whilst CS is more frequent in IBD patients, we found that all IBD indications were absolute. Emergency CS incidence is no greater in IBD patients than non-IBD, implying that Caesarean is recommended appropriately in the Combined IBD Antenatal Clinic. Perineal tears are a theoretical risk for poor future IBD outcomes. As significant perineal tears are not more common in IBD patients and healed well in our series, the promotion of normal vaginal delivery (barring other indication for CS) is advisable.

DOP29

Pregnancy outcomes in IBD patients treated with vedolizumab, anti-TNF, or conventional therapy

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Background: Women with inflammatory bowel diseases (IBD) often receive biologicals during pregnancy to maintain disease remission prior to conception and throughout pregnancy. However, data on vedolizumab exposed pregnancies (VDZE) are scarce.
Methods: This retrospective multi-centre observational study assessed outcomes of VDZE pregnancies in IBD patients (group A). European gastroenterologists were asked to report all VDZE pregnancies. Details of underlying IBD, pre- and postnatal outcomes were collected. Results were compared with anti-TNF exposed (TNFE, group B) or both immunomodulatory and biologic unexposed (IBU, group C) pregnancies. The control groups were prospectively enrolled from two separate centres.
Results: Group A included 86 pregnancies in 81 women [53% Crohn's disease (CD), 70 live births] from 31 centres in 11 countries. Groups were comparable regarding baseline characteristics though group A included more women with ileocolonic CD and perianal involvement. At conception 35% of VDZE women had active disease, 17% were on steroids and 20% on immunomodulators. Also, 54% previously failed two biologicals. Group B and C included 186 pregnancies in 155 women and 185 pregnancies in 164 women respectively (83% vs. 55% CD, 162 vs. 163 live births). Controls had less active disease at conception (B:16%, C:24%) and fewer were taking steroids (B: 8%, C: 14%). More miscarriages were seen in group A compared with B (16% vs. 13%, p = 0.46) and C (16% vs. 8%, p = 0.03). However, after excluding patients with reported active disease in pregnancy, the number of miscarriages was similar in group A compared with B (14% vs. 14%, p = 1.0) and C (14% vs. 12%, p = 0.80). Neonatal outcomes are displayed in Table 1. In live-born infants, median gestational age and birth weight were similar between groups. Also median Apgar score at birth was numerically equal in all groups. The number of premature born infants was

Abstract DOP29 – Table 1. Baseline characteristics live-born children ($n = 395$)

	Group A VDZE (n=70)	Group B TNFE (n=162)	Group C IBU (n=163)	P-value (A vs B)	P-value (A vs C)
Gender (F) (%)	42/70 (60)	86/144 (60)	77/150 (51)	1.000	0.248
Median (IQR) gestational age (weeks)	39 (38-40)	39 (38-40)	39 (38-40)	0.166	0.710
Median (IQR) Apgar score at birth	9 (9-10)	9 (9-9)	9 (9-9)	0.004	0.012
Median (IQR) birth weight (grams)	3298 (2868-3600)	3215 (2835-3555)	3237 (2867-3500)	0.452	0.393
Premature born children (%)	11/70 (16)	14/162 (9)	12/163 (7)	0.164	0.058
Small for gestational age (%)	4/70 (6)	6/162 (4)	7/163 (4)	0.494	0.738
Breastfeeding (%)	42/69 (61)	85/142 (60)	88/138 (64)	1.000	0.761
Congenital anomalies (%)	3/70 (4)	4/162 (2)	3/163 (2)	0.434	0.368
Infections during the first year of life (%)	5/70 (7)	7/67 (10)	7/59 (12)	0.556	0.380
Malignancies during the first year of life (%)	0	0	0	NA	NA

F: female; IBU: immunomodulatory and biologic unexposed; IQR: interquartile range; TNFE: anti-TNF exposed; VDZE: vedolizumab exposed. Fisher's exact test used for categorical data and Mann-Whitney U test for continuous data.

not significantly different between groups nor was the amount of reported congenital anomalies. The percentages of breastfed children were similar in all groups. During the first year of life, no malignancies were reported and the infants' infection risk did not significantly differ between groups.

Conclusions: VDZE pregnancies were associated with more miscarriages; however, active disease in pregnancy rather than drug effect seems to have been the driver of this adverse pregnancy outcome, since no significant difference was observed after exclusion of patients with reported active disease. Still, larger prospective studies are needed for confirmation.

DOP30

Factors associated with life satisfaction in people with Crohn's disease and ulcerative colitis: results from the national 2018 Crohn's and Colitis UK Inflammatory Bowel Disease Quality of Life Survey

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Background: Crohn's disease and ulcerative colitis have a negative impact on health-related quality of life (HRQoL). HRQoL is valued by patients as a 'real-world' measure of how illness impacts their day-to-day lives, going beyond direct measures of health status. Life satisfaction is a vital component of subjective HRQoL and one of the three indicators of well-being, also adversely impacted by inflammatory bowel disease (IBD). Evaluation of the factors associated with low life satisfaction in IBD may identify possible targets amenable to intervention, to improve well-being and HRQoL. The aim of this study was to identify the key factors associated with life satisfaction in a large sample of people with IBD.

Methods: Participants were invited to complete a survey, administered online and via post to members and supporters of the charity Crohn's and Colitis UK. The survey was designed to assess seven hallmarks of HRQoL, and was informed by theory of change, patient and wider IBD community priorities. The hallmarks included understanding IBD, maintaining well-being, feeling in control, overcoming stigma and reducing isolation. Exploratory χ^2 analyses were conducted to examine the factors associated with life satisfaction, including disease, demographics, and psychological variables.

Results: After data cleaning, 8061 participants with IBD were included (response rate 22.2%, mean age 45.3 years, SD 16.4). The majority of respondents were female (F, 69.2%) and had Crohn's disease (CD, 78.5%). Low satisfaction with life was identified in 11.9% of respondents. Analyses identified significant relationships between low life satisfaction and disease type (CD 13.2%, ulcerative colitis 7.1%, $p < 0.001$); disease activity (active 18%, remission 6.6%, $p < 0.001$); ethnicity (White British 11.6%, Asian, Black, Mixed, or Other ethnic group 16.4%, $p < 0.05$); perception of control over disease ($p < 0.001$); coping ($p < 0.001$); feeling left out ($p < 0.001$); feeling involved in care ($p < 0.001$); understanding own disease ($p < 0.001$); and experiencing stigma ($p < 0.001$). No

significant association was found for gender (F 12%, male 11.8%, $p = 0.281$).

Conclusions: In a large sample of participants with IBD, low life satisfaction was associated with disease characteristics (CD; active disease); individual characteristics (ethnicity); and psychological constructs (sense of control; coping; loneliness; involvement in care; understanding; perceived stigma). The psychological constructs may be amenable to intervention and support. There is the need to improve public understanding of IBD to limit the stigma felt by those with the diagnosis. Modelling of the current data and longitudinal data collection would aid our understanding of the relationships between the key variables over time.

DOP31

Development and validation of the IBD-REFER criteria: when should a general practitioner or paediatrician refer a patient for suspected IBD?

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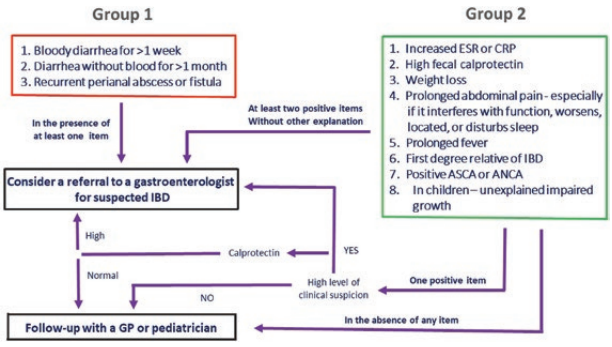
Background: Early treatment of IBD is associated with more favourite outcomes, but this requires prompt diagnosis. Unfortunately, the delay from onset of symptoms to the diagnosis of IBD may range from 6–24 months. We thus aimed to develop and validate a screening tool intended for primary care physicians that can identify early symptomatic patients as being at risk for having IBD, thereby guiding early referral.

Methods: A Delphi group of 13 experts in adult and paediatric IBD generated a list of symptoms and signs associated with IBD, supplemented by review of the literature. The list was reduced in an iterative process based on applicability and graded based on importance. For validation and data-driven formatting, the charts of 300 consecutive subjects were reviewed: 100 adult IBD patients, 100 paediatric IBD patients, and 100 controls visiting the gastroenterology clinics but not having IBD. For each subject the IBD-REFER items were scored as well as the contending available Red Flag criteria from the International Organization for the study of IBD (IOIBD). Final adjustments were applied to optimise sensitivity and specificity.

Results: The Delphi process retained 5 items as major criteria (in which ≥1 item is sufficient for early referral) and 11 as minor (≥2 items required for referral). Following removal of uninformative items and further formatting in the data-driven chart review, 11 core items were retained: 3 as major and 8 as minor (Figure).



IBD reffer criteria

https://planner.smart-abstract.com/ecco2019/submission/en/abstract/12651/content#

The final IBD-REFER criteria had a sensitivity/specificity of 98%/94% in children, and 94%/88% in adults. The concurrent performance of the IOIBD Red-Flags criteria was inferior (60%/96% in children and 63%/88% in adults, respectively).

Conclusions: The IBD-REFER criteria is a new toll suggested for guiding the selection of patients for expedited gastrointestinal consultation. In addition, gastroenterology clinics can utilise these criteria for prioritising urgent cases.

DOP32

Withdrawal of thiopurines in Crohn's disease treated with scheduled adalimumab maintenance: a prospective randomised clinical trial (DIAMOND2)

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Background: The risk:benefit ratio of concomitant use of thiopurines with scheduled adalimumab (ADA) maintenance therapy for Crohn's disease is controversial. To study the influence of withdrawal of thiopurines in patients in remission with combination therapy in an open-label, randomised, controlled trial (DIAMOND2; UMIN UMIN000009596).

Methods: Patients in corticosteroid-free clinical remission (CFCR) for ≥6 months with ADA (40 mg, s.c., every other week [e.o.w.]) scheduled maintenance combined with thiopurines were randomised to continue (Con) or discontinue (Dis) thiopurines, whereas all patients received scheduled ADA maintenance therapy for 52 weeks. The primary endpoint was the proportion of patients who had CFCR at Week 52. Secondary endpoints were mucosal healing, trough levels of ADA in serum, and safety.

Results: Fifty patients were randomised to Con or Dis groups. The Crohn's Disease Activity Index (p = 0.866), Simple Endoscopic Score for Crohn's Disease score (p = 0.450), and serum C-reactive protein (CRP) level (p = 0.694) at baseline were not significantly different between groups. CFCR prevalence at Week 52 was not significantly different between groups (log-rank, p = 0.704). Prevalence of endoscopic remission at Week 52 was not significantly different between groups (p = 1.000). Trough levels of ADA in serum were not significantly different between groups (p = 0.515). The proportion of patients with AAA positivity at Week 52 was not significantly different (p = 0.437). No serious adverse effects were observed in either group.

Conclusions: Continuation of thiopurines >6 months offers no clear benefit over scheduled ADA monotherapy. CFCR, endoscopic activity, and ADA trough level at Week 52 were not significantly different between groups (UMIN000009596).

DOP33

Long-term clinical efficacy of ustekinumab in refractory Crohn's disease : a multi-centre Belgian cohort study

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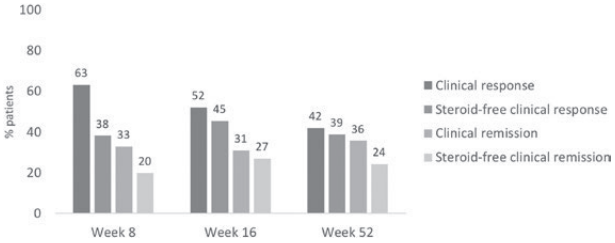
Background: Ustekinumab (UST) was recently approved in Belgium for moderate to severe Crohn's disease (CD). Long-term real-life data are currently scarce, especially in refractory populations.

Methods: We collected data in patients initiating UST therapy between September 2016 and September 2017. Patients received intravenous (IV) UST 6 mg/kg at baseline, with 90 mg subcutaneously thereafter every 8 weeks. The primary endpoints, clinical response and remission at 1 year, were defined as a reduction in Harvey Bradshaw Index (HBI) of ≥3 and an HBI ≤4, respectively. Biological response was defined as 50% drop in C-reactive protein (CRP) and/or CRP <5 mg/l and biological remission as CRP < 5 mg/l, if CRP >5 mg/l at baseline. Primary nonresponse was defined as drug stop due to the absence of clinical improvement before Week 8 while loss of response as drug stop due to secondary loss of response after initial response to the drug. Data were analysed in an intention-to-treat manner.

Results: Demographic and baseline data of the study population of 163 patients are presented in Table 1.

			Patients at baseline (n= 163) (112 females (68.7%))		
Age, years (min-max)			40 (19 - 74)		
Disease features n, (%)					
Age at diagnosis, years (min-max)			22 (6 - 66)		
A1 (< 17 years)	L1	B1	8 (4.9)	26 (16)	72 (44.1)
A2 (17-40 years)	L2	B2	110 (67.5)	31 (19)	50 (30.7)
A3 (>40 years)	L3	B3	43 (26.4)	106 (65)	40 (24.5)
Unknown	+ L4	Unknown	2 (1.2)	18 (11)	1 (0.7)
Peri-anal disease			64 (39.3)		
Concomitant conditions n, (%)					
Primary sclerosing cholangitis			4 (2.4)		
Rheumatoid arthritis			1 (0.6)		
Psoriatic arthritis			2 (1.2)		
Ankylosing spondylitis			20 (11.9)		
Psoriasis			7 (4.2)		
Uveitis/episcleritis			10 (5.9)		
Past history of CD surgery n, (%)			101 (61.9)		
Smoking status n, (%)					
Current			47 (28.9)		
Never			72 (44.2)		
Former			38 (23.3)		
Unknown			6 (3.6)		
Prior exposure to biologic n, (%)					
1 anti-TNF#			162 (99.4)		
2 anti-TNF			126 (77.3)		
2 anti-TNF + vedolizumab			116 (71.2)		
Concomitant medications at baseline n, (%)					
Steroids			73 (43.7)		
Azathioprine/ 6MP			20 (11.9)		
Methotrexate			9 (5.4)		
None			76 (47.9)		
Clinical and biological data at baseline median (IQR 25 -75)					
Harvey-Bradshaw index (n= 153; n ≤ 4= 11)			10 (7-14)		
C-Reactive Protein (mg/lit) (n= 150; n ≤ 5mg/l= 40)			16.2 (10.6 – 28.8)		

Importantly all patients were refractory to at least one anti-TNF and >70% of patients to anti-TNF and vedolizumab. Data at 1 year were available for all but 8 patients due to loss of follow-up. Eleven patients with HBI ≤ 4 at baseline were excluded. By 1 year of follow-up, 42.1% experienced a clinical response including 35.7% of patients with clinical remission. 38.8% and 24.3% of the population obtained a steroid-free clinical response and remission, respectively.



Treatment intensification (new IV infusion and/or q4w) was reported in 6.6% of patients. UST was discontinued in 35.5% of patients after 1 year. Reasons for UST withdrawal were primary nonresponse (n = 3), intense arthralgia (n = 1), loss of response (n = 47), and patient decision (n = 4). CRP significantly decreased from baseline (16.1 mg/l, IQR [10.6–28.8]) to 6.6 mg/l at 1 year (IQR [6.6–15.1], $p < 0.0001$). At Week 52, a 50% drop in CRP was observed in 33.6% and 25.4% achieved a biological remission. Eleven patients (6.7%) of patients experienced side effects, including one patient who discontinued therapy due to intense arthralgia.

Conclusions: This real-life cohort study confirms the clinical efficacy of ustekinumab at 1 year even in a population of highly refractory CD patients.

DOP34

Disease activity patterns during the first 5 years after diagnosis in children with ulcerative colitis: a population-based study

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Background: The aim of this study was to define clusters of disease activity of paediatric UC in a population-based inception cohort during the first 5 years after diagnosis and to identify prognostic risk factors based on findings at the diagnosis and in the first 6 months after.

Methods: All UC patients from SIGENP IBD registry and a follow-up of at least 5 years were included. Patients with incomplete data (disease location, hospitalisations, endoscopy, PUCAI, medication use, surgery) were excluded. Active disease was defined for each yearly semester as follows: clinical activity (PUCAI>35); endoscopic activity (Mayo>1); hospitalisation; surgery; need for treatment escalation. Formula-based clusters were then generated based on five previously published activity patterns in adults.[1] Prediction models were created based on clinical, endoscopic, and laboratory findings at the diagnosis and at 6-month follow-up.

Results: Two hundred and twenty-six patients were identified (53% F; median age 11, IQR 7–13). One hundred nine (48%) had a moderate-to-severe disease at the diagnosis. One hundred twenty-seven (53%) presented with a pancolitis, 29 (13%) with an extensive colitis, 24 (14%) with a left-sided colitis, and 36 (16%) with a proctitis. Clusters of disease activity are shown in Figure 1. Ulcerative colitis was classified as moderate–severe chronically active in 19% of patients (N = 42), chronic-intermittent in 14% (N = 31), while in 33% (N = 75) the disease was classified as quiescent. Overall, 57% of the entire population (N = 129) had an active UC in the first 2 years after the diagnosis, then a sustained remission. A high CRP (OR 3.79; 95% CI 1.28–11.2) and platelet count (OR 3.41; 95% CI 1.17–9.93) at the diagnosis were positively associated with a chronically active disease at follow-up, while an endoscopic recurrence at 6 months was negatively associated with a quiescent course thereafter (OR 0.37; 95% CI 0.13–0.96). Eight per cent of patients needed surgery at the end of the follow-up, none in the quiescent group (p = 0.04).

Conclusions: More than one-third of paediatric patients with UC present a chronically active or chronic intermittent disease course during the first 5 years after the diagnosis. A significant group of patients has an active disease in the first 2 years and a sustained remission thereafter. Interestingly, about 30% of patients experience a disease flare at the diagnosis followed by a quiescent disease course in the next 5 years of follow-up.

Clusters of disease activity

Reference

1. Henriksen M, Jahnsen J, Lygren I, *et al*. Ulcerative colitis and clinical course: results of a 5-year population-based follow-up study (The IBSEN Study). *Inflamm Bowel Dis* 2006;12:543–50.

DOP35

Innate immune dysregulation, detectable up to 6 years before the diagnosis of Crohn's disease, is significantly amplified in patients with a complicated phenotype

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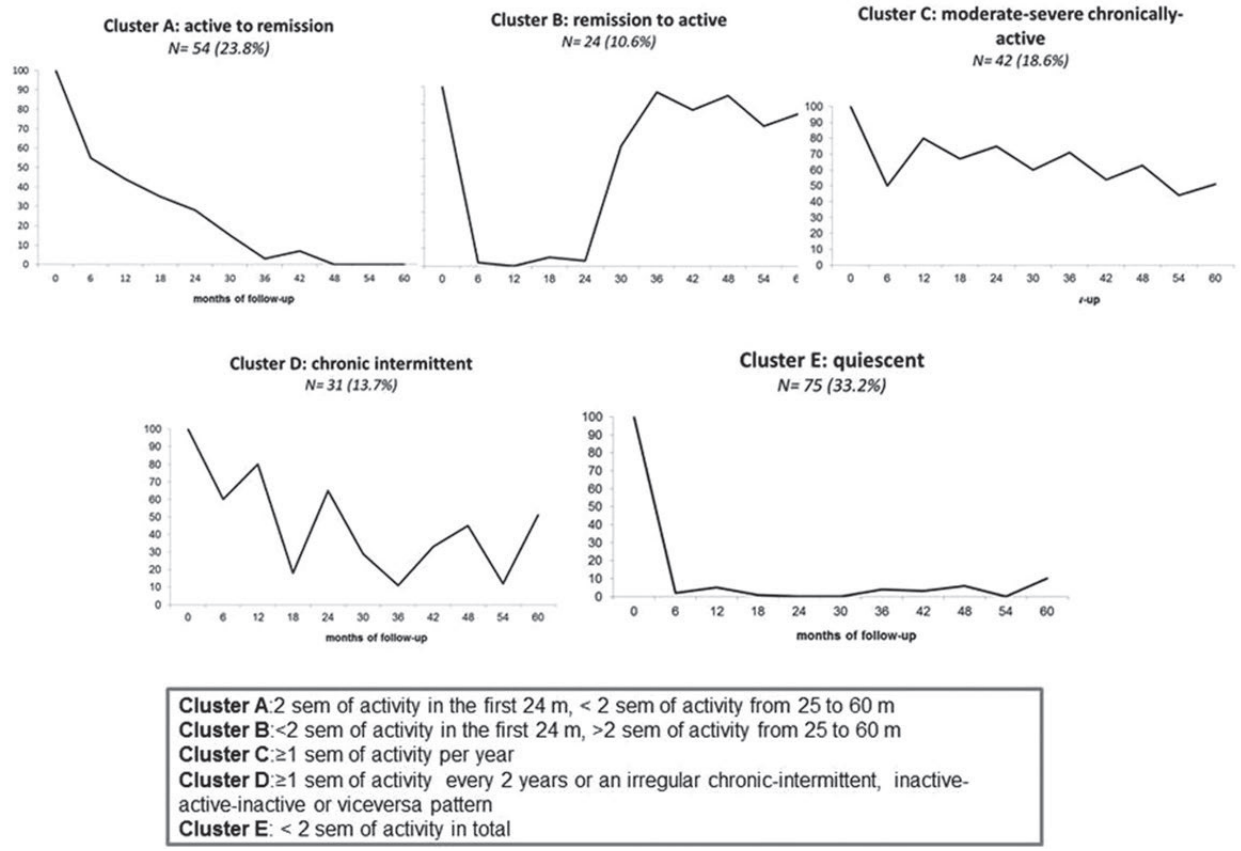
Background: Crohn's disease (CD) is a progressive and destructive disease. At diagnosis, up to 1/3 of patients have a complicated phenotype defined as stricturing (B2), internal penetrating (B3) CD, or surgery. We evaluated anti-microbial antibodies and protein markers in multiple samples long before diagnosis to assess whether complicated vs. non-complicated CD at diagnosis was associated with pre-diagnostic biomarkers.

Abstract DOP34



Methods: Pre-diagnosis serum samples (~2, 4, and 6 years prior to diagnosis) were obtained from 200 patients with CD and 200 healthy controls (HC). Samples were tested for a panel of anti-microbial antibodies and 1129 protein markers (SomaLogic panel). A complicated CD phenotype at diagnosis was defined based on ICD-9 or CPT codes (B2, B3, or surgery). The association between each marker and complication was assessed via Cox regression. Significant markers passing a false-discovery rate of 20% were selected for different time before diagnosis (–2Y, –4Y, and -6Y). In addition, for proteomic markers, biological pathways enriched in the set of predictive markers were identified via Fisher exact test.
Results: Forty-seven subjects (24%) had a B2 (n = 36) or B3 (n = 9) phenotype or surgery (n = 2) at diagnosis. Figure 1 shows anti-microbial antibodies as well as protein markers selected at different years before diagnosis. At 6 years prior to diagnosis, the difference of anti-microbial antibody titers was already significant between complicated and non-complicated CD. Thirty protein markers, involved in the activation of immune system and/or inflammation, were associated with complicated CD. Most protein markers such as CRP, C9, and C5 were up-regulated, while few markers including SERPINA4 and c-Kit were down-regulated in patients developing complications. Pathway analysis identified higher activation of the innate immune system and complement/coagulation cascades for both 4 and 6 years before diagnosis in complicated CD vs. uncomplicated CD. The difference of those activated pathways was prominent at 6 and 4 years before diagnosis and disappeared as approaching the time of diagnosis. Most of pre-diagnostic biomarkers were increased in both complicated and non-complicated CD vs. healthy controls.
Conclusions: Complicated CD at diagnosis is associated with higher serum levels of anti-microbial antibodies and a different profile of proteins, vs. non-complicated CD, years before diagnosis. Findings suggest that innate immune activation with involvement of complement pathways occur early in the natural history of complicated CD many years before diagnosis.

DOP36

Gut microbial variations in patients with quiescent Crohn's disease predict subsequent disease flare

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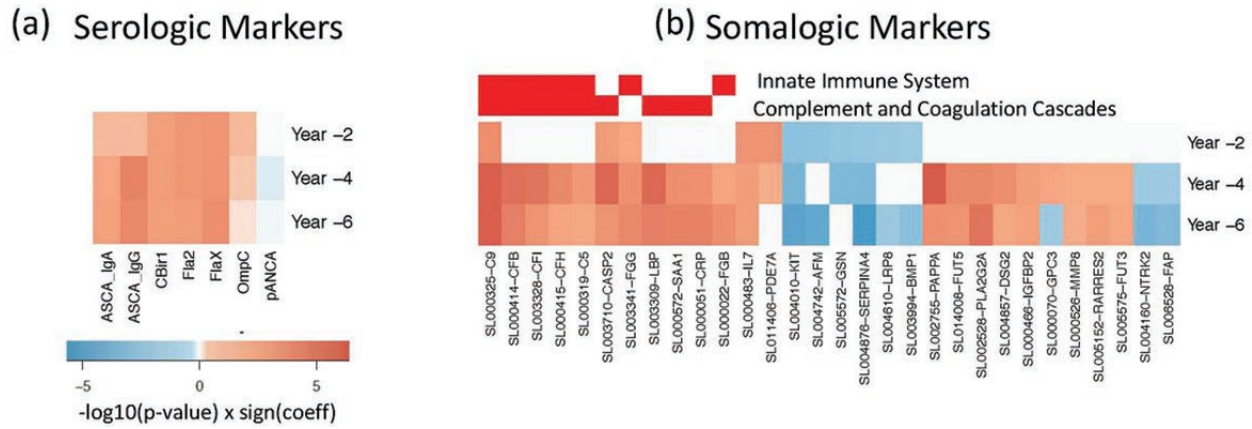
Background: Crohn disease (CD) is a chronic relapsing-remitting gut inflammatory disorder with a heterogeneous unpredictable course. Dysbiosis occurs in CD, however, whether microbial dynamics in quiescent CD are instrumental in increasing the risk for a subsequent



Abstract DOP35 – Figure 1. Heatmap showing the association between Serologic (a) as well as SomaLogic markers (b) with complication in Crohn's disease based on Cox regression. (a) For all Serologic markers, the heatmap shows the *p*-value of association in the $-\log_{10}$ scale multiplied by the sign of the coefficient in the Cox regression. OmpC and pANCA were not found to be significantly associated to complications ($p > 0.05$). (b) Selected proteomic markers passing a 20% false discovery rate, which were selected in at least two of the three time points. As shown, some of the markers, including KIT, AFM, GSN, SERPINA4, and LRPP8, were found to be down-regulated in patients developing complication.

flares remains undefined. We aimed to identify whether changes in the microbiome precede and predict clinical relapse.

Methods: We analysed the long-term dynamics of microbial composition in a prospective observational cohort of patients with quiescent CD (45 cases, 217 samples) undergoing rigorous clinical, biochemical, and mucosal follow-up over 2 years or until a clinical flare occurred. Clinical assessment, faecal calprotectin, faecal microbial characterisation, and CRP were measured routinely every 3 months. Patient underwent video capsule endoscopy (VCE) every 6 month. 16S rRNA gene V4 variable region using Illumina adapted universal primers 515F/806R was conducted to characterise microbial variation. Machine learning was employed to prioritise microbial and clinical factors that discriminate between relapsers and non-relapsers in the quiescent phase.

Results: Of the 45 patients with quiescent CD, 12 (27%) flared during follow-up. Samples in quiescent patients preceding flare showed significant reduced abundance of Christensenellaceae and S24.7, and increased abundance of Gemellceae in comparison to those patients in remission throughout, and a composite 'flare index' summarising those microbial taxa, was significantly higher in patient who subsequently flared vs. those who remained in remission (p = 9.2e–11). Notably, higher individualised microbial instability in the quiescent phase was associated with higher risk of subsequent flares (hazard ratio 11.32, 95% CI 3–42, p = 0.0035) using two pre-flare samples. When prioritising clinical, demographic, and microbial factors in a supervised learning Random Forest algorithm to predict a subsequent flare, the top contributing factors were the 'flare index' and the intra-personal microbial instability. Those were followed by BMI, capsule endoscopy Lewis score, and microbial richness. Importantly, CRP, treatment exposure, and calprotectin were not within the top 5 contributing factors in the prediction model

Conclusions: Individualised microbial variations in quiescent CD can precede and predict future exacerbation. These results may imply that microbiome changes during the quiescent phase may be the cause or an associated reporter of other factors upstream of the inflammatory process pre-flare that subsequently lead to a disease flare.

DOP Session 5 - Old and new treatment

DOP37

Vedolizumab-induced endoscopic remission in anti-TNF exposed and anti-TNF naïve IBD patients: a large single-centre experience

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Background: Vedolizumab (VDZ), a gut-focussed biological agent targeting α4β7 and hence preventing leukocyte trafficking into the intestinal wall, has demonstrated efficacy and safety in patients with Crohn's disease (CD) and ulcerative colitis (UC). Real-life endoscopic remission data are still very limited, especially in anti-TNF naïve patients. The present study compared VDZ-induced endoscopic outcome in anti-TNF naïve and exposed patients.

Methods: We retrospectively assessed the medical charts of all IBD patients (n = 408) who initiated VDZ therapy at our tertiary referral centre after the pivotal clinical trials, from January 2015 till April 2018, and who had a minimal follow-up of 6 months at our centre. Patients with an ostomy (n = 11) or ileoanal pouch (n = 20), as well patients without active disease (n = 41) at start were excluded from the analysis. All patients received VDZ 300 mg IV at Week 0, 2, 6, and q8w thereafter. CD patients received an additional dosage at Week 10. Endoscopic remission was defined as a Mayo endoscopic subscore ≤1 at Week 14 (as per national reimbursement criteria) for UC, and absence of ulcerations at month 6 for CD. All endoscopies were performed by the same 3 IBD staff members. Non-responder imputation was applied for patients discontinuing VDZ prior to the endoscopic endpoint.

Results: Of the 336 patients included (53.3% CD, 46.7% UC), 80.1% had been exposed to at least one anti-TNF agent (37.2% one, 39.0% two, 3.9% three anti-TNF agents), with endoscopic outcome available in 96.1% of patients. After a median (IQR) of 14.0 (13.6–14.6) weeks, 56.4% of UC patients achieved endoscopic remission, whereas 41.9% of CD patients experienced endoscopic remission after 22.1 (21.6–25.0) weeks (L2 (62.5%) vs. L1+L3 (38.5%), $p = 0.03$). No difference in disease duration could be found between remitters and non-remitters ($p = 0.70$). Significantly more anti-TNF naïve vs. exposed patients achieved endoscopic remission (OR 2.9, Figure 1).

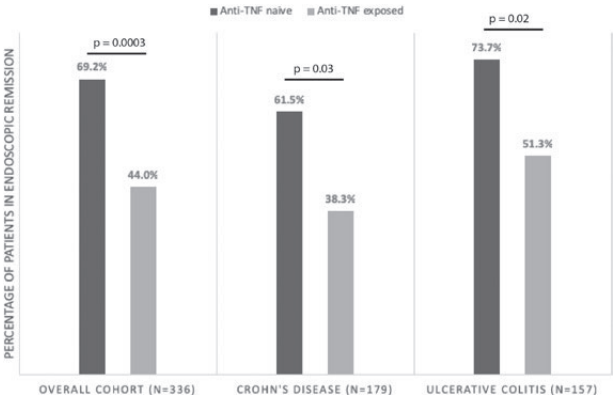

Figure 1. Percentage of patients achieving endoscopic remission, compared between anti-TNF naive and anti-TNF exposed patients.

No difference in remission rates was observed between patients failing 1 vs. ≥2 anti-TNF agents ($p = 0.26$). Similarly, no effect of corticosteroids or immunomodulators during induction could be observed with regard to endoscopic remission ($p = 0.61$, $p = 0.86$ respectively).

Conclusions: This is the biggest, real-life, single-centre cohort study confirming that VDZ can induce endoscopic remission in both CD and UC patients, without any effect of concomitant therapy during induction. Although anti-TNF naive patients had a significantly better outcome, 44% of anti-TNF exposed patients did achieve endoscopic remission.

DOP38

A vedolizumab specific four-gene colonic signature accurately predicting future endoscopic remission in patients with inflammatory bowel disease

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Background: Vedolizumab, a monoclonal antibody targeting α4β7 integrin and mainly inhibiting gut lymphocyte trafficking, has been approved for the treatment of both Crohn's disease (CD) and ulcerative colitis (UC). Due to the increasing availability of therapeutic compounds in inflammatory bowel disease (IBD), predictive biomarkers are urgently awaited in order to help clinicians decide between anti-TNF, vedolizumab or other therapies.

Methods: We obtained inflamed colonic biopsies from 31 patients (20 UC, 11 CD) prior to initiation of vedolizumab. Similarly, inflamed colonic biopsies (15 UC, 9 CD) were collected from 24 patients initiating anti-TNF therapy (Table).

	Vedolizumab ($n = 31$)	Anti-TNF cohort ($n = 24$)
Diagnosis, *n* (%) UC / CD	20 (64.5) / 11 (35.5)	16 (66.7) / 8 (33.3)
Age, years (median, IQR)	45.3 (29.6–56.3)	36.0 (22.0–54.9)
Gender, *n* women (%)	17 (54.8)	15 (62.5)
Disease duration, years (median, IQR)	8.4 (4.0–15.3)	0.5 (1.9–7.0)
Disease location L1-L2-L3-L4 / E1-E2-E3	0-2-9-2 / 3-10-7	0-2-6-1 / 0–13-3
Disease behaviour B1-B3-B3 perianal	6-3-2-5	4-3-1-2
Steroid use during induction, n (%) Topical—Systemic	10 (32.3)–8 (25.8)	5 (16.1)–7 (22.6)
Previous-anti-TNF exposure	21	NA
Endoscopic remission, number (%)	19 (61.3)	8 (33.3)

Clinical characteristics of the vedolizumab and anti-TNF treated cohort

RNA was extracted and single-end RNA sequencing was performed using Illumina HiSeq4000. Normalisation and differential expression was done using DESeq2 R package. Pathways were analysed with Ingenuity Pathway Analysis (IPA). Using randomised generalised linear modelling (RGLM), a predictor for vedolizumab-induced endoscopic remission (absence of ulcerations at month 6 for CD; Mayo endoscopic sub-score ≤1 at Week 14 for UC) was identified in a randomly generated test cohort ($n = 20$) and validated in 11 independent samples. Through unsupervised consensus clustering, we validated the marker in a publicly available microarray dataset (GSE73661), and studied vedolizumab specificity in the anti-TNF treated cohort.

Results: Forty-four genes (25 down, 19 up) were significantly differently expressed between future vedolizumab remitters and non-remitters. Involved pathways included glucocorticoid receptor signalling, differential regulation of cytokines in intestinal epithelial cells, granulocyte adhesions and diapedesis. Using these 44 differentially expressed genes as input for the RGLM modelling, we identified a 4-gene signature which could accurately split remitters and non- remitters in both the discovery (accuracy 90.9%, $p = 0.02$) and validation (100%, $p = 0.006$) set. Using the same 4-gene signature we could accurately discriminate prospective future remitters from non-remitters in a publicly available microarray data set of 13 open-label vedolizumab treated UC patients (84.6%, $p = 0.02$). In contrast, this 4-gene signature was not predictive for anti-TNF induced endoscopic remission (62.5%, $p = 0.65$).

Conclusions: We identified and validated the first, vedolizumab-specific predictive 4-gene expression signature which may guide treatment strategy in IBD patients with colonic involvement.

DOP39

Safety of combination biologic and anti-rejection therapy post-liver transplantation in patients with inflammatory bowel disease: London Ontario experience

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Background: Despite anti-rejection immunosuppressive therapies post-liver transplantation (LT), patients with concurrent inflammatory bowel disease (IBD) may have persistent bowel inflammation that requires addition of biologic therapy. The aim of this study was to evaluate the safety of combination biologic and anti-rejection therapy in IBD patients after LT.
Methods: The LT Registry at London Health Sciences Centre (LHSC) was searched to identify all patients undergoing LT from 1985 to 2018. IBD patients initiated on biologic treatment post-LT, in addition to anti-rejection therapy, were eligible for inclusion. Medical chart review was conducted to extract safety outcomes, including rates of infections, malignancy, colectomy and death.
Results: Nineteen patients were included (78.9% male, mean age 46.0 years, 8 patients with ulcerative colitis), followed for a median duration of 19 months (IQR 5.8, 30.8). Indications for LT included: primary sclerosing cholangitis (PSC) (14/19, 73.7%), autoimmune hepatitis (AIH) (2/19, 10.5%), AIH-PSC overlap syndrome (2/19, 10.5%), and biliary atresia (1/19, 5.3%). Post-LT, six patients were treated with only TNF antagonists (infliximab in 5 patients, golimumab in 1 patient); eight patients with only anti-integrin therapies (vedolizumab in 7 patients, natalizumab in 1 patient); and five patients with sequential TNF antagonists followed by either ustekinumab (n = 2) or vedolizumab (n = 3). Six patients required long-term prednisone. The most commonly used anti-rejection therapies were tacrolimus and mycophenolate mofetil. Disease course was complicated by infections in nine patients (47.4%), most commonly Clostridium difficile colitis (4/19, 31.6%). One patient had recurrent C. difficile infection and one patient had CMV colitis and viremia. Other infections included cholangitis (n = 2), perianal abscess (n = 1), JC virus seroconversion but without progressive multifocal leukoencephalopathy (n = 1) and hospital-acquired pneumonia (n = 1). Two patients required colectomy for refractory colitis. One patient required re-transplantation due to PSC recurrence. No deaths or malignancies were reported although one patient developed low-grade colonic dysplasia.
Conclusions: This is the largest reported case series from a single centre to date evaluating the safety of combination biologic therapy with anti-rejection regimens in IBD patients post-LT. Whilst there appeared to be an increased risk of enteric infections, especially C. difficile, there were no life-threatening infections reported. Active screening for enteric infections should be pursued in these patients presenting with increased IBD symptoms.

DOP40

Effectiveness and safety of reference infliximab and biosimilar in Crohn's disease: a French equivalence study

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Background: CT-P13 is a biosimilar of the reference product (RP) infliximab with demonstrated efficacy and safety in rheumatoid arthritis and spondylarthritis. It has been approved for the treatment of Crohn's disease (CD) based on that experience without specific studies conducted to examine its effects in CD. The aim of the present study was to compare the effectiveness and safety of CT-P13 and the RP in infliximab-naive patients with CD.
Methods: This comparative equivalence cohort study was conducted using the nationwide health administrative database (SNDS) which covers more than 99% of the French population (around 65,000,000 people) and contains all outpatient (drugs, imaging or endoscopic investigations) and inpatient information (diagnoses, procedures performed and expensive drugs dispensed). Infliximab-naive patients with CD over 15 years of age who started RP or CT-P13 with no other indications for infliximab were included. The primary outcome was a composite endpoint (death, CD-related surgery, all-cause hospitalisation and reimbursement of another biotherapy). Equivalence was defined as a 95% confidence interval (CI) of the hazard ratio (HR) of CT-P13 vs. RP in a multi-variable marginal Cox model situated within the prespecified margins [0.80–1.25].
Results: In total, 5050 patients were included between 1 March 2015 and 30 November 2016 (2551 received RP and 2499 received CT-P13). Patient characteristics at cohort entry were well balanced. Overall, 1147 patients in the RP group and 952 patients in the CT-P13 group met the composite endpoint (including 838 and 719 hospitalisations in RP and CT-P13 groups, respectively). In multivariable analysis of the primary outcome, CT-P13 was equivalent to RP (HR 0.92; 95% CI: 0.85–0.99). Combination therapy with a thiopurine with (HR 0.71; 95% CI: 0.63–0.80) or without (HR 0.81; 95% CI: 0.73–0.90) prior use of thiopurine was associated with a lower composite event rate. Multi-variable analysis of secondary outcomes did not reveal any significant differences between CT-P13 and RP in terms of the following events: CD-related hospitalisation (HR 1.00; 95% CI: 0.90–1.11), and CD-related surgery (HR 1.09; 95% CI: 0.92–1.28). No differences in safety outcomes were observed between the two groups, (serious infections (HR 0.82; 95% CI: 0.61–1.11), tuberculosis (HR 1.10; 95% CI: 0.36–3.34) and solid or haematological malignancies (HR 0.66; 95% CI: 0.33-1.32).
Conclusions: The effectiveness of CT-P13 appears to be equivalent as that of RP for infliximab-naive patients with CD. No difference was observed for safety outcomes.

DOP41

Efficacy and safety of open-label treatment with tofacitinib 10 mg twice daily in patients with ulcerative colitis with clinical response, but not remission, after 52 weeks of maintenance therapy: data from the OCTAVE studies

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Background: Tofacitinib is an oral, small-molecule JAK inhibitor approved in several countries for the treatment of ulcerative colitis (UC). We evaluated efficacy and safety of tofacitinib in patients with clinical response, but not remission, after 52 weeks of maintenance therapy in the OCTAVE Sustain study, who subsequently received tofacitinib 10 mg twice daily (BID) in an ongoing, open-label, long-term extension (OLE) study (OCTAVE Open; data as of November 2017).[1]

Methods: We evaluated clinical response, remission, and mucosal healing based on Mayo score (using local endoscopic reading and non-responder imputation) in patients with clinical response but not remission (based on central endoscopic reading at Week 52 of OCTAVE Sustain) who received tofacitinib 10 mg BID in the OLE study. Efficacy is reported at Month (M) 2, M12, and M24 of the OLE by subgroups of prior tumour necrosis factor inhibitor (TNFi) failure (yes/no). Safety was assessed throughout the study.

Results: Eighty patients were included in the analysis (18 received placebo in OCTAVE Sustain; 28 received tofacitinib 5 mg BID; 35 received 10 mg BID; 1 patient was randomised into OCTAVE Sustain in error and received 10 mg BID in the OLE). Thirty-eight of 82 (46.3%) had prior TNFi failure per induction baseline. Clinical response at M24 was maintained by 69.5% (41/59), 65.4% (17/26), and 72.7% (24/33) of patients overall, and with and without prior TNFi failure, respectively. By M2, the proportion of patients who had improved to remission, overall and for patients with and without prior TNFi failure, was 58.5% (48/82), 60.5% (23/38), and 56.8% (25/44), respectively. M2 remission rates were 77.8% (14/18) for patients who had received placebo in OCTAVE Sustain, 57.1% (16/28) for patients who had received 5 mg BID, and 50.0% (18/36) for patients who had received 10 mg BID (Figure 1). A summary of safety in the OLE clinical responder subpopulation is presented (Table 1).

Conclusions: Over 50% of patients with UC who completed OCTAVE Sustain as clinical responders improved to remission within 2 months of receiving 10 mg BID in the OLE study. Efficacy was observed regardless of prior TNFi failure status. No new safety concerns associated with tofacitinib emerged with regard to the overall study population.[1]

Reference

1. Lichtenstein GR. Tofacitinib, an oral Janus kinase inhibitor, in the treatment of ulcerative colitis: open-label, long-term extension study. *Am J Gastroenterol* 2017;112(S1): Abstract 714.

DOP42

Dietary therapies induce rapid response and remission in active paediatric Crohn's disease

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Background: Dietary therapies are increasingly utilised to induce remission in children with active Crohn's disease (CD). Medical therapies such as steroids and anti-TNF induce rapid response within the first 2–3 weeks. The goal of this study was to evaluate the early response rate (significant response or remission) in response to two different dietary therapies by Week 3 and to assess whether response by Week 3 was predictive of remission by Week 6.

Methods: We utilised the data from the 3 and 6 week visits in the Crohn's disease exclusion diet (CDED) trial, which was a multi-centre randomised controlled trial using two different and successful strategies for induction of remission. It was conducted among children with mild-to-moderate luminal CD, receiving either exclusive enteral nutrition (EEN), using 100% of calories from EN (Modulen, Nestle Health) or the CDED with partial enteral nutrition (PEN; 50% of calories from PEN). Patients were evaluated at baseline, Week 3, and Week 6. Remission was assessed by the use of the paediatric Crohn's disease activity index (PCDAI; defined as a PCDAI ≤10) using intention to treat (ITT) analysis. Response was defined as a drop in ITT PCDAI of 12.5 points or remission. Response, remission, CRP, albumin, and adherence to diet were evaluated at each visit.

Results: Seventy-four patients were randomised, 40 allocated to CDED+PEN and 34 to EEN. Mean (±standard deviation) age was 14.2 ± 2.7 years in total cohort. Pooled response rate was present in 61/74 (82.4%) patients by Week 3. Pooled remission rate was obtained in 69% by Week 3. By Week 6, 56/74 patients were in ITT clinical remission (75.6%). Among patients in remission at Week 6, 85% were already in clinical remission by Week 3, and a significant drop in inflammation was present (Table 1)

Table 1. Clinical and inflammatory parameters.

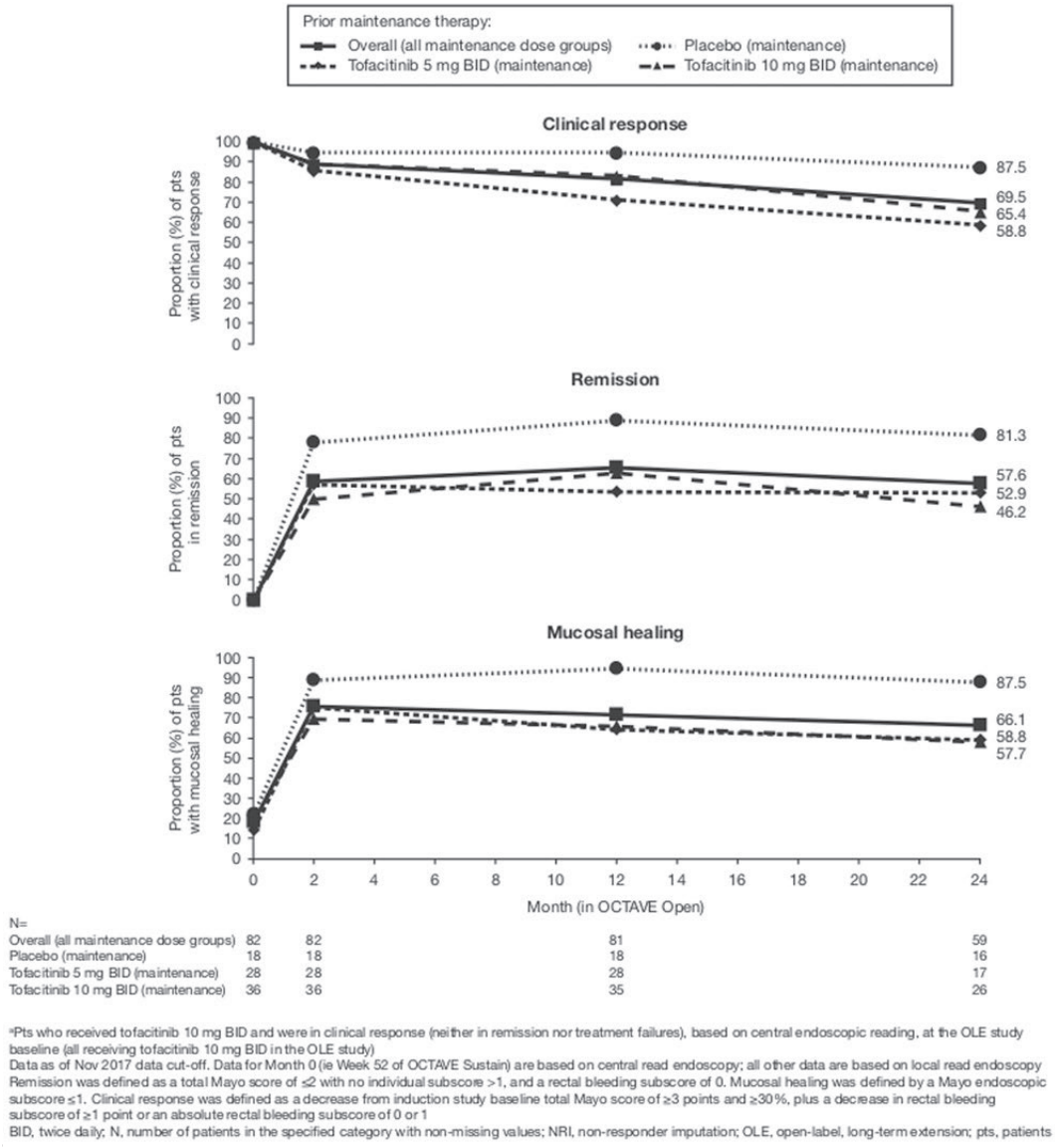
Parameter	CDED+PEN	EEN	Total
PCDAI week 0 (Median)	25 (IQR 20-35)	27.5 (IQR 18.75-32.5)	27.5 (IQR 20- 34.37)
PCDAI Week 3 (Median)	5 (IQR 0-12.5)	5 (IQR 0-10)	5 (IQR 0-10.62)
CRP week 0 (Median)	23.6 (IQR 9.8-54.2)	24 (IQR 10-52.5)	24 (IQR 9.8-52.8)
CRP week 3 (Median)	5 (IQR 3.4-8.2)	5 (IQR 1.1-7.7)	5 (IQR 2.4-8.1)
Albumin week 0 (Mean±std)	3.74±0.4	3.67±0.45	3.71±0.42
Albumin week 3 (Mean±std)	4±0.4	4.13±0.4	4.06±0.41
Response week 3	34/38, 89.4%	27/34, 79.4%	61/74 ,82.4%
Remission week 3	27/38, 71%	24/34, 70.5%	51/74, 68.9%
% response week 3/ remission week 6	30/31, 96.7%	24/25, 96%	54/56, 96.4%
% remission wk3 /remission week 6	26/31, 83.8%	22/25, 88%	48/56, 85%

** None of the variables were significantly difference between groups.

Among patients in remission at Week 6, 54/56 (96.4%) had obtained a good response or remission to therapy by 3 weeks.

Conclusions: Dietary therapy caused a rapid clinical improvement and response by Week 3, which was equivalent with both diets. Patients who failed to respond by Week 3 were unlikely to reach remission by Week 6.

Abstract DOP41



[a]Pts who received tofacitinib 10 mg BID and were in clinical response (neither in remission nor treatment failures), based on central endoscopic reading, at the OLE study baseline (all receiving tofacitinib 10 mg BID in the OLE study)
Data as of Nov 2017 data cut-off. Data for Month 0 (ie Week 52 of OCTAVE Sustain) are based on central read endoscopy; all other data are based on local read endoscopy
Remission was defined as a total Mayo score of ≤2 with no individual subscore >1, and a rectal bleeding subscore of 0. Mucosal healing was defined by a Mayo endoscopic subscore ≤1. Clinical response was defined as a decrease from induction study baseline total Mayo score of ≥3 points and ≥30%, plus a decrease in rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of 0 or 1
BID, twice daily; N, number of patients in the specified category with non-missing values; NRI, non-responder imputation; OLE, open-label, long-term extension; pts, patients

Figure 1. Rates of clinical response, remission, and mucosal healing in the OLE study maintenance clinical responder subpopulation[a] overall and by maintenance treatment received in the prior OCTAVE sustain study, NRI. [a]Patients who received tofacitinib 10 mg BID and were in clinical response (neither in remission nor treatment failures), based on central endoscopic reading, at the OLE study baseline (all receiving tofacitinib 10 mg BID in the OLE study). Data as of November 2017 data cut-off. Data for Month 0 (ie, Weak 52 of OCTAVE sustain) are based on central read endoscopy; all other data are based on local read endoscopy. Remission was defined as a total Mayo score of ≤2 with no individual subscore >1, and a rectal bleeding subscore of 0. Mucosal healing was defined by a Mayo endoscopic subscore ≤1. Clinical response was defined as a decrease from induction study baseline total Mayo score of ≥3 points and ≥30%, plus a decrease in rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of 0 or 1.
BID, twice daily; N, number of patients in the specified category with non-missing values; NRI, non-responder imputation; OLE, open-label, long-term extension; pts,, patients.

DOP43

Long-term efficacy of tofacitinib in patients who received extended induction therapy: results of the OCTAVE open study for tofacitinib delayed responders

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Background: Tofacitinib is an oral, small-molecule JAK inhibitor approved in several countries for the treatment of ulcerative colitis (UC). The efficacy and safety of tofacitinib was shown in three Phase 3, randomised, placebo-controlled trials in patients

Abstract DOP41 – Table 1. Summary of safety in the OLE study for the maintenance clinical responder subpopulation.

Table. Summary of safety in the OLE study for the maintenance clinical responder subpopulation	
Treatment Emergent Adverse Events,[a] n (%)	**Maintenance clinical responder subpopulation (N=82)**
Adverse event	61 (74.4)
Serious adverse event	9 (11.0)
Serious infection	2 (2.4)
Opportunistic infection[b]	0 (0.0)
Herpes zoster adverse event	2 (2.4)
Herpes zoster serious adverse event	1 (1.2)
Malignancies (excl. NMSC)[b]	0 (0.0)
NMSC[b]	2 (2.4)
MACE[b]	0 (0.0)
Gastrointestinal perforation[b]	0 (0.0)
[a]All causalities [b]Adjudicated events Data as of Nov 2017 data cut-off MACE, major adverse cardiovascular event; N, number of patients in the clinical responder subpopulation; n, number of patients with the specified response within the given category; NMSC, non-melanoma skin cancer; OLE, open-label, long-term extension; SAE, serious adverse event	

with moderately to severely active UC.[1] Patients who received tofacitinib 10 mg twice daily (BID) for 8 weeks in OCTAVE Induction 1 and 2 (NCT01465763 and NCT01458951) and did not achieve clinical response—ie, induction non-responders (IndNR)—could enter an ongoing, Phase 3, multi-centre, open-label, long-term extension (OLE) study (NCT01470612). Data up to 3 years for IndNR patients who responded to extended induction with tofacitinib 10 mg BID (delayed responders) are presented.

Methods: We present an update of previous analyses of delayed responders to 16 weeks of tofacitinib 10 mg BID (8 weeks' induction + 8 weeks' OLE; as of November 2017, database not locked). Patients who did not show clinical response after 16 weeks on tofacitinib 10 mg BID were required to discontinue. For delayed responders, clinical response, remission, and mucosal healing (MH) were evaluated at Months (M) 2, 12, 24, and 36 in the OLE study. Subgroup analysis by prior tumour necrosis factor inhibitor (TNFi) failure status was performed.

Results: Of 295 IndNR patients, 50.7% achieved clinical response (delayed responders) by OLE M2, of whom 72.2%, 61.3%, and 54.3% showed clinical response at M12, M24, and M36, respectively. Corresponding values starting at M12 for MH were 56.8%, 52.7%, and 51.4%, respectively; approximately 45% of patients were in remission at each time point after M2 (Table 1). Analyses by prior TNFi failure subgroup showed similar trends over time. M12 efficacy measures of delayed responder patients were similar to M12 responses of 8-week tofacitinib 10 mg BID clinical responders who stayed on this dose in OCTAVE Sustain (41.0% remission; 46.2% MH; 61.8% clinical response). Proportions of delayed responder patients with adverse and safety events of special interest were similar to 8-week clinical responder patients.

Conclusions: The majority of delayed responder UC patients who achieved clinical response after extended induction with tofacitinib 10 mg BID demonstrated a durable response up to 3 years. A substantial number of patients maintained clinical response, MH and remission. Effects were generally similar regardless of prior TNFi failure status. Proportions of delayed responder patients who achieved clinical response, MH and remission at M12 were similar to patients who responded to 8 weeks of treatment.

Table 1. Summary of efficacy endpoints of delayed responder patients in OLE (NRI).

Table. Summary of efficacy endpoints of delayed responder pts[a] in OLE (NRI)				
	M2[b]	**M12[c]**	**M24[c]**	**M36[c]**
Remission, n (%)[d,e]				
All delayed responders	41/148 (27.7)	66/144 (45.8)	64/142 (45.1)	47/105 (44.8)
Prior TNFi failure				
Yes	16/85 (18.8)	34/84 (40.5)	34/80 (42.5)	27/64 (42.2)
No	25/63 (39.7)	32/60 (53.3)	30/62 (48.4)	20/41 (48.8)
Mucosal healing, n (%)[d,f]				
All delayed responders	61/148 (41.2)	84/148 (56.8)	77/146 (52.7)	55/107 (51.4)
Prior TNFi failure				
Yes	27/85 (31.8)	46/85 (54.1)	43/83 (51.8)	33/66 (50.0)
No	34/63 (54.0)	38/63 (60.3)	34/63 (54.0)	22/41 (53.7)
Clinical response, n (%)[d,g]				
All delayed responders	144/148[h] (97.3)	104/144 (72.2)	87/142 (61.3)	57/105 (54.3)
Prior TNFi failure				
Yes	81/85[h] (95.3)	61/84 (72.6)	48/80 (60.0)	35/64 (54.7)
No	63/63 (100.0)	43/60 (71.7)	39/62 (62.9)	22/41 (53.7)
[a]Pts who did not demonstrate a clinical response[g] to 8 wks in OCTAVE Induction but did show a clinical response (based on local read) following an additional 8 wks of tofacitinib 10 mg BID in OLE [b]Based on central read endoscopy [c]Based on local read endoscopy [d]FAS, NRI data based on local read of endoscopy in OLE, reported up to the 10 Nov 2017 data cut-off; pts were treated as non-responders after the time of discontinuation up to the visit they would have reached if they had stayed in the study. No imputation for missing data was applied for ongoing pts [e]Total Mayo score ≤2 with no individual subscore >1, and an RBS of 0 [f]Mayo endoscopic subscore ≤1 [g]≥3-point and ≥30% decrease from induction study baseline total Mayo score, plus a ≥1-point decrease in RBS or an absolute RBS of 0 or 1 [h]Four patients were included in this analysis based on local read of the clinical response at M2, but they were classified as non-responders based on their central read score at M2 BID, twice daily; FAS, full analysis set; IndNR, induction non-responder; M, Month; N, number of patients in the treatment group; n, number of unique patients; NRI, non-responder imputation; OLE, open-label, long-term extension; pts, patients; RBS, rectal bleeding subscore; SD, standard deviation; TNFi, tumour necrosis factor inhibitor; wks, weeks				

Reference

1. Sandborn WJ et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2017;376:1723–36. https://www.nejm.org/doi/full/10.1056/NEJMoa1606910

DOP44

Efficacy and safety of tacrolimus in ulcerative colitis: a nationwide, multi-centre study from GETECCU

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Background: Ulcerative colitis (UC) is a chronic disorder of the gut. Tacrolimus (TCR) is a calcineurin inhibitor drug commonly used for prophylaxis of rejection in renal and liver transplantation. There is some evidence supporting the short- and medium-term efficacy and safety of tacrolimus in UC but data are still limited. The primary aim of our study was to evaluate the efficacy and safety of tacrolimus in UC in clinical practice in Spain.

Methods: We performed a retrospective, multi-centre study in 22 inflammatory bowel disease units in Spain. We included all adult patients with a previous established diagnosis of UC in whom oral TCR was prescribed for this underlying condition. Clinical response was assessed by means of partial Mayo score and physician global assessment after 3 months. Follow-up period was considered until the last visit during therapy or 12 months after stopping the drug. Descriptive statistics and non-parametric test were used in the statistical analysis.

Results: A total of 58 patients received TCR between January 1999 and June 2018 (mean age 40 years; 40% female; median CRP 8.8 mg/l). The most common indications for TCR were steroid-dependency (55%) and steroid-refractory disease (29%). Previous exposure to anti-TNF agents was observed in 71%, and 22% to vedolizumab, while 43% had been exposed to ≥2 anti-TNF. At the time of starting TCR, 9% were receiving it concomitantly with an anti-TNF agent or vedolizumab (10%). Blood drug levels during induction were 5–10 ng/ml in 35% and 10–15 ng/ml in 33%. During maintenance, blood drug levels were between 5 and 10 ng/ml in most cases (59%). The median clinical follow-up was 25 months (21–67). Partial Mayo score showed a statistically significant decrease after 3 months (mean 1.6 [SD 1.3], $p = 0.0001$). At this moment, clinical remission was achieved in 24%, while 36% were in partial response. CRP levels showed statistically significant differences after 1, 3, and 6 months when compared with baseline ($p < 0.03$). One third of patients (35%) suffered adverse events related to the drug (40% tremor, 20% asthenia), leading in 35% to discontinuation of the drug. The drug was stopped in 81% of patients after a median of 14 months (10–24), with 47% of patients requiring a new immunomodulator, 28% hospitalisation and 33% requiring colectomy during follow-up.

Conclusions: Tacrolimus offers a clinical benefit in medically refractory UC cases in the short-term, but its long-term effectiveness and safety represent important limitations.

DOP45

Adequate infliximab exposure during the induction phase is associated with early complete fistula response in patients with fistulizing Crohn's disease: a post-hoc analysis of the ACCENT-2 trial

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Background: Therapeutic drug monitoring is used in clinical practice to optimise infliximab (IFX) therapy in patients with Crohn's disease (CD). However, IFX induction concentration cut-points associated with early post-induction complete response in patients with fistulizing CD are unknown. We aimed to investigate the association of IFX serum concentrations at weeks (W)2, 6, and 14 with complete fistula response assessed at Week 14 (CFR14).

Methods: We analysed data from the ACCENT-2 trial,[1] which included 282 patients with active fistulizing CD treated with IFX. In this study, CFR14 was defined as a complete absence of draining fistulas. Receiver-operating characteristic curve analysis was performed to identify IFX concentration cut-points with combined maximal sensitivity and specificity that corresponded to CFR14. A multi-variable logistic regression analysis was performed to evaluate the association of IFX exposure, patient demographics, and disease characteristics with CFR14.

Results: In patients who achieved CFR14 compared with those who did not, the median [interquartile range, IQR] IFX concentrations were significantly higher at W6 (18.4 [12.7–27.8] µg/ml vs. 15.2 [9.1–26.0] µg/ml; $p = 0.038$) and W14 (6.4 [2.3–10.8] µg/ml vs. 3.7 [1.5–7.3] µg/ml; $p = 0.001$) (Table 1). IFX cut-points of 13.9 µg/ml at W6 and 4.8 µg/ml at W14 were associated with CFR14 (Table 2). Multivariable logistic regression analysis identified W14 IFX concentration as the only independent factor associated with CFR14 with an odds ratio [95% confidence interval] of 1.31 [1.06–1.61]; $p = 0.013$.

Table 1. Serum infliximab concentration by efficacy outcome status.

Infliximab concentration	Complete fistula response at week 14 (n=282)		
	Yes (n=144; 51.1%)	No (n=138; 48.9%)	P-value
Week 2			
Median (IQR) µg/mL	24.3 (18.8-33.5)	25.8 (21.2-33.1)	0.24
Week 6			
Median (IQR) µg/mL	18.4 (12.7-27.8)	15.2 (9.1-26.0)	0.038
Week 14			
Median (IQR) µg/mL	6.4 (2.3-10.8)	3.7 (1.5-7.3)	0.001

IQR: Interquartile range

Table 2. Infliximab threshold concentration associated with CFR14.

Timepoint (week)	IFX cut-point concentration (μg/mL)	SN (%)	SP (%)	PPV (%)	NPV (%)	AUROC (95% CI)	P-value
6	13.9	67	50	59	59	0.57 (0.51-0.64)	0.036
14	4.8	52	69	63	58	0.61 (0.54-0.68)	0.001

CFR14: complete fistula response at week 14; SN: sensitivity; SP: specificity; PPV: positive predictive value, NPV: negative predictive value; AUROC: area under receiver operating characteristics curve

Conclusions: Higher IFX concentrations during induction are associated with early complete fistula response in patients with fistulizing CD. Early accelerated dosing of IFX in a subset of patients with subtherapeutic drug exposure may lead to better outcomes.

Reference

1. This study, carried out under YODA Project #, (2017), -1276, used data obtained from the Yale University Open Data Access Project, which has an agreement with Janssen Research & Development, L.L.C. The interpretation and reporting of research using these data are solely the responsibility of the authors, and does not necessarily represent official views of the Yale University Open Data Access Project, or Janssen Research & Development, L.L.C.

DOP Session 6 - Novel treatments

Abstract DOP46 – Table 1

	Blinded Induction Treatment Groups (Wk-12 Clinical Nonresponders)			
	Induction Miri NR		Induction Pbo NR	
Wk 24	**OL EI Miri 600mg Q4W (N=20)**	**OL EI Miri 1000mg Q12W (N=64)**	**OL EI Miri 600mg Q4W (N=12)**	**OL EI Miri 1000mg Q4W (N=32)**
Clinical response[a], n (%)	10 (50.0)	28 (43.8)	7 (58.3)	23 (71.9)
Clinical remission[b], n (%)	3 (15.0)	6 (9.4)	3 (25.0)	8 (25.0)
ES=0/1[c], n (%)	4 (20.0)	10 (15.6)	3 (25.0)	12 (37.5)
ES=0[d], n (%)	0 (0)	2 (3.1)	0 (0)	3 (9.4)
Treatment-emergent AEs, n (%)	12 (60.0)	31 (48.4)	5 (41.7)	14 (43.8)
Serious AEs, n (%)	0 (0.0)	2 (3.1)	1 (8.3)	3 (9.4)
Discontinuations from study due to AE, n (%)	0 (0.0)	3 (4.7)	0 (0.0)	1 (3.1)

[a] **Clinical response:** Decrease in 9-point Mayo score ≥ 2 points and ≥ 35% from baseline, and either a decrease in rectal bleeding (RB) subscore ≥1 or RB subscore of 0 or 1

[b] **Clinical remission:** 9-point Mayo score: RB subscore=0, stool frequency subscore=0 or 1 with ≥ 1 point decrease from baseline, and endoscopy subscore=0 or 1

[c] **ES=0/1:** centrally read Mayo endoscopic subscore=0 or 1

[d] **ES=0:** centrally read Mayo endoscopic subscore= 0

[1]Sandborn WJ, et al. Presented at DDW 2018: 882-Efficacy and Safety of Anti-Interleukin-23 Therapy with Mirikizumab (LY3074828) in Patients with Moderate-To-Severe Ulcerative Colitis in a Phase 2 Study. Gastroenterology. 2018 May 31;154(6):S-1360.

AE=Adverse Event; EI=Extended Induction; OL=Open Label; NR=no clinical response at induction Week 12 (nonresponder)

DOP46

Extended induction treatment with mirikizumab in patients with moderately to severely active ulcerative colitis: results from a Phase 2 trial

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Background: Mirikizumab (miri) is a p19-directed IL-23 antibody that has demonstrated clinical efficacy and was well-tolerated following 12 weeks of induction treatment in a Phase 2 trial in patients with ulcerative colitis (UC).[1] Patients without clinical response at Week 12 had access to an open-label (OL) extended induction (EI) for an additional 12 weeks. Week-24 extended-induction results (12 weeks induction plus 12 weeks extended induction) are reported.

Methods: Patients with moderately to severely active UC (Mayo score 6–12 with a minimum endoscopic subscore [ES] ≥2) were randomised 1:1:1:1 to receive intravenous (IV) placebo (pbo, *N* = 63), miri 50 mg (*N* = 63) or 200 mg (*N* = 62) with possibility of exposure-based (EB) dose increases, or miri 600 mg (*N* = 61) every 4 weeks (Q4W), with efficacy assessment at Week 12. Non-responders (NR; see Table 1 for definition) at Week 12 had access to OL miri: extended induction for an additional 12 weeks for patients who had received induction miri (miri NR) and 12 weeks miri for patients who had received induction pbo (pbo NR). The first group of patients to enter the EI arm received OL miri 600 mg IV Q4W (*N* = 20). After a protocol amendment, subsequent patients entering the EI arm received OL miri 1000 mg IV Q4W (*N* = 64). Safety and clinical outcome (see Table 1 for definitions) data were collected throughout EI, with primary clinical activity assessment at Week 24 of study.

Results: Among miri NR, 50.0% and 43.8% receiving 12 weeks of 600 mg or 1000 mg miri, respectively, achieved clinical response, 15.0% and 9.4% achieved clinical remission, 20.0% and 15.6% had ES = 0/1, and 0 and 3.0% had an ES = 0 at the end of the EI (Week 24). Among pbo NR, 58.0% and 71.9% receiving 12 weeks of 600 mg or 1000 mg miri, respectively, achieved clinical response, 25.0% and 25.0% achieved clinical remission, 25.0% and 37.5% had ES = 0/1, and 0 and 9.4% had an ES = 0 at the end of the EI (Week 24). Treatment-emergent adverse events (AEs), discontinuations due to AE, and serious AEs were similar across treatment groups during the EI.

Conclusions: An additional 12 weeks of induction treatment allowed 43.8–50.0% of induction miri NR to achieve clinical response. Patients treated with 600 mg or 1000 mg miri Q4W had few serious AEs and discontinuations due to AEs. No new safety concerns were identified during 24 weeks of induction treatment with miri.

DOP47

Sustained remission in patients with moderate to severe ulcerative colitis: Results from the Phase 3 UNIFI maintenance study

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Background: The UNIFI randomised-withdrawal maintenance study evaluated the safety and efficacy of subcutaneous (SC) ustekinumab in patients with moderately to severely active ulcerative colitis (UC) who had responded to intravenous (IV) ustekinumab during induction. In this analysis, we describe the durability of remission through maintenance Week 44.

Methods: At Week 0 of the maintenance study, 523 patients who had responded to IV ustekinumab induction were randomly assigned in a 1:1:1 ratio to placebo SC, ustekinumab SC 90 mg q12w, or ustekinumab SC 90 mg q8w. Although maintenance of clinical remission at Week 44 was a major secondary endpoint (reported elsewhere), partial Mayo scores, rectal bleeding, and stool frequency Mayo subscores, endoscopic healing, and Inflammatory Bowel Disease Questionnaire (IBDQ) scores were also used to assess remission at the level of patient-reported symptoms, endoscopy, and health-related quality of life (see Table for definitions).

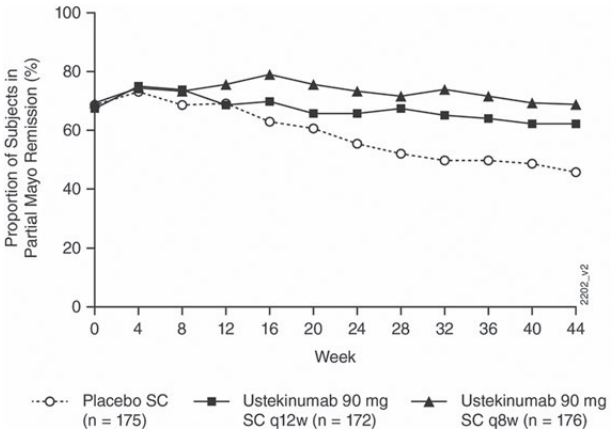
Results: At baseline of the maintenance study, the proportions of patients in symptomatic remission and IBDQ remission were generally similar among the treatment groups (Table).

Abstract DOP47 – Table. Sustained remission through Week 44, as measured by partial Mayo remission, symptomatic remission, endoscopic healing, and IBDQ remission, in patients who achieved clinical response 8 weeks after receiving ustekinumab IV induction therapy

	Placebo SC[a]	Ustekinumab SC 90 mg q12w	Ustekinumab SC 90 mg q8w
Primary efficacy analysis data set, n	175	172	176
Durable partial Mayo remission through Week 44,[b] n (%)	62 (35.4%)	83 (48.3%)	101 (57.4%)
p-value		0.010	<0.001
Symptomatic remission,[c] n (%)			
Baseline	122 (69.7%)	122 (70.9%)	119 (67.6%)
Maintenance of symptomatic remission through Week 44[d]	56 (45.9%)	77 (63.1%)	79 (66.4%)
p-value		0.009	0.002
Endoscopic healing,[e] n (%)			
Baseline	71 (40.6%)	68 (39.5%)	57 (32.4%)
Maintenance of endoscopic healing at Week 44[d]	25 (35.2%)	41 (60.3%)	37 (64.9%)
p-value		0.002	<0.001
IBDQ remission,[f] n (%)			
Baseline	107 (61.1%)	109 (63.4%)	103 (58.5%)
Maintenance of IBDQ remission through Week 44[d]	53 (49.5%)	75 (68.8%)	68 (66.0%)
p-value		0.002	0.019

[a]Patients who responded to ustekinumab IV induction dosing and were randomly assigned to placebo SC upon entry into the maintenance study.
[b]The partial Mayo score includes stool frequency, rectal bleeding, and physician's global assessment subscores and ranges from 0 to 9. Durable partial Mayo remission (partial Mayo score ≤2) through Week 44 was defined as achieving partial Mayo remission at ≥80% of all visits (at least 9 out of 11 visits) prior to Week 44 and in partial Mayo remission at Week 44.
[c]Symptomatic remission was defined as a Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0. Maintenance of symptomatic remission was defined as symptomatic remission at ≥80% of the visits from Week 4 to week 40 (at least 8 out of 10 visits) and at Week 44 among patients who were in symptomatic remission at maintenance baseline.
[d]Denominator is the number of patients who had achieved this endpoint at maintenance baseline.
[e]Endoscopic healing (also described as endoscopic improvement in the appearance of the mucosa) was defined as a Mayo endoscopy subscore of 0 or 1. Maintenance of endoscopic healing was defined as endoscopic healing at Week 44 among patients who had endoscopic healing at maintenance baseline.
[f]Inflammatory Bowel Disease Questionnaire (IBDQ) remission was defined as an IBDQ score ≥170. Maintenance of IBDQ remission was defined as IBDQ remission at both Week 20 and Week 44 among patients who were in IBDQ remission at maintenance baseline.

The proportion of patients with endoscopic healing at baseline was lower in the ustekinumab q8w group (32.4%) compared with the ustekinumab q12w (39.5%) and placebo groups (40.6%). Through Week 44, the proportions of patients in partial Mayo remission were sustained in the ustekinumab treatment groups, while the proportion of patients in the placebo group decreased, with consistent numerical separation from the ustekinumab q8w group by Week 8 and the q12w group by Week 16 (Figure).



Abstract DOP47 – Figure. Proportion of patients in partial Mayo remission (partial Mayo score ≤2) over time through Week 44

In addition, significantly greater proportions of patients in the ustekinumab q8w and q12w groups compared with placebo maintained symptomatic remission and IBDQ remission through Week 44 and maintained endoscopic healing at Week 44 among patients who achieved each respective endpoint at maintenance baseline. Similarly, greater proportions of ustekinumab-treated patients had durable partial Mayo remission through Week 44 compared with placebo.

Conclusions: Both doses of ustekinumab SC maintenance therapy sustained remission, measured by patient-reported symptoms and endoscopic and quality of life assessments, in patients with moderately to severely active UC.

DOP48

Amiselimod, a selective S1P receptor modulator in Crohn's disease patients: a proof-of-concept study

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Background: The treatment of Crohn's disease (CD) remains unsatisfactory for many patients leading to poor quality of life and surgery. Amiselimod (AMS) is a new selective oral S1P receptor modulator, which is being developed for the treatment of various autoimmune-mediated disease including CD.

Methods: This was a prospective, randomised, placebo (PLC) controlled clinical trial in which patients with active CD (CDAI 220-450) and elevated biomarkers received 0.4 mg of AMS or PLC for 14 weeks, followed by open-label extension treatment. Patients had to have been previously treated with corticosteroids or immunosuppressants and/or anti-TNF-α agents for CD. The primary endpoint was clinical response defined as drop in the CDAI by 100 points at Week 12 (CDAI100).

Results: One hundred and eighty patients underwent screening and 78 (median age 33, 61.8% male, median baseline CDAI 307, 60.5% anti-TNF exposed) were randomised (40 to AMS and 38 to PLC). Baseline characteristics were similar among groups. Twenty-eight of 40 patients on AMS and 33/38 on PLC completed the induction trial. The primary endpoint CDAI100 was attained in 19/39 (48.7%) on AMS vs. in 20/37 (54.1%) on PLC (NS). CDAI 70 and clinical remission (CDAI<150) were observed in 21/39 (53.8%) and 11/39 (28.2%) on AMS and in 24/37 (64.9%) and 15/37 (40.5%) on PLC, respectively. No clinically meaningful differences were observed in serum CRP concentrations and faecal calprotectin in either groups. Mean lymphocyte counts on AMS showed significant reduction by Week 4 (47.7% of baseline), after which, mean lymphocyte counts reached graphical plateau. This lymphocyte counts reduction was considered weaker than the other indications and simulated data from MT-1303 Phase I studies. TEAEs were observed in 66.7% of patients on AMS and in 55.3% on PLC with infections occurring in twice as many patients on AMS than in PLC (26 vs. 13%). Cardiac disorders were reported in 3 patients on AMS (TEAEs: ventricular tachycardia, bradycardia, supraventricular extrasystoles, and ventricular extrasystoles) and in 1 on PLC (ventricular tachycardia). They were all mild and considered non-serious. There were no clinically relevant findings between AMS and PLC in the mean hourly HR, and no clinically significant reports of bradycardia, AV block and ventricular tachycardia. Macular oedema was confirmed in 1 patient on AMS (mild and considered non-serious).

Conclusions: Treatment with AMS 0.4 mg was generally well tolerated and no new safety concerns related to AMS were reported in this study. AMS 0.4 mg/day for 12 weeks did not have an effect on clinical or biochemical disease activity in refractory CD, and the high placebo response rate and weaker lymphocyte reduction were considered to contribute to the negative efficacy result in this study.

DOP49

Efficacy of the anti-mucosal addressin cell adhesion molecule-1 (MAdCAM-1) antibody SHP647 in ulcerative colitis: results from the open-label extension study TURANDOT II

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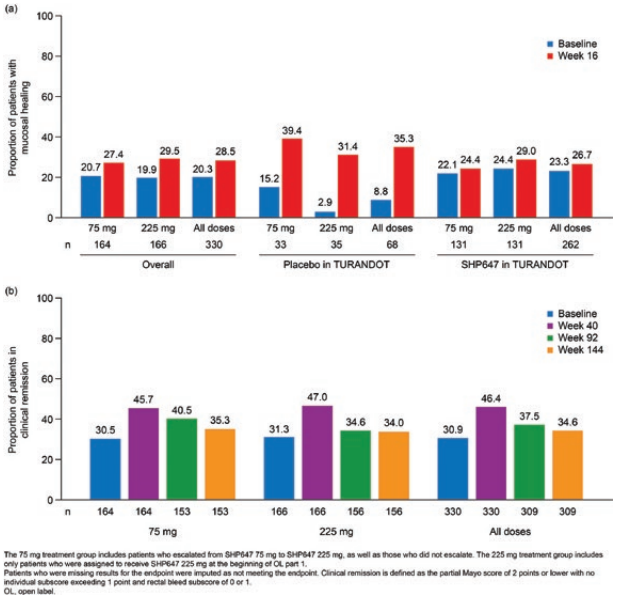
Background: SHP647, a fully human IgG_2 monoclonal antibody, binds to MAdCAM-1, reducing lymphocyte homing to the GI tract. In the TURANDOT II trial, SHP647 was well-tolerated and clinical benefit was seen up to 144 weeks in patients with moderate-to-severe ulcerative colitis (UC). This analysis reports efficacy by dose in TURANDOT II, and by prior treatment and response in the TURANDOT induction study.

Methods: TURANDOT II (NCT01771809) is a Phase 2, multicentre, two-part, open-label (OL) study of SHP647 in patients with moderate-to-severe UC who completed TURANDOT on placebo or SHP647 7.5, 22.5, 75, or 225 mg sc every 4 weeks. At TURANDOT II baseline, patients were randomised to SHP647 75 or 225 mg sc every 4 weeks for 72 weeks (OL1). Dose escalation from 75 to 225 mg was permitted at the investigator's discretion from Week 8 to Week 72 in the case of clinical exacerbation or no response. In OL2, all patients received 75 mg every 4 weeks for 72 weeks. Mucosal healing (Mayo endoscopy subscore ≤1), clinical remission (total Mayo score ≤2 with no individual subscore >1, rectal bleed subscore ≤1) and response (based on total Mayo score) were assessed at Week 16 (centrally read endoscopy). Long-term efficacy was assessed by clinical response and remission (partial Mayo score) up to 144 weeks.

Results: In total, 330 patients were randomised and treated (SHP647 in TURANDOT, n = 262; placebo in TURANDOT, n = 68). Mucosal healing increased from 20.3% at TURANDOT II baseline (67/330) to 28.5% (94/330) at Week 16 (Figure 1a). Overall, 67 patients (20.3%) were in remission at Week 16, compared with 38 (11.5%) at baseline. Of those not in remission at the end of TURANDOT, 14.0% (41/292) had achieved remission by Week 16 of TURANDOT II—23 of these had been on SHP647 in TURANDOT (23/262; 8.8%) and 18 had been on placebo (18/68; 26.5%). Of patients with clinical response at the end of TURANDOT, 79% maintained response at Week 16; of non-responders in TURANDOT, 38% achieved response by Week 16. Figure 1b shows long-term clinical remission by partial Mayo score; clinical response showed a similar trend. Overall, the mean partial Mayo score improved from 3.8 (SD, 2.29) at TURANDOT II baseline to 1.0 (1.31) at Week 144 in patients who remained in the study (n = 127). The mean change from TURANDOT baseline to Week 144 was –4.7 (1.73).



The 75 mg treatment group includes patients who escalated from SHP647 75 mg to SHP647 225 mg, as well as those who did not escalate. The 225 mg treatment group includes only patients who were assigned to receive SHP647 225 mg at the beginning of OL part 1. Patients who were missing results for the endpoint were imputed as not meeting the endpoint. Clinical remission is defined as the partial Mayo score of 2 points or lower with no individual subscore exceeding 1 point and rectal bleed subscore of 0 or 1. OL, open label.

Figure 1. (a) Proportion of patients with mucosal healing at Week 16, overall and by dose and treatment arm in TURANDOT; (b) proportion of patients in clinical remission (partial Mayo score) over time. The 75 mg treatment group includes patients who escalated from SHP647 75 mg to SHP647 225 mg, as well as those who did not escalate. The 225 mg treatment group includes only patients who were assigned to receive SHP647 225 mg at the beginning of OL part 1. Patients who were missing results for the endpoint were imputed as not meeting the endpoint. Clinical remission is defined as the partial Mayo score of 2 points or lower with no individual subscore exceeding 1 point and rectal bleed subscore of 0 or 1. OL, open label.

Conclusions: Clinical response and remission in the induction study continued in the extension study, persisting over the long term in most patients who reached these thresholds. The observed clinical benefit supports continued study of SHP647 in Phase 3 trials.

DOP50

Effect of upadacitinib on extra-intestinal manifestations in patients with moderate to severe Crohn's disease: data from the CELEST study

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Background: Extra-intestinal manifestations (EIMs), such as arthropathy, are common in patients with Crohn's disease (CD).[1] The efficacy of Janus Kinase (JAK) inhibition on EIMs is not known in CD. We assessed the prevalence of EIMs at baseline (BL) and the changes over time in EIMs with upadacitinib (UPA), an oral, selective JAK1 inhibitor in the CELEST study.

Methods: CELEST was a multi-centre, randomised, double-blind, placebo-controlled, Phase 2 study in adults with moderate-to-severe CD and inadequate response/intolerance to immunosuppressants or tumour necrosis factor inhibitors (TNFi). Patients were randomised to 16-week induction therapy with placebo or UPA 3-, 6-, 12-, or 24-mg twice-daily (BID) or 24-mg once-daily (QD). The presence of EIMs (axial and/or peripheral arthropathy, episcleritis/uveitis/iritis, oral aphthous ulcers, erythema nodosum, pyoderma gangrenosum, Sweet's syndrome, anaemia, auto-immune hepatitis, bronchiectasis, chronic obstructive pulmonary disease, nephrolithiasis, primary sclerosing cholangitis, venous thromboembolism) was collected at BL and Week 16 based on medical interview and physical examination; Fisher exact test was used to compare the UPA groups to placebo for any EIM, classic EIMs (axial and/or peripheral arthropathy, episcleritis/uveitis/iritis, oral aphthous ulcers, erythema nodosum, pyoderma gangrenosum, Sweet's syndrome), and arthropathy. Resolution of EIMs was analysed in patients who had EIMs at baseline and was defined as zero EIMs at Week 16; patients with missing Week 16 data were classified as not resolved.

Results: Among 220 randomised patients, 111 (50.5%) had at least one EIM at BL and 31 (28%) of these had two or more EIMs. Patients who had at least one EIM at BL had median (min–max) CD Activity Index (CDAI) 295 (222–447), CD duration 10.8 (0.1–44.7) years, and 85 (96.6%) had failed one or more TNFi. At BL, more patients in the placebo and 3 mg BID groups had at least one EIM compared with UPA 6 and 12 BID, and 24 mg QD. The most commonly reported EIMs were peripheral and/or axial arthropathies (n = 87), anaemia (n = 31), and oral aphthous ulcers (n = 11).

At Week 16, compared with placebo, a numerically greater proportion of patients achieved resolution of any EIM, classic EIMs, and arthropathy with UPA 12 and 24 mg BID, and UPA 24 mg QD doses (Table).

Table. Proportion of patients achieving resolution of any EIMs, classic EIMs, and arthropathy at Week 16.

Endpoints, n/N (%)	Placebo N=23	3 mg BID N=26	6 mg BID N=15	12 mg BID N=11	24 mg BID N=21	24 mg QD N=15
Resolution of any EIMs	7/23 (30.4)	10/26 (38.5)	4/15 (26.7)	6/11 (54.5)	11/21 (52.4)	7/15 (46.7)
Resolution of classic EIMs	6/18 (33.3)	9/24 (37.5)	3/12 (25.0)	4/8 (50.0)	10/17 (58.8)	7/13 (53.8)
Resolution of arthropathy	5/17 (29.4)	10/24 (41.7)	3/12 (25.0)	3/7 (42.9)	9/16 (56.3)	6/11 (54.5)

Data are reported in the modified intent-to-treat population. Resolution of extra-intestinal manifestations (EIMs) was defined as zero EIMs at Week 16. Resolution of classic EIMs was defined as zero peripheral arthropathy, axial arthropathy, episcleritis, uveitis, oral aphthous ulcers, iritis erythema nodosum, pyoderma gangrenosum, Sweet's syndrome at Week 16. Resolution of arthropathy was defined as zero axial and peripheral arthropathies at Week 16.

Conclusions: In this small patient population, a numerical resolution in EIMs was observed with UPA, suggesting a clinical benefit induced by UPA.

Reference

1. De Felice K, Raffals LH. Extraintestinal manifestations of Crohn's disease. In: Fichera A, Krane M, editors. *Crohn's Disease: Basic Principles*. Switzerland: Springer International Publishing; 2015, 245–53.

DOP51

Biomarker and pharmacokinetic data from the TURANDOT II open-label extension study of the anti-mucosal addressin cell adhesion molecule-1 (MAdCAM-1) antibody SHP647 in patients with ulcerative colitis

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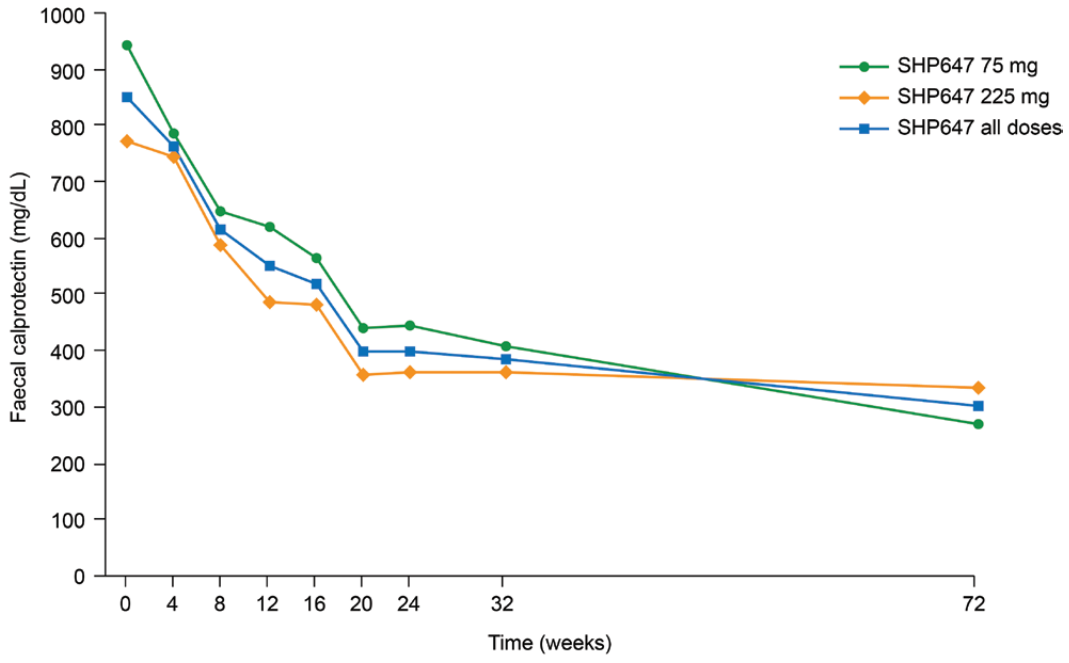
Background: SHP647, a fully human IgG_2 monoclonal antibody, binds to human mucosal addressin cell adhesion molecule-1 (MAdCAM-1) thus reducing lymphocyte homing to the gastrointestinal tract. Results from the Phase 2, extension study TURANDOT II (NCT01771809) showed that SHP647 was well tolerated for up to 144 weeks and resulted in continued clinical benefit in patients with moderate-to-severe ulcerative colitis (UC). This analysis from the TURANDOT II trial reports biomarker and pharmacokinetic (PK) data from the first 72 weeks of the study.



The 75 mg treatment group includes patients who escalated from SHP647 75 mg to SHP647 225 mg (n = 94), as well as those who did not escalate (n = 69). The 225 mg treatment group includes only patients who were assigned to receive SHP657 225 mg at the beginning of OL part 1 (n = 164).
OL, open label.

Figure 1. Geometric mean faecal calprotectin levels from TURANDOT II baseline (Week 12 of TURANDOT) to Week 72.

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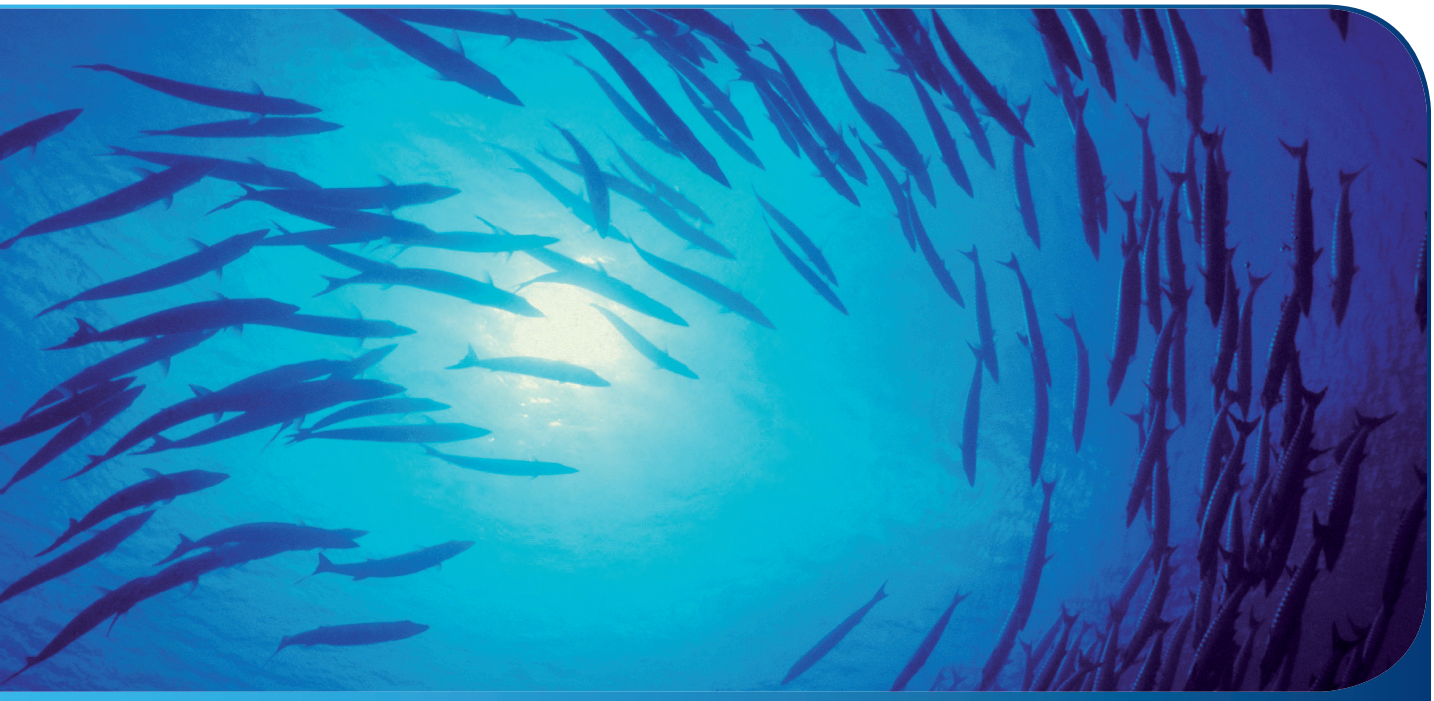

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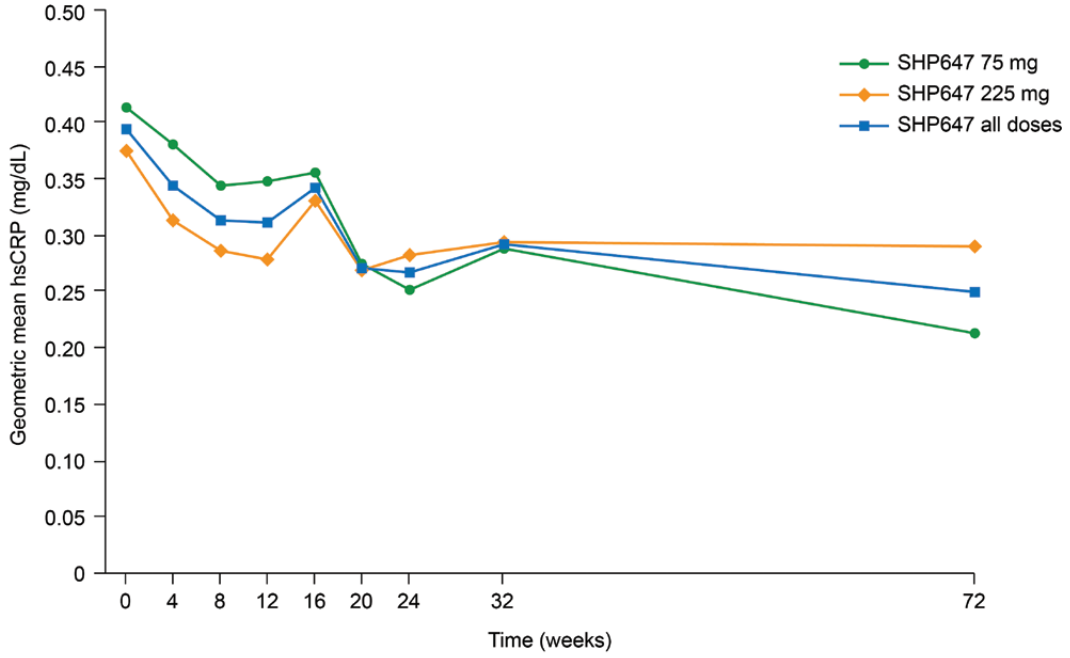

The 75 mg treatment group includes patients who escalated from SHP647 75 mg to SHP647 225 mg (n = 94), as well as those who did not escalate (n = 69). The 225 mg treatment group includes only patents who were assigned to receive SHP647 225 mg at the beginning of OL part 1 (n = 164).
hsCRP, high-sensitivity C-reactive protein; OL, open label.

Abstract DOP51 – Figure 2. Geometric mean hsCRP levels over time from TURANDOT II baseline (Week 12 of TURANDOT) to Week 72.

Methods: TURANDOT II was a Phase 2, multi-centre, 2-part open-label (OL) study of SHP647 in patients with moderate-to-severe UC who completed TURANDOT on placebo or SHP647 7.5, 22.5, 75, or 225 mg s.c. every 4 weeks. At TURANDOT II baseline, patients were randomised to SHP647 75 or 225 mg s.c. every 4 weeks for 72 weeks (OL part 1). Dose escalation from 75 to 225 mg was permitted at the investigator's discretion at any time from 8 to 72 weeks in the event of clinical exacerbation or no treatment response. In OL part 2, all patients received 75 mg every 4 weeks for a further 72 weeks. In OL part 1, high-sensitivity C-reactive protein (hsCRP) and faecal calprotectin (FCP) were analysed every 4 weeks until Week 24, and then at 32 and 72 weeks. Soluble MAdCAM-1 levels were measured at Weeks 0 and 16, and plasma SHP647 concentrations were measured every 4 weeks. No biomarker or PK data were collected in OL part 2.
Results: Of the 330 patients treated, 329 were included in the pharmacodynamic population (SHP647 75 mg, *n* = 163; SHP647 225 mg, *n* = 166). Two patients in the 225 mg dose group were not included in the PK population. FCP and hsCRP levels reduced consistently over the 72 weeks of OL part 1 in both dose groups (Figures 1 and 2). Mean plasma concentrations of SHP647 increased dose-dependently. Geometric mean soluble MAdCAM-1 concentrations were lower in both dose groups at Week 16 vs. baseline, with changes of –74%, –86%, and –81% in the 75 mg, 225 mg, and total groups, respectively.
Conclusions: This analysis of data from the TURANDOT II study shows that SHP647 treatment is associated with a reduction in biomarkers specific to its mode of action, as well as long-term reductions in inflammatory biomarkers.

DOP52

Reduction in inflammatory biomarkers in a Phase 2 study of mirikizumab in patients with moderately to severely active ulcerative colitis

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Background: Interleukin (IL)-23 is a cytokine involved in the pathogenesis of ulcerative colitis (UC). Mirikizumab (miri) is a p19-directed IL-23 antibody that demonstrated efficacy and was well-tolerated following 12 weeks of induction treatment in a Phase 2 randomised clinical trial (AMAC, NCT02589665).[1] Exploration of IL-23 pathway biomarkers supports an understanding of drug activity and mechanism of action. This abstract describes exploratory biomarker results for IL-23 pathway cytokines IL-22 and IL-17A, and their associations with clinical outcomes in this study.
Methods: Patients with moderately to severely active UC (Mayo score 6–12 with a minimum endoscopic subscore [ES] ≥2) were randomised 1:1:1:1 to receive intravenous (IV) placebo (pbo) (*N* = 63), miri 50 mg (*N* = 63) or 200 mg (*N* = 62) with possibility of exposure-based (EB) increases, or fixed miri 600 mg (*N* = 61) every

Abstract DOP52 – Table 1.

	Treatment Groups			
	Pbo (N=63)	Miri 50mg EB (N=63)	Miri 200mg EB (N=62)	Miri 600mg (N=61)
Biomarkers				
BL IL-17A pg/ml, geomean (-/+ SE)	0.28 (0.23-0.34)	0.32 (0.26-0.38)	0.33 (0.27-0.40)	0.31 (0.26-0.38)
Wk-12 IL-17A pg/ml, geomean (-/+ SE)	0.28 (0.23-0.33)	0.15 (0.12-0.18)	0.11 (0.09-0.13)	0.13 (0.11-0.16)
IL-17A, Pbo-adjusted % improvement from BL (MMRM), mean (-/+ SE)	NA	53.4 (42.5-62.2)***	66.0 (58.2-72.4)***	57.1 (47.0-65.2)***
BL IL-22 pg/ml, geomean (-/+ SE)	12.3 (10.7-14.3)	11.8 (10.2-13.6)	14.3 (12.4-16.5)	16.1 (13.9-18.5)
Wk-12 IL-22 pg/ml, geomean (-/+ SE)	12.5 (10.8-14.4)	8.1 (7.0-9.4)	7.8 (6.7-9.0)	10.2 (8.9-11.8)
IL-22, Pbo-adjusted % improvement from BL (MMRM), mean (-/+ SE)	NA	31.5 (22.3-39.6)**	46.1 (38.9-52.4)***	36.8 (28.3-44.3)***
Clinical Outcomes				
Wk-12 Clinical remission[a][1], n (%)	3 (4.8)	10 (15.9)	14 (22.6)**	7 (11.5)
Wk-12 Clinical response[b][1], n (%)	13 (20.6)	26 (41.3)*	37 (59.7)***	30 (49.2)**

P-value vs. Pbo for clinical outcome; P-value compared to baseline adjusted for pbo
*p < 0.05; **p < 0.01; ***p < 0.001

[a] Clinical remission: 9-point Mayo score: rectal bleeding (RB) subscore=0, stool frequency subscore=0 or 1 with ≥ 1 point decrease from baseline, and endoscopy subscore=0 or 1
[b] Clinical response: Decrease in 9-point Mayo score ≥ 2 points and ≥ 35% from baseline, and either a decrease in RB subscore ≥1 or RB subscore of 0 or 1

[1] Sandborn WJ, et al. Presented at DDW 2018: 882-Efficacy and Safety of Anti-Interleukin-23 Therapy with Mirikizumab (LY3074828) in Patients with Moderate-To-Severe Ulcerative Colitis in a Phase 2 Study. Gastroenterology. 2018 May 31;154(6):S-1360.

BL=baseline; MMRM=Mixed effect Model Repeat Measurement

4 weeks, with efficacy assessment at Week 12. Plasma EDTA samples were collected at Weeks 0, 4, and 12 to evaluate circulating levels of IL-17A and IL-22. The ultrasensitive Quanterix Simoa platform (IL-17A) and a custom Meso Scale Discovery assay (IL-22) were used to evaluate cytokine levels. Biomarker results were analysed using a Mixed-effect Model Repeat Measurement statistical model (pharmacodynamic effects) and receiver-operating characteristic (ROC) curves (clinical outcomes association to biomarker changes).
Results: Baseline (BL) characteristics were similar among treatment groups. Most patients (63%) had previously received biological therapy. At Week 12, numerically greater geometric mean changes from BL in IL-17A and IL-22 levels were seen in each miri group vs. pbo (Table 1). The area under the ROC curve (AUC) analyses of fold decrease in serum IL-17A (BL to Week 12) association with Week-12 clinical response and clinical remission using all study participants were 0.78 [0.72–0.84] and 0.71 [0.58–0.83], respectively. The ROC AUCs for fold decrease in serum IL-22 association with Week-12 clinical response and clinical remission using all study participants were 0.71 [0.64–0.78] and 0.60 [0.46–0.73], respectively.
Conclusion: Patients who were treated with mirikizumab had greater reductions from BL in serum levels of the IL-23-dependent pro-inflammatory cytokines IL-17A and IL-22, compared with pbo. Changes in serum cytokine expression (BL to Week 12) were associated with clinical outcomes. These data confirm the biological activity of mirikizumab in patients with moderately to severely active UC.

DOP53

Clinical, endoscopic, histological and biomarker activity following treatment with the gut-selective, pan-JAK inhibitor TD-1473 in moderately to severely active ulcerative colitis

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Abstract DOP53

TD-1473 dose	Subjects achieving clinical response (*n*, %)	Subjects with improvement in rectal bleeding subscore by ≥ 1 point (*n*, %)	Subjects with improvement in endoscopy subscore by ≥ 1 point (*n*, %)	Subjects with mucosal healing	Serum CRP (placebo adjusted change from baseline; %, 95% CI)	Faecal calprotectin (placebo adjusted change from baseline; %, 95% CI)	Robarts Histologic Index (mean ± SD)	Distal biopsy pSTAT1 expression (change from baseline, pg/µl; geometric mean ratio, 95% CI)	Distal biopsy pSTAT3 expression (change from baseline, pg/µl; geometric mean ratio, 95% CI)
Placebo (*n* = 9)	1 (11%)	4 (44%)	0 (0%)	0 (0%)	NA	NA	–2.0 (5.61)	1.29 (0.91, 1.84)	1.40 (0.91, 2.16)
20 mg (*n* = 10)	2 (20%)	3 (30%)	2 (20%)	2 (20%)	–61 * (–84, –1)	+62 (–76, +987)	–4.5 (12.19)	0.72 (0.47, 1.10)	0.73 (0.44, 1.21)
80 mg (*n* = 10)	2 (20%)	7 (70%)	3 (30%)	2 (20%)	–57 (–83, +6)	–31 (–89, +344)	1.8 (8.07)	1.07 (0.60, 1.91)	1.00 (0.56, 1.79)
270 mg (*n* = 11)	6 (55%)	8 (73%)	2 (18%)	1 (9%)	–70 * (–88, –28)	–26 (–88, +351)	–5.3 (11.22)	0.69 (0.49, 0.95) *	0.61 (0.39, 0.93) *

$p < 0.05$.

Serum C-reactive protein (CRP) decreased relative to placebo at all dose levels. Faecal calprotectin decreased in subjects treated with 80 mg and 270 mg. 4 weeks of treatment with TD-1473 at 20 mg and 270 mg was associated with dose-related reductions in RHI, along with colonic levels of phospho-STAT (pSTAT)1 and pSTAT3 proteins with statistical significance in the 270 mg group. RNAseq analysis suggests that TD-1473 has a local effect on the UC-transcriptomics signature. Thus, the results suggest a clinical and molecular effect at all three doses of TD-1473. Histological and pSTAT assessments demonstrated trends for reduction at 20 mg and 270 mg (not at 80 mg due to low baseline histological scores). RNA expression profiling data are consistent with local modification of the UC-transcriptomics signature by TD-1473.

Background: TD-1473 is an orally administered and gut-selective pan-Janus kinase (JAK) inhibitor that, at doses up to 270 mg, results in low systemic exposure and high concentration in gut tissue which is anticipated to result in local pan-JAK inhibition. The aim was to assess the clinical and molecular effects of TD-1473 in subjects with moderately to severely active UC after 4 weeks of treatment.

Methods: In this double-blind, placebo-controlled, multi-centre Phase 1b study, 40 subjects were enrolled and administered placebo (*n* = 9), 20 mg (*n* = 10), 80 mg (*n* = 10), or 270 mg (*n* = 11) TD-1473 once daily for 28 days after meeting eligibility criteria (including Mayo rectal bleeding subscore of ≥1, stool frequency subscore of ≥1, and centrally read endoscopic subscore of ≥ 2). Clinical and histological outcomes were assessed by central reading for modified Mayo endoscopic scores and Robarts' Histologic Index (RHI), respectively. Colonic tissue biomarker protein levels and transcriptomics were measured by ELISA and RNAseq, respectively, at baseline and at Day 28.

Results: There were trends for higher rates of clinical response, endoscopic healing, and improvement by ≥1 point in rectal bleeding and endoscopy subscores with TD-1473 relative to placebo.

Conclusion: Signals for clinical, endoscopic, histological, and biomarker activity were observed in subjects with moderately to severely active UC treated with TD-1473.

DOP54

Efficacy and safety of ustekinumab through Week 16 in patients with moderate-to-severe ulcerative colitis randomised to ustekinumab: results from the UNIFI induction trial

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Background: The objective was to evaluate the efficacy and safety of ustekinumab (UST) through Week 16 induction among patients with moderate–severe UC randomised to UST in the UNIFI Phase 3 clinical trial. Week 8 induction data have been previously reported.[1]

Methods: Rates of overall clinical response and clinical remission among blinded patients randomised to IV UST induction were used to evaluate efficacy through Week 16. The number of patients who achieved each endpoint included patients who achieved the endpoint at Week 8 after initial IV UST induction and patients who achieved the same endpoint at Week 16 following a blinded dose of UST 90 mg SC at Week 8 if they were not in clinical response at Week 8.

Results: Among patients randomised to UST at Week 0, 77.6% achieved clinical response within 16 weeks: 56.5% at Week 8 after IV induction and an additional 21.1% at Week 16 after receiving UST SC at Week 8. Among the Week 8 non-responders to UST IV induction who received UST SC at Week 8, 57.9% achieved clinical response at Week 16. Among patients randomised to UST at Week

0, 18.8% achieved clinical remission within 16 weeks: 15.6% at Week 8 after IV induction and an additional 3.2% at Week 16 after receiving an additional UST dose at Week 8. Among the Week 8 non-responders to UST IV induction who received UST SC at Week 8, 9.4% achieved clinical remission at Week 16. The proportions of patients who achieved clinical response within 16 weeks was lower for patients with a history of biological failure compared with non-biological failure patients: 70.6% vs. 84.9% (Table 1). Similarly, the proportions of patients who achieved clinical remission during induction within 16 weeks were lower for biological failure patients compared with non-biological failure patients: 13.3% vs. 24.7% (Table 2). The AE profile for patients who received a single UST IV dose and those with an additional UST dose SC at Week 8 were similar and consistent with the AE profile for patients that received PBO.

Abstract DOP54 – Table 1. Patients in clinical response during induction by randomised UST treatment group and biological failure status.

	Ustekinumab		
	130 mg	6 mg/kg [a]	Combined
Primary Efficacy Analysis Set	320	322	642
Biologic failure patients, N	164	166	330
Patients in clinical response at Week 8 or Week 16 [b]	113 (68.9%)	120 (72.3%)	233 (70.6%)
Patients in clinical response at Week 8	74 (45.1%)	95 (57.2%)	169 (51.2%)
Patients who received additional treatment at Week 8 [c]	79	58	137
Patients in clinical response at Week 16 [d]	40 (50.6%)	25 (43.1%)	65 (47.4%)
Non-biologic failure patients, N	156	156	312
Patients in clinical response at Week 8 or Week 16 [b]	129 (82.7%)	136 (87.2%)	265 (84.9%)
Patients in clinical response at Week 8	90 (57.7%)	104 (66.7%)	194 (62.2%)
Patients who received additional treatment at Week 8 [c]	53	43	96
Patients in clinical response at Week 16 [d]	40 (75.5%)	34 (79.1%)	74 (77.1%)

[a] Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55 kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight > 85 kg).
[b] A patient was counted only once if the patient was in clinical response at both Week 8 and Week 16
[c] Patients received a dose of ustekinumab 90 mg SC at Week 8.
[d] Includes patients in clinical response at Week 8 who received additional treatment at Week 8

Source: TEFCRES11

Abstract DOP54 – Table 2. Patients in clinical remission during induction by randomised UST treatment group at Week 0 and biological failure status.

	Ustekinumab		
	130 mg	6 mg/kg [a]	Combined
Primary Efficacy Analysis Set	320	322	642
Biologic failure patients, N	164	166	330
Patients in clinical remission at Week 8 or Week 16 [b]	22 (13.4%)	22 (13.3%)	44 (13.3%)
Patients in clinical remission at Week 8	19 (11.6%)	21 (12.7%)	40 (12.1%)
Patients who received additional treatment at Week 8 [c]	79	58	137
Patients in clinical remission at Week 16 [d]	3 (3.8%)	1 (1.7%)	4 (2.9%)
Non-biologic failure patients, N	156	156	312
Patients in clinical remission at Week 8 or Week 16 [b]	41 (26.3%)	36 (23.1%)	77 (24.7%)
Patients in clinical remission at Week 8	31 (19.9%)	29 (18.6%)	60 (19.2%)
Patients who received additional treatment at Week 8 [c]	53	43	96
Patients in clinical remission at Week 16 [d]	10 (18.9%)	8 (18.6%)	18 (18.8%)

[a] Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55 kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight > 85 kg).
[b] A patient was counted only once if the patient was in clinical remission at both Week 8 and Week 16
[c] Patients received a dose of ustekinumab 90 mg SC at Week 8.
[d] Includes patients in clinical remission at Week 8 who received additional treatment at Week 8

Conclusions: UST is safe and effective induction therapy in patients with moderate–severe UC. Similar to results from the Crohn's disease programme, these data support a clinical rationale for continuing treatment with UST through at least one SC dose 8 weeks after IV induction in patients with moderate–severe UC.

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DOP Session 7 - Recent advances of biologic therapies

DOP55

ZNF133 is associated with infliximab responsiveness in patients with inflammatory bowel diseases using whole-exome sequencing

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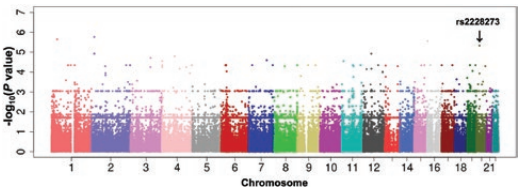
Background: Infliximab has been widely prescribed for treating inflammatory bowel disease (IBD). However, the response rates to infliximab differ among patients. Thirteen per cent to 30% patients do not respond to the initial treatment, and 23%–46% patients who initially respond to IFX ultimately experience loss of response with time.[1–4] Therefore, we aimed to identify the genetic and clinical markers that predict infliximab response.

Methods: One hundred and thirty-nine Korean patients with IBD who were treated by infliximab were classified according to infliximab response as follows: (1) primary response vs. non-response and (2) sustained response vs. loss of response. We conducted an association study using whole-exome sequencing data to identify genetic variants associated with infliximab response. Candidate variants were validated in 77 German patients with IBD. Stepwise multi-variate logistic regression was performed to identify predictors.

Results: We found five candidate variants which were associated with primary non-response to infliximab ($p < 5 \times 10^{-6}$).



Association mapping of genetic variants with primary non-response to infliximab in Korean patients with inflammatory bowel disease. Genetic variants related with primary non-response were plotted according to their chromosomal position.

Of the five variants, rs2228273 in *ZNF133* was validated in German patients (Combined $p = 6.49 \times 10^{-7}$). We also identified the best genetic variant (rs9144, $p = 4.60 \times 10^{-6}$) associated with loss of infliximab response. In multi-variate regression analysis, rs2228273 ($p = 2.10 \times 10^{-5}$), concurrent azathioprine/6-mercaptopurine use, and body weight at the first infliximab use (<50 kg) were associated with primary non-response. In addition, the Crohn's disease activity index at the first infliximab use and rs9144 ($p = 0.001$) were independently associated with loss of response in patients with Crohn's disease.

Conclusions: We identified clinical and genetic markers associated with infliximab response in patients with IBD. Our findings could provide insights to maximise the efficacy of infliximab therapy in IBD.

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DOP56

Dashboard driven vs. conventional dosing of infliximab in inflammatory bowel disease patients: the PRECISION trial

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Background: Loss of response to infliximab (IFX) complicates the management of inflammatory bowel disease (IBD). Up to date, no prospective study has demonstrated the benefit of proactive dose adjustment based on serum IFX levels. However, more personalised dosing strategies using a dashboard to achieve and maintain well-defined IFX target trough levels (TLs) may prevent loss of response. The aim of the PRECISION trial was to investigate the efficacy of dashboard-driven IFX dosing in IBD patients during 1 year.

Methods: In this multi-centre 1:1 randomised prospective trial, patients in clinical remission (Harvey–Bradshaw Index [HBI] ≤4 for Crohn's disease [CD] or partial mayo score [PM] ≤2 for ulcerative colitis [UC]) receiving IFX maintenance treatment were included. Patients in the precision dosing group (PG) received IFX dosing guided by a Bayesian pharmacokinetic model, aiming to achieve and maintain an IFX TL of 3 µg/ml by treatment (de-)escalation as indicated by the dashboard.[1] Patients in the control group (CG) continued IFX treatment regimen given prior to randomisation without dose adaptation. Biochemical remission was defined as a faecal calprotectin <250 µg/g and CRP < 0.5 mg/l. Clinical loss of response was defined as an HBI >4 or PM score >2 at two consecutive visits.

Results: In total, 80 patients were included (66 CD and 14 UC). Baseline characteristics are listed in Table 1.

Characteristic	PG (*N* = 40)	CG (*N* = 40)
IFX treatment duration in years [IQR]	3.5 (2–7.8)	4.0 (1.3–5.8)
Serum CRP mg/l [IQR]	2.0 (0.9–5.3)	2.1 (1.0–6.5)
Serum TL µg/ml [IQR]	3.7 (1.6–6.4)	3.0 (1.9–5.2)
Serum albumin g/l [IQR]	43 (41–45)	42 (40–45)
Biochemical remission, *n* (%)	25 (62.5)	22 (55)
Standard IFX treatment regimen	25 (62.5)	23 (57.5)
Intensified IFX treatment regimen	11 (27.5)	13 (32.5)
De-intensified IFX treatment regimen	4 (10)	4 (10)
Combination therapy with IM	15 (37.5)	17 (42.5)

Baseline patient characteristics per treatment group. Values are median (interquartile range). IM, immunomodulator (thiopurine or methotrexate). Per protocol analysis showed loss of clinical response in 14/39 (36%) patients in the CG compared with 4/32 (13%) patients in the PG (p = 0.03). Three patients (7.5%) in the PG were considered failures because of re-opening of their perianal fistula after dose de-escalation to achieve a TL of 3 µg/ml. Time to relapse was evaluated using Kaplan–Meier analysis (Figure 1).

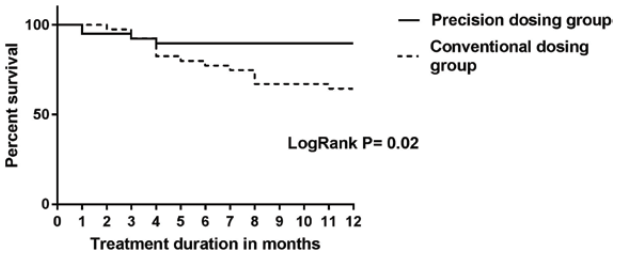

Figure 1. Kaplan–Meier

Conclusions: The PRECISION study is the first prospective trial demonstrating a clinical benefit from personalised dosing in IBD patients. Dashboard-guided dosing resulted in a significant higher proportion of patients who maintained clinical remission during 1 year of treatment compared with patients that continued treatment without proactive adjustments. In patients with perianal disease, de-escalating treatment to obtain an IFX TL of 3 µg/ml resulted in re-opening of their old fistula, suggesting that, in these patients, higher TLs are needed for disease control.

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DOP57

Monitoring response to anti-TNF therapy in ulcerative colitis patients by gastrointestinal ultrasound: sub-analysis from TRUST&UC

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Background: In ulcerative colitis GIUS (GastroIntestinal UltraSound) is discussed to be a reliable surrogate parameter for inflammatory activity next to faecal calprotectin (FC), and to some extend

C-reactive protein (CRP). Treat to target (T2T) is an emerging concept of IBD management, which might lead to superior outcomes with regard to mucosal healing, steroid-free remission, and hospitalisation as shown with anti-TNF therapies in previous studies.[1] To ensure a stringent T2T approach, it is crucial to facilitate non-invasive, inexpensive, and reliable diagnostics to monitor disease activity. Recently, we published a multi-centre study evaluating the capability of GIUS to monitor therapy response in Crohn's disease patients.[2,3] Here we provide a first subgroup analysis of the TRUST&UC study (TRansabdominal UltraSonography of the bowel To monitor disease activity in subjects with ulcerative colitis) focussing on the monitoring of anti-TNF therapy response in ulcerative colitis patients.

Methods: In this sub-analysis of TRUST&UC, a prospective, observational multi-centre study, GIUS, clinical (Simple Clinical Colitis Activity Index, SCCAI) and laboratory parameters (CRP, FC) were assessed during anti-TNF therapy at week 0, 2, 6, and 12 in patients with active UC (SCCAI ≥ 5) and an increased bowel wall thickening (BWT) at baseline. Threshold for normal BWT was >4 mm for sigmoid colon and >3 mm for the descending colon.

Results: Within the study population, 29% (65/224) of patients received an anti-TNF therapy (adalimumab, infliximab, or golimumab) at least at one time during the study. Mean disease duration was 7.56 ± 8.39 years. A majority of TNF-treated patients had an increased BWT at baseline, a high clinical activity, represented by an SCCAI of 9.52 ± 2.62, and an increased FC level (n = 39, 1609 ± 1721.7 µg/g). The clinical activity changed significantly within 6 weeks for 61.5% (n = 40) of the patients (9.08 ± 2.27 vs. 4.23 ± 4.00, p < 0.001). Of the patients with anti-TNF therapy at baseline and Week 6 (n = 44) 47.7% (n = 21) experienced a normalisation and 34.1% (n = 15) a reduction of BWT at sigmoid colon or descending colon already within 6 weeks upon anti-TNF therapy. Patients with an ongoing vascularisation at Week 6 and 12 had a significantly higher SCCAI compared with patients with no colour Doppler signal (p < 0.001).

Conclusions: We demonstrated that anti-TNF treatment results in normalisation/reduction of BWT in a majority of UC patients as early as 6 weeks after start of anti-TNF therapy. Consequently, GIUS is useful in early monitoring of therapy response to anti-TNF therapy in UC patients enabling a non-invasive, easy, and repeatable means of tight control in daily practice.

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DOP58

IdeaL: a multi-centre prospective infliximab dose to level pharmacokinetic study during induction in paediatric Crohn's disease

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Background: Infliximab (IFX) is an effective therapy for Crohn's disease (CD), but pharmacokinetic data during induction are sparse. The objective of this study was to model the pharmacokinetic (PK) and use individual clearance (CL) estimates to explore relationships between PK and clinical remission in children with CD receiving IFX induction.

Methods: A prospective study was conducted at 3 Canadian Children IBD Network sites. Baseline data collected included simple endoscopic score (SES-CD) and weighted Paediatric CD Activity index (wPCDAI). IFX doses ranged 5 to 10 mg/kg. Up to 8 IFX levels per subject were collected: trough and peak at doses 2 and 3, trough prior dose 4, between doses 3 and 4, and trough prior to dose 5. Free antibody to IFX (ATI) levels measured at doses 3, 4, and 5. Faecal calprotectin (FCP), wPCDAI, CBC, albumin (ALB), ESR, and CRP samples were also collected at each dose. NONlinear Mixed Effects Modelling was used to develop a population PK model using standard model building approaches. Covariate factors had to be significant at p < 0.001 and clinically relevant (>20% change in CL) to be retained. Dose and frequency may be adjusted clinically or based on preceding trough levels.

Results: Thirty-five subjects, 18 males, were recruited and followed for up to 22 weeks over 5 doses. Median age was 12.3 years (IQR: 10.2–14.8). Median dose for Dose 1 was 6.0 mg/kg (IQR: 5.0–7.0) and increased to 7.0 mg/kg (IQR: 5.0–8.3) for Dose 5. Eighty per cent of patients did not follow the standard induction and maintenance regimen of 0, 2, 6, and 14 weeks. Dose 4 had the most variability in frequencies with the median of Q6W. IFX CL was marked varied between subjects and improved during follow-up. Median baseline CL was 0.31 (IQR: 0.24,0.40). During single covariate evaluations, the following factors were identified as potentially predictive of IFX CL: ALB (negative correlation) and FCP, CRP, SES-CD, wPCDAI, and ESR (positive correlation). On back elimination, only ALB and CRP were important predictors. CL had a nonlinear correlation with weight where CL/kg was higher in those weigh < 30 kg vs. those >30 kg (p = 0.005). Twenty-nine subjects (83%) went into complete remission (wPCDAI <12.5). IFX CL of ≤0.39 l/day was a good predictor of remission status determined by wtPCDAI at Dose 5 (AUC [95% CI] = 0.828[0.63–1.00], p = 0.013). ATI levels drawn at Doses 4 and 5 were all negative.

Conclusions: IFX CL is variable and affected by factors including weight, ALB, disease activity and endoscopic severity. Under dosing is common in lower age bracket, due to higher drug CL/kg using current weight-based dosing. Paediatric IBD patients may benefit from precision medicine using PK model-based (dashboard) dose adjustments where individualised dosing can be calculated based on individual patient factors.

DOP59

Proactive infliximab drug monitoring is superior to conventional management in inflammatory bowel disease

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Background: There is increasing evidence supporting the use of therapeutic drug monitoring (TDM) of anti-TNF therapies following loss of response in inflammatory bowel disease (IBD). On the other hand, it is still unknown whether proactive TDM can improve clinical outcomes in these patients. The aim of this study was to evaluate clinical and endoscopic outcomes of a proactive TDM strategy following infliximab (IFX) induction therapy.
Methods: Patients completing IFX induction therapy were prospectively assigned to a proactive TDM protocol (pTDM). Before the fourth infusion and every 2 infusions, IFX drug levels and anti-drug antibodies were measured using a drug-sensitive assay (Theradiag®, Lisa Tracker). Treatment was proactively escalated aiming at an IFX trough level of 3–7 μg/ml—Crohn's disease (CD) or 5–10 μg/ml—ulcerative colitis. A retrospective cohort of patients treated with IFX but without TDM was used as a control group (noTDM). Endpoints included the need for surgery (perianal or bowel resection), hospitalisation, treatment discontinuation (due to loss of response or serious adverse event), and rates of mucosal healing up until 2 years of follow-up. Primary IFX non-responders were excluded from either group.
Results: In total, 240 patients were included in the study [pTDM, n = 57 and noTDM, n = 183]; [75.4% with CD]. Disease characteristics, prior anti-TNF exposure and baseline C-reactive protein levels were non-significant between groups. IFX escalation was more common in pTDM patients (73.7% vs. 25.7%, $p < 0.001$). PTDM patients required less surgery (8.8% vs. 21.3%, $p = 0.032$) and presented higher rates of mucosal healing (71.9% vs. 44.3%, p <0.001) than noTDM patients. PTDM and noTDM presented similar needs for hospitalisation ($p = 0.094$) and IFX discontinuation ($p = 0.722$). A composite endpoint of any unfavourable outcome was more common in noTDM patients (68.3% vs. 49.1%, $p = 0.011$). Regression analysis identified proactive TDM (OR 3.26; 95% CI 1.68–6.31; $p < 0.001$) and immunomodulator use (OR 2.44; 95% CI 1.36–4.36; $p = 0.003$) as independently associated with mucosal healing. Proactive TDM was also independently associated with fewer IBD-related surgeries [OR: 0.36; 95% CI 0.13–0.95; $p = 0.039$].
Conclusions: Proactive TDM was associated with less surgeries and higher rates of mucosal healing than conventional non-TDM based management.

DOP60

The interleukin 22 transcriptional programme is activated in human colonic inflammation and associated to anti-TNFα primary non-response in Crohn's

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Background: Interleukin 22 (IL-22) is an effector cytokine regulated by IL-23, a key player in IBD pathogenesis and target of novel biologics. Preclinical studies suggest a protective role for IL-22 in the context of acute intestinal injury and an inflammatory one in chronic inflammation. Little is known though about its role in human IBD.
Methods: Considering that the only tissue responsive to IL-22 is the intestinal epithelium, we generated colonic organoids (colonoids) from biopsies taken from healthy controls (n = 4) and treated them with IL-22, or other cytokines relevant to IBD pathogenesis (TNFα, IL-17A, and IFNγ). Whole transcriptome profiling was performed using the Illumina platform. Association to clinical phenotypes was performed with gene set variation analysis (GSVA) by testing for enrichment of the generated IL-22 transcriptional signature (top 50 up-regulated transcripts) in our own (controls: 6; UC: 16) and reposited datasets (GSE59071 and GSE16879).
Results: The IL-22 transcriptional programme was the second largest based on number of differentially expressed genes (DEG) induced in human colonoids by IBD-relevant cytokines (IL-22: 1251, IFNγ: 1310, TNFα: 716, IL17A: 245, filtering on FDR < 0.01). Most of the transcripts regulated by IL-22 were shared with the other transcriptional programmes (79% of DEG) while in hierarchical clustering IL-22 clustered closely to TNFα and IL17A. Among the most highly enriched GO terms for all four cytokines were 'cytokine-mediated signalling pathway', 'cytokine production', 'response to wounding', 'regulation of cell adhesion' with concordant activation across conditions (up-regulation). All transcriptional signatures, including IL-22, were enriched in active inflammation regardless of phenotype (UC, colonic CD). Enrichment for the IL-22 and TNFα transcriptional profiles prior to starting anti-TNFα therapy was associated with primary non-response in CD (area under the ROC curve: 0.88, $p = 0.007$ and 0.87, $p = 0.009$) but not UC.
Conclusions: We identify, for the first time, striking transcriptional similarities between IL-22 and other pro-inflammatory cytokines known to drive IBD. We show that the IL-22 regulated transcriptional programme is active in the context of human colonic inflammation and, importantly, enriched in those CD patients who failed anti-TNFα induction. Our findings highlight the therapeutic potential of IL-22 targeted personalised medicine approaches for human intestinal inflammation.

DOP61

A nationwide cohort study of colectomy rates for ulcerative colitis during the introduction of biologic therapy

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Background: Conflicting studies exist regarding changing colectomy rate for ulcerative colitis (UC) over time. Clinical trials suggest high-cost biologic medications reduce colectomy rates, but this has not been corroborated in English population data. This study aimed to use English population-level data to investigate colectomy rates over time during the introduction of infliximab use for UC.
Methods: The Hospital Episode Statistics (HES) were interrogated between 2003 and 2016. Emergency cohort inclusion criteria: UC primary diagnosis or secondary diagnosis with a primary acute colitis diagnosis, age >17, emergency admission ≥ 3 days. Total population cohort inclusion criteria: All colectomies with a primary UC diagnosis. Infliximab (IFX) coding was available from 2006. Kaplan–Meier, Cox regression, and average annual

percentage change (AAPC) were used to investigate colectomy rate over time. Interrupted time series (ITS) analysis was used to investigate colectomy rate change after National Institute for Clinical Excellence (NICE) approval for IFX use in moderate–severe UC in December 2008.

Results: Emergency cohort: 37 981 patients included; 49% female and median age 46. Cumulative incidence of colectomy at 30 and 90 days, 1, 3, and 5 years after emergency admission was 0.10, 0.12, 0.17, 0.21, and 0.23, respectively (SE 0.002)

Figure 1 shows colectomy rates at 30 days, 1 and 3 years, and rate of IFX use within 30 days by year. AAPCs for 30-day, 90-day, 1-, 3-, and 5-year colectomies were –1.6, –1.3, –1.8, –0.7 and –0.3, respectively. AAPC for 30-day IFX use was +52.6.

ITS showed changes in 30 and 90-day colectomy rates but not 1 or 3 years (Table 1)

Population cohort: 17 580 UC colectomies included. AAPCs for total, emergency and elective cases were –1.31, –0.24, and –1.83, respectively. ITS analysis showed reduction in colectomy rate after 2008 of 2.4% per year.

Conclusions: Mixed analyses suggest that the rate of colectomy has decreased modestly over time. In some cases, rates reduce after 2008 but this is likely multi-factorial, as the IBD Standards were also introduced in 2009. The reduction in short-term colectomy rates is not reflected in medium-term colectomy rates. It is not clear whether the reduction in colectomy rates has plateaued or is still reducing. A lack of clinical information regarding disease severity precludes further detailed interpretation.

DOP62

A novel formulation of CT-P13 (infliximab biosimilar) for subcutaneous administration: 1-year result from a Phase I open-label randomised controlled trial in patients with active Crohn's disease

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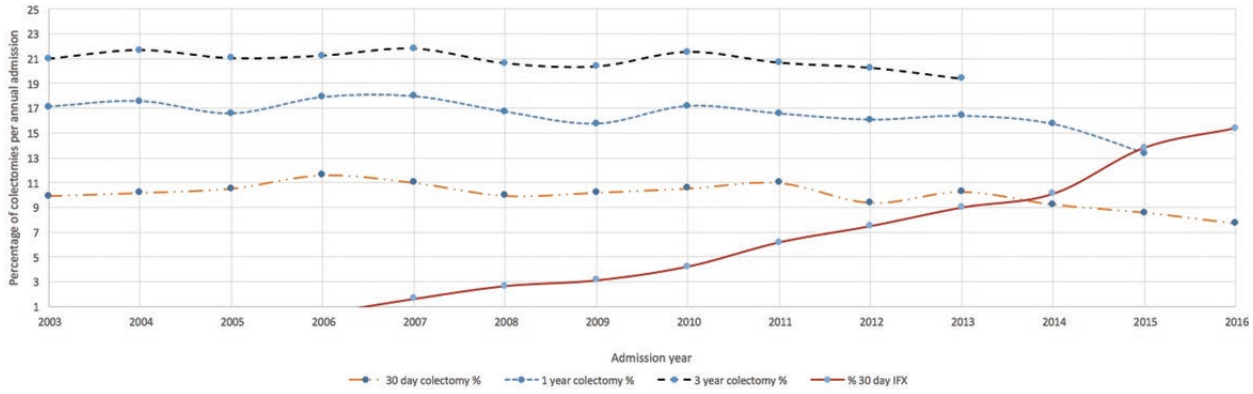
Background: Efficacy and safety of new subcutaneous (SC) formulation of CT-P13 (CT-P13 SC) up to Week 30 were comparable with intravenous (IV) formulation in both patients with Crohn's disease[1] (CD) and rheumatoid arthritis.[2] The aim of this study was to report pharmacokinetics (PK), efficacy and overall safety of CT-P13 SC in patients with CD throughout the 1-year treatment period.

Methods: Patients with moderate-to-severe CD (CDAI score 220–450) were administered CT-P13 IV 5 mg/kg at Weeks 0 and 2, and randomised into four cohorts at Week 6. Cohort 1 received CT-P13 IV 5 mg/kg every 8 weeks and Cohorts 2–4 received CT-P13 SC 120 mg, 180 mg, and 240 mg,, respectively, every 2 weeks up to Week 54. Blood samples were collected before study drug administration at each visit and drug levels were determined by electrochemiluminescent assay. Efficacy parameters of CDAI-70 response, clinical remission (CDAI<150), endoscopic response and remission, and overall safety were evaluated.

Results: In total, 44 patients were randomly assigned to 4 cohorts (1:1:1:1 ratio). Overall clinical response results were comparable between IV and SC cohorts after randomisation at Week 6 up to Week 30, whereas clinical remission appears to be numerically higher in the SC cohorts at Week 54. (Table 1). The mean C_{trough} (pre-dose serum concentration of CT-P13 before next dose injection) in the SC cohorts throughout the study visits were higher than those of IV cohort after randomisation. C_{trough} values increased with SC dose and were substantially greater than the target therapeutic concentration (5 μg/ml)[3] throughout the study period (Figure 1). Safety profiles for CT-P13 SC cohorts were also comparable to the IV cohort. In total, injection site reactions were



Line graph showing annual colectomy rate by admission year for various colectomy intervals and annual Infliximab use

Outcome	Time period	Odds ratio (*) (95% CI)	Risk difference (**) (95% CI)	Within period *p*-value (+)	Interaction *p*-value (+)
30 day colectomy	Pre NICE IFX	1.01 (0.98, 1.04)	0.1 (–0.2, 0.4)	0.52	0.003
30 day colectomy	Post NICE IFX	0.96 (0.94, 0.98)	–0.4 (–0.6, –0.2)	<0.001	0.003
90 day colectomy	Pre NICE IFX	1.01 (0.98, 1.04)	0.1 (–0.2, 0.4)	0.54	0.008
90 day colectomy	Post NICE IFX	0.96 (0.95, 0.98)	–0.4 (–0.6, –0.2)	<0.001	0.008
1-year colectomy	Pre NICE IFX	1.00 (0.98, 1.03)	0.0 (–0.4, 0.4)	0.97	0.08
1-year colectomy	Post NICE IFX	0.97 (0.95, 0.99)	–0.4 (–0.7, –0.1)	0.004	0.08
3 year colectomy	Pre NICE IFX	1.00 (0.97, 1.02)	0.0 (–0.4, 0.3)	0.81	0.36
3 year colectomy	Post NICE IFX	0.98 (0.95, 1.01)	–0.3 (–0.8, 0.2)	0.18	0.36
	(*) Odds ratio represents relative change in the odds of colectomy for a 1-year increase	(**) Risk difference represents the absolute change in % risk of colectomy for a 1-year increase	(+) *p*-values from logistic regression analysis		

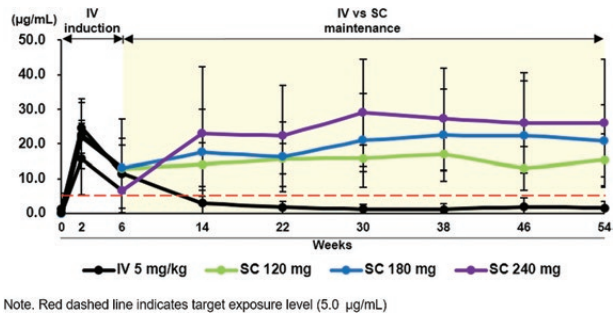
Interrupted time series analysis of annual colectomy rates after emergency admission with UC, comparing time series before and after NICE approval for IFX in moderate to severe UC.

reported in 11.4% of the patients, but all cases were of Grade 1 or 2 in intensity (Table 1).

Table 1. Summary of efficacy and safety results up to Week 54.

		Cohort 1 IV 5 mg/kg (N=12[a])	Cohort 2 SC 120 mg (N=11)	Cohort 3 SC 180 mg (N=12)	Cohort 4 SC 240 mg (N=7[a])
CDAI-70 response, n (%)	Week 6	7 (58.3)	9 (81.8)	7 (58.3)	5 (71.4)
	Week 22	9 (75.0)	9 (81.8)	9 (75.0)	5 (71.4)
	Week 30	8 (66.7)	9 (81.8)	10 (83.3)	5 (71.4)
	Week 54	7 (58.3)	9 (81.8)	7 (58.3)	6 (85.7)
Clinical remission, n (%)	Week 6	3 (25.0)	6 (54.5)	2 (16.7)	1 (14.3)
	Week 22	5 (41.7)	7 (63.6)	4 (33.3)	3 (42.9)
	Week 30	7 (58.3)	9 (81.8)	7 (58.3)	5 (71.4)
	Week 54	4 (33.3)	8 (72.7)	7 (58.3)	4 (57.1)
Endoscopic response, n/N(%) [b,d]	Week 30	4/6 (66.7)	6/7 (85.7)	7/7 (100.0)	4/5 (80.0)
	Week 54	5/7 (71.4)	8/8 (100.0)	4/4 (100.0)	3/4 (75.0)
Endoscopic remission, n/N(%) [c,d]	Week 30	3/7 (42.9)	3/8 (37.5)	3/9 (33.3)	1/6 (16.7)
	Week 54	3/7 (42.9)	6/9 (66.7)	1/4 (25.0)	2/6 (33.3)
		Cohort 1 IV 5 mg/kg (N=13)	Cohort 2 SC 120 mg (N=11)	Cohort 3 SC 180 mg (N=12)	Cohort 4 SC 240 mg (N=8)
Safety, n (%)	Treatment-emergent AEs	10 (76.9)	9 (81.8)	8 (66.7)	6 (75.0)
	Administration-related reactions	1 (7.7)	0	0	1 (12.5)
	Injection site reactions	0	1 (9.1)	3 (25.0)	1 (12.5)
	Infections	3 (23.1)	7 (63.6)	2 (16.7)	4 (50.0)

[a] One patient was excluded due to early withdrawal and no efficacy assessment done after Week 6 treatment.
[b] Endoscopic response was defined as ≥50% decrease of SES-CD score from the baseline.
[c] Endoscopic remission was defined as ≤2 points of SES-CD score.
[d] Patients who did not have mucosal abnormalities at previous assessment or early discontinued from the study were excluded from the denominator.



Note. Red dashed line indicates target exposure level (5.0 μg/mL)

Figure 1. Mean (±SD) pre-dose concentration of CT-P13 vs. time by cohort.

Conclusions: The results from 1-year treatment suggest similar efficacy and safety of CT-P13 SC to CT-P13 IV. The mean serum concentration in all SC cohorts consistently exceeded the threshold of target therapeutic concentration. These results show that the novel SC formulation of CT-P13 may expand treatment options for use of infliximab biosimilar by providing high consistency in drug exposure during maintenance treatment.

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DOP63

DOP63 is a late-breaking abstract and is published on www.ecco-ibd.eu/publications and www.academic.oup.com/ecco-jcc

DOP Session 8 - Intestinal healing

DOP64

Minimal additional benefits in adding faecal haemoglobin to faecal calprotectin in predicting endoscopic disease activity in patients with inflammatory bowel disease

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Background: Accurate evaluation of disease activity is essential in patients with inflammatory bowel disease (IBD). While endoscopic remission is the ideal therapeutic goal, non-invasive serum and faecal biomarkers are more acceptable to patients and less costly. We aimed to evaluate the performance of these non-invasive

biomarkers on prediction of clinical and endoscopic disease activity in IBD patients.

Methods: Patients diagnosed with ulcerative colitis (UC) or Crohn's disease (CD) with regular follow-up in our unit were recruited. The clinical activity scores were recorded. Serum biomarkers included C-reactive protein (CRP), albumin, and haemoglobin. Faecal biomarkers included faecal calprotectin (FCT) and faecal immunochemical test (FIT). These biomarkers were compared with endoscopic disease activity in patients who had recent sigmoidoscopy or ileocolonoscopy within 1 year.

Results: One hundred and thirteen patients (mean age 44.7 ± 17.6, 63.7% male, 54.9% UC: 45.1% CD) were recruited. FCT correlated well with FIT (r = 0.583), CRP (r = 0.56), albumin (r = –0.543) and haemoglobin (r = –0.352; all p < 0.001). The levels of these biomarkers were not significantly different between patients in clinical remission (72.2%) and those not in clinical remission (all p > 0.05). Out of 66 patients with recent endoscopy, 41 (62.1%) had endoscopically active disease. These patients were younger (36.4 vs. 47.2 years, p = 0.025), had higher FCT (632 vs. 49 µg/g, p < 0.001), higher FIT (65 vs. 16 µg/g, p < 0.001), higher CRP (1.15 vs. 0.37 mg/dl, p = 0.005), lower albumin (41 vs. 45 g/l, p = 0.001) and lower haemoglobin (12.7 vs. 13.7 g/dl, p = 0.024). Among the 5 biomarkers (Figure A), FCT demonstrated the best performance characteristics (AUROC 0.96). Using a derived cut-off level of FCT for endoscopically active disease of 168 µg/g, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) being 82.9%, 100%, 100%, and 78.1%,, respectively. For FIT, the AUROC was 0.80. Using a derived cut-off level of FIT for endoscopically active disease of 16 µg/g, the sensitivity, specificity, PPV, and NPV was 65.9%, 92%, 99.1%, and 62.2%, respectively. FCT works equally well for UC (AUROC 0.98) and CD (AUROC 0.94), while FIT works better for UC (AUROC 0.843) than CD (AUROC 0.773) (Figure B). Combining FCT and FIT improved the overall NPV to 85.2% (Figure C).

Conclusions: Elevated FCT, but not FIT, accurately identified all patients with endoscopically active IBD. Combination of FCT and FIT further increased the NPV only.

DOP65

The association of faecal calprotectin level and combined mucosal and transmural healing in patients with Crohn's disease

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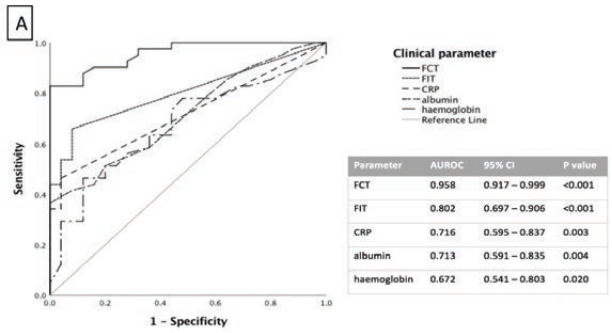
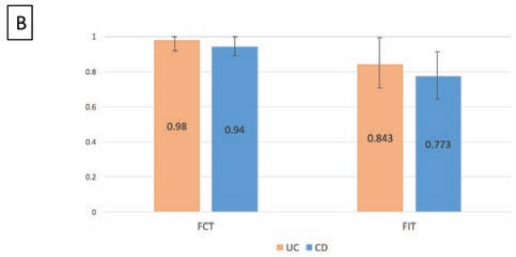
Background: Combined mucosal and transmural healing of inflammatory lesions in patients with Crohn's disease (CD) are regarded as the predictor of favourable outcomes. However, non-invasive markers for predicting combined mucosal and transmural healing is needed for patients' acceptance and tighter monitoring. This study aimed to evaluate the role of faecal calprotectin (FC) as a non-invasive marker for predicting combined mucosal and transmural healing in Korean patients with CD on anti-TNF therapy.

Methods: A total of 226 CD patients on anti-TNF therapy who underwent endoscopic evaluation, radiologic evaluation and FC measurement between August 2017 and July 2018 were enrolled in this study. Endoscopic mucosal healing was independently assessed by two certified endoscopists and defined as no visible ulcers related to CD in colon and small bowel. Transmural healing in computed tomography enterography or magnetic resonance enterography was assessed by one certified radiologist.

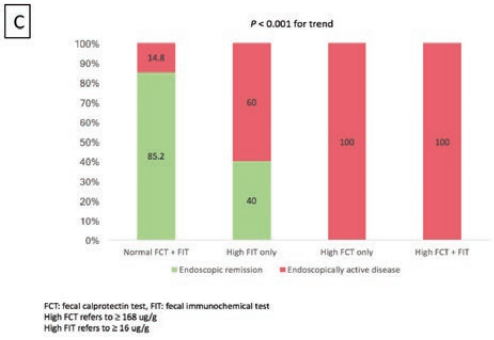


Parameter	AUROC	95% CI	P value
FCT	0.958	0.917 – 0.999	<0.001
FIT	0.802	0.697 – 0.906	<0.001
CRP	0.716	0.595 – 0.837	0.003
albumin	0.713	0.591 – 0.835	0.004
haemoglobin	0.672	0.541 – 0.803	0.020

AUROC: area under receiver-operating characteristic curve, CI: confidence interval, CRP: C-reactive protein, FCT: fecal calprotectin test, FIT: fecal immunochemical test



AUROC: area under receiver-operating characteristic curve, CD: Crohn's disease, FCT: fecal calprotectin test, FIT: fecal immunochemical test, UC: ulcerative colitis
Error bars represent 95% confidence interval



FCT: fecal calprotectin test, FIT: fecal immunochemical test
High FCT refers to ≥ 168 ug/g
High FIT refers to ≥ 16 ug/g

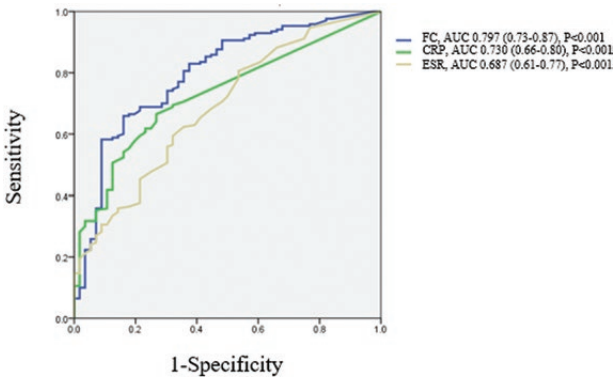
(A) Performance characteristics of different clinical parameters in predicting endoscopic active inflammatory bowel disease. (B) AUROC of faecal biomarkers for endoscopically active disease. (C) Endoscopic disease activity according to FCT and FIT profile.

Deep healing was defined as a combination of mucosal and transmural healing.

Results: Out of 226 patients, 157 (69.5%) were men, and the median age at diagnosis of CD was 24 years (IQR, 18–29 years). The median disease duration prior to FC measurement was 10 years (IQR, 6–14 years). At the time of evaluation, ileocolonic location was observed in 181 patients (80.1%) and stricturing or penetrating behaviour was observed in 153 patients (67.7%). Out of 226 patients, 56 (24.8%) had deep healing, 34 (15.0%) had mucosal healing without transmural healing, 33 (14.6%) had transmural healing without mucosal healing, and 103 (45.6%) had both mucosal and transmural inflammation.

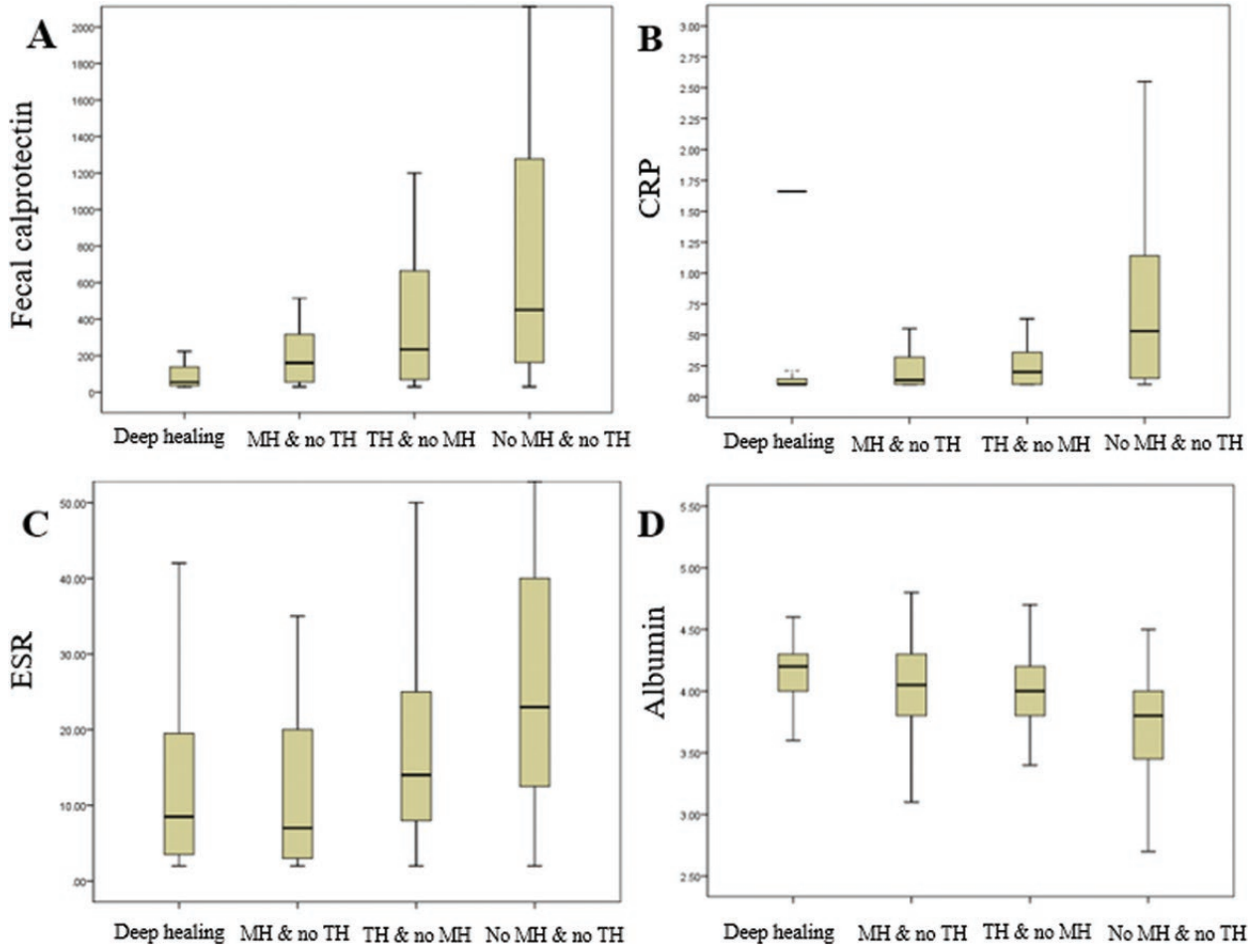
The median level of FC in patients with deep healing was lower than that of other groups (55.1 mg/kg vs. 305.0 mg/kg, $p < 0.001$).

The FC cut-off level of 164.5 mg/kg indicated deep healing with a sensitivity and specificity of 0.659 and 0.839, respectively (area under the receiver-operating characteristic curve, 0.797; 95% confidence interval, 0.728–0.865).



Receiver-operating characteristic (ROC) curve analysis of each marker to predict deep healing in patients with Crohn's disease (n = 226). FC, faecal calprotectin; AUC, area under curve.

Conclusions: The FC level could be used as a reliable indicator for combined mucosal and transmural healing in patients with Crohn's disease.



Faecal calprotectin (A), CRP (B), ESR (C), and albumin (D) in those with mucosal healing, transmural healing, and deep healing. MH, mucosal healing; TH, transmural healing.

	Deep healing (n = 56)	Mucosal or transmural inflammation (n = 170)	p-value
Male, n (%)	41 (73)	116 (68)	0.483
Age at CD diagnosis (years), median (IQR)	23 (18–28)	22 (18–29)	0.829
Age at FC-level measurement (years), median (IQR)	32 (26–39)	34 (27–42)	0.093
Montreal location L1/L2/L3, n (%)	9/4/43 (16/7/77)	22/10/138 (13/6/81)	0.775
Montreal behaviour B1/B2/B3, n (%)	26/9/21 (46/16/38)	47/33/90 (28/19/53)	0.032
Medication, IFX monotherapy/ ADA monotherapy/anti-TNF+ IM, n (%)	16/7/33 (28.6/12.5/58.9)	46/26/98 (27.1/15.3/57.6)	0.873
FC (mg/kg), median (IQR)	55.1 (34.6–138.5)	305.0 (100.6–871.0)	<0.001
CRP (mg/l), median (IQR)	0.1 (0.1–0.17)	0.29 (0.1–0.91)	<0.001
ESR (mm/h), median (IQR)	8.5 (3.25–19.8)	19.0 (8.0–34.3)	<0.001

Patient's characteristics according to deep healing status. CD, Crohn's disease; FC, faecal calprotectin; IFX, infliximab; ADA, adalimumab; IM, immunomodulators; IQR, interquartile range.

DOP66

Surveillance colonoscopies in ulcerative colitis: does it make a difference?

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Background: Patients with ulcerative colitis (UC) and Crohn's disease (CD) have a higher risk of colorectal cancer compared with the general population. Surveillance colonoscopy for detection of dysplasia is advised; however, the ideal intervals for surveillance have not been established. This study aims to identify the association between colonoscopy surveillance intervals for UC patients in Ontario and the incidence and CRC stage.
Methods: This study was approved by the Ontario Institute for Clinical Evaluative Sciences (ICES), which permitted access to data from the Ontario Cancer Registry (OCR) and Ontario Health Insurance Plan (OHIP) claims. This allowed us to retrospectively identify UC patients diagnosed from 1994 onwards with an OHIP billing code 556 and their incidence of CRC with an OHIP billing code 153. The primary endpoint was CRC stage at the time of CRC diagnosis compared between patients who did not have screening colonoscopies, average screening interval ≤3 years and an average screening interval >3 years. We defined low-risk CRC stage as patients according to the Cancer Care Society (CCS) to have a 5-year survival >80% compared with high-risk CRC as patients with 5-year survival <80%. According to CCS, CRC stages I, IIa, III and IIIa were classified as low-risk and CRC stages IIb, IIc, IIIb, IIIc, IIINOS, IV were high risk. Analysis was conducted using SAS 9.4 statistical software. Chi-square testing was used to compare frequencies.
Results: Within the ICES database, a total of 631 UC patients developed CRC and 264 of them had staging information available. Among these patients, those who had average follow-up colonoscopies at a frequency ≤ 3 years presented with an earlier stage of CRC (58.6% of the time) compared with those with follow-up colonoscopies at a frequency > 3 years (44% of the time) and those with no follow-up colonoscopies (18.5% of the time) (Mantel–Haenszel chi-square p-value < 0.001). In addition, mortality benefit was observed at 15-years after time of eligibility for surveillance colonoscopies, with survival seen in 75.1% of UC patients who had CRC and average colonoscopies ≤ 3 years, compared with 70.1% in the average colonoscopies > 3 years cohort and 57.8% in the no colonoscopy surveillance cohort (p = 0.004).
Conclusions: UC patients who underwent colonoscopies at average intervals of ≤ 3 years had CRC detected at earlier stages compared with those who underwent colonoscopies at >3 year intervals or those who did not have follow-up colonoscopies. Mortality benefit was also observed in those patients with UC and CRC who had colonoscopies at average intervals ≤ 3 years. This supports a surveillance interval for UC of ≤ 3 years.

DOP67

Magnification endoscopy with optical chromoendoscopy for *in vivo* assessment of histological inflammation in patients with inflammatory bowel disease

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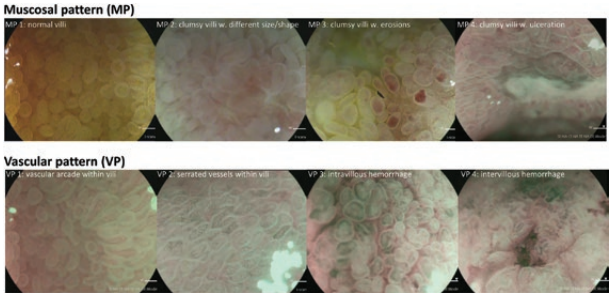
Background: Apart from mucosal healing as an established treatment goal in inflammatory bowel diseases (IBD), recent evidence suggests that histological healing is another key prognostic parameter in IBD patients. Herein we aimed to evaluate whether magnification endoscopy in combination with optical chromoendoscopy can accurately assess histological inflammation in IBD patients.
Methods: In this prospective study, 82 IBD patients (30 UC, 52 CD) were included. The *in vivo* histological inflammation was made with magnification endoscopy in combination with optical chromoendoscopy by three independent endoscopists using a novel magnification score (Figure 1). Targeted biopsies of the imaged areas were obtained and results were compared against two histological scores in UC (Robarts Histopathology Index, RHI; Nancy Histology Index, NHI) and one score in CD (modified Riley index, mRI). Moreover, interobserver agreement was calculated.



Results: Magnification endoscopy evaluating inflammatory activity based on the mucosal and vascular pattern showed strong correlation with histopathologic scoring in both UC (RHI: r = 0.83, NHI: r = 0.78, both $p < 0.05$) and CD (mRI: r = 0.74, $p < 0.05$) with high accuracy, sensitivity and specificity for assessing the histological inflammation. Furthermore, 25% of patients with mucosal healing on standard endoscopy showed signs of microinflammation on magnification endoscopy in combination with optical chromoendoscopy while none of the patients with mucosal and vascular healing under magnification endoscopy in combination with optical chromoendoscopy exhibited microscopic inflammation. Interobserver agreement for grading intestinal inflammation by magnification endoscopy with optical chromoendoscopy was substantial ($\kappa > 0.7$).

Conclusions: Magnification endoscopy in combination with optical chromoendoscopy allows for a precise real-time assessment of histological inflammation in IBD patients. Therefore, this approach holds the potential to reduce the need of physical biopsies for monitoring of inflammatory activity in patients with IBD during colonoscopy.

DOP68

Histological remission (NANCY index) is superior to endoscopic mucosal healing in predicting relapse-free survival in patients with ulcerative colitis in clinical and endoscopic remission

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Background: Histological grade is increasingly recognised as an important predictor of relapse in ulcerative colitis (UC) patients. Current treatment targets aim at mucosal healing, however many patients continue to have histological activity. We aimed to assess histological activity using the validated Nancy histological activity score as a predictor of future relapse in UC patients in endoscopic and clinical remission.

Methods: Patients with UC attending the inflammatory bowel disease clinic at a single tertiary centre between 2015 and 2018 were included. Patients in clinical and endoscopic remission who underwent a surveillance colonoscopy between 2009 and 2017 were identified. Clinical remission was defined by partial Mayo score (MSp) <2, and endoscopic remission was defined by Mayo Endoscopic Subscore (MES) ≤1. Patients with inadequate biopsies, <18 years old, previous colectomy, on oral or intravenous steroids, or hospitalised were excluded. Blind assessment of biopsies were performed by two expert histopathologists, and assigned a Nancy score with histological remission defined by Nancy ≤ 1 and histological activity Nancy 2-4. Predictive factors associated with relapse were analysed. Relapse was defined as MSp > 2, initiation of steroids, hospitalisation, and escalation or alteration of therapy.

Results: 74 patients in both clinical and endoscopic remission were included in the study. Median follow-up time was 42 months (IQR 26–63 months) with median relapse free period of 30 months (IQR 18–48 months). Patients with MES 0 (p = 0.02, Figure 1) and histological remission ($p \leq 0.0001$, Figure 2) demonstrated significantly longer relapse free survival. On multi-variate analysis only histological activity remained as an independent risk factor of future clinical relapse (hazard ratio 4.36, 95% CI 1.68–11.27; p = 0.002).

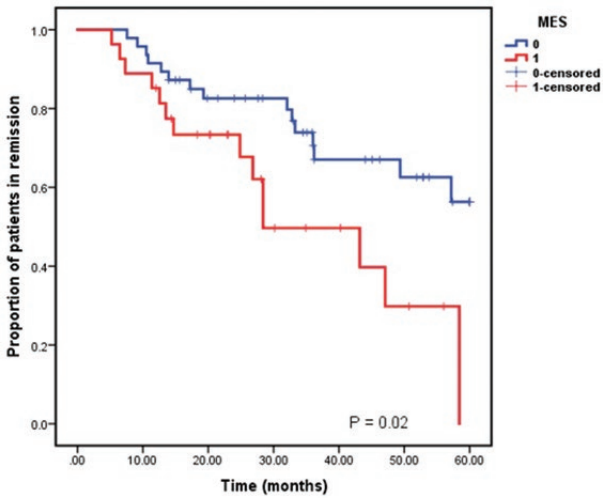

Figure 1. Kaplan–Meier curve comparing Mayo endoscopic subscore (MES) and clinical relapse.

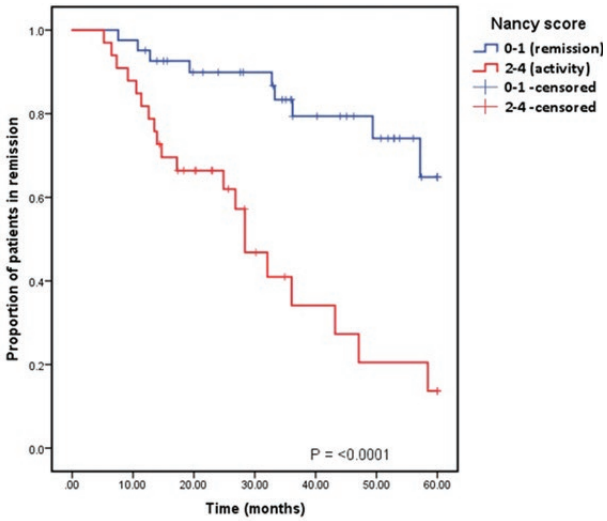

Figure 2. Kaplan–Meier curve comparing Nancy histological index and clinical relapse.

Conclusions: Histological grade is an important prognostic marker in UC patients in clinical and endoscopic remission. Histological remission independently predicts significantly longer relapse-free survival and thus may be a superior therapeutic target than endoscopic remission. Long-term prospective studies are needed to determine whether histological remission improves clinical and patient-reported outcomes.

DOP69

The detection with targeted biopsy and characterisation of neoplastic lesions by magnifying chromoendoscopy and NBI in surveillance colonoscopy of patients with ulcerative colitis: a sub-analysis of the Navigator Study

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Background: We recently reported the UC surveillance colonoscopy (SC) pancolonic NBI observation was not inferior to panchromoendoscopy (PCE) for the detection of both neoplastic lesions (13.4% vs. 9.0%) and colitis-associated dysplasia or cancer (CC/D) (6.3% vs. 4.9%). Moreover, the total examination time with NBI (15.0 min) was significantly shorter than that with PCE (19.8 min) ($p < 0.01$). This sub-analysis aimed to evaluate the magnified chromoendoscopic and NBI findings of detected lesions in the preceding prospective multi-centre randomised controlled trial (Navigator Study), and to also investigate the utilities of existing endoscopic classification to characterise the neoplastic lesions.

Methods: In total, 263 patients were randomised to either the PCE group ($n = 130$) or the NBI group ($n = 133$). SC in both groups was performed mainly with targeted biopsy. After either procedure detected a suspected neoplastic lesion, both procedures (Kudo's classification by chromoendoscopy and J-NET classification by NBI) were allowed to characterise the lesion with magnified observation. The central pathological diagnoses were made by two expert pathologists based on examinations including immunohistochemical staining (p53, Ki-67).

Results: In total, 20 sporadic adenomas, 10 indefinite dysplasia lesions, 9 low-grade dysplasia (LDG) lesions, 7 high-grade dysplasia (HGD), or cancer lesions were detected. Only 2 indefinite dysplasia lesions were identified by random biopsy, the others (96.1%) were identified by targeted biopsy. There were no significant differences in locations between sporadic adenoma and CC/D ($p = 0.12$). Most sporadic adenomas showed the type 3L pit pattern in contrast to CC/D, which were distributed from the 3L to the 5 irregular pit pattern ($p < 0.01$). However, Kudo's pit pattern was not useful for differentiating between LGD and HGD/cancer ($p = 0.62$). Most detected lesions (40/46, 87.0%) were brownish on NBI. The J-NET surface pattern and vessel pattern were also both useful for differentiating between sporadic adenoma and CC/D ($p = 0.05$, $p = 0.02$). Most sporadic adenomas showed type 2A of J-NET surface pattern or vessel pattern in contrast to CC/D, which were divided into type 2A and type 2B ($p = 0.05$, $p = 0.02$). However, J-NET surface pattern or vessel pattern also was not useful for differentiating between LGD and HGD/cancer ($p = 0.52$, $p = 0.76$).

Conclusions: Identification of neoplastic lesions by SC that depends on targeted biopsy is a reasonable approach. Brownish colouring on NBI observation may provide improved detectability in pancolonic NBI SC. The existing endoscopic classifications has limitations in terms of characterising CC/D. A newly developed endoscopic classification to judge the indications for endoscopic resection is thus warranted.

DOP70

An integrated multi-omics biomarker predicting endoscopic response in ustekinumab treated patients with Crohn's disease

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Background: Ustekinumab (UST), an anti-IL12/23p40 monoclonal antibody, has been approved for Crohn's disease (CD). The aim of this study was to identify baseline predictors of response using several omics layers, which ultimately may result in a multi-omics panel allowing individualised UST therapy.

Methods: Inflamed colonic ($n = 25$) and ileal ($n = 22$) biopsies were retrieved prior to first UST administration in patients with active CD, in addition to sorted circulating CD14+ monocytes and CD4+ T cells ($n = 39$). RNA was extracted from both lysed biopsies and sorted cells, and RNA sequencing performed. Proteomic analysis was performed on baseline serum samples ($n = 86$) using OLINK Proseek inflammation. Genotyping data were generated using Immunochip ($n = 38$). The genetic risk burden was determined for every patient using the SNPs which overlap with genes encoding functional proteins or RNAs. The six above-described layers of omics data were integrated and analysed using Multi-Omics Factor Analysis (MOFA). The strongest omic layers in terms of variance contribution to the latent factors explaining endoscopic response (≥50% in SES-CD by w24) were identified. Dimensionality reduction and feature extraction from the strongest -omic layers were performed followed by predictive modelling on the top-ranked features. Cross-validation using distinct test and training sets was performed for the ensemble and individual classifiers, as an internal validation to avoid over-fitting.

Results: MOFA identified 19 latent factors (LF, minimum explained variance 2%), with 3 LFs correlating with endoscopic response at w24 ($r = -0.24$, $r = 0.27$, $r = -0.25$; $p = 0.03$, $p = 0.01$, $p = 0.02$). The genomic and CD14 transcriptomic layers contributed significantly to the prediction of endoscopic response. Predictive modelling based on the results of the most dominant omic layers revealed a 10-feature

panel predicting endoscopic response at w24 with an accuracy of 98%. In contrast, classification performance based on 10 randomly selected features resulted in a drastic drop in accuracy (66%). Only 2 of the 10 features exhibited significant correlation with baseline faecal calprotectin, and 1 with CRP, suggesting that this panel is not a simple surrogate of baseline inflammation. From the genetic risk burden, we identified a 15-gene panel which could classify (accuracy 96.6%) the patients based on endoscopic response.

Conclusions: Through multi-omic data integration, we discovered pathways contributing to UST response, and identified a 10-feature transcriptomic and 15-feature genomic panel predicting endoscopic response to UST standard dosage. Further validation in larger and independent cohorts is warranted, as well as its UST specificity.

DOP71

Effects of ustekinumab induction therapy on endoscopic and histological healing in the UNIFI Phase 3 study in ulcerative colitis

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Background: Ustekinumab (UST) is an effective therapy for moderate–severe UC; however, data regarding histological healing and the combination of histological and endoscopic healing (also described as endoscopic improvement in the appearance of the mucosa) are unknown.

Methods: We evaluated the effects of UST on histological and endoscopic activity in the UNIFI Ph3 induction study of UST in moderate–severe UC(n = 961). Two colonic biopsies were collected from distal colon at screening and induction Wk8. Subjects not in response to placebo (PBO) at Wk8 received UST 6 mg/kg IV, and those not in response to UST IV received UST 90 mg SC; biopsies were obtained at Wk16. Endoscopic healing (EH; also described a endoscopic improvement in the appearance of mucosa) was defined as a Mayo endoscopy score <1; histological healing (HH) comprised the following Geboes score-based criteria: absence of erosion or ulceration, absence of crypt destruction, and <5% of crypts with epithelial neutrophil infiltration. To encompass both macro- and microscopic scales, histo-endoscopic mucosal healing (HEMH) was defined as achieving both EH and HH.

Results: At Wk8, EH was achieved in 26.6% and 13.8% of subjects treated with UST (combined 130 mg and 6 mg/kg IV doses)and PBO, respectively (adjusted tx difference, 12.8%; 95% CI, 7.9–17.8; p < 0.001). HH was achieved in 36.8% and 21.9% of UST and PBO-treated subjects, respectively (adjusted tx difference, 15.0%; 95% CI, 9.0–21.0; p < 0.001). Histo-endoscopic mucosal (HEMH) was achieved in 19.3% and 8.9% of UST and PBO-treated subjects, respectively (adjusted tx difference, 12.5%; 95% CI, 6.2–14.8; p < 0.001). Similar rates of EH, HH, and HEMH were achieved following induction with UST 130 mg or 6 mg/kg IV. Subjects not in response to PBO or UST at Wk8 were treated with UST at that time and re-evaluated at Wk16; of these, 12.1% and 16.5% of subjects who initially received UST or PBO IV, respectively, achieved HEMH. HH at Wk8 or Wk16 (irrespective of induction tx) was significantly associated with EH and HEMH (p < 0.001) and with both absolute levels and post-tx changes in Mayo score, partial Mayo score, and Mayo symptom sub-scores for stool frequency and rectal bleeding.

Table 1. Clinical outcomes for subjects with or without histological healing at Week 8 and Week 16 in the UNIFI Phase 3 induction study

Clinical Outcomes	Histologic Healing[a]	Without Histologic Healing[a]	p-value[b]
Week 8	N=283	N=533	
Mayo Score	3.95±2.57	6.89±2.53	<0.0001
Partial Mayo Score	2.45±1.84	4.39±2.21	<0.0001
Stool Frequency	1.09±0.95	1.81±1.03	<0.0001
Rectal Bleeding	0.30±0.56	0.86±0.89	<0.0001
Change in Mayo Score	-4.53±2.65	-2.15±2.39	<0.0001
Change in Partial Mayo Score	-3.46±2.14	-1.89±2.12	<0.0001
Change in Stool Frequency	-1.08±1.01	-0.63±0.90	<0.0001
Change in Rectal Bleeding	-1.18±0.91	-0.69±0.96	<0.0001
Week 16	N=140	N=209	
Mayo Score	3.71±1.94	6.01±2.43	<0.0001
Partial Mayo Score	1.98±1.27	3.44±2.08	<0.0001
Stool Frequency	0.96±0.83	1.56±1.02	<0.0001
Rectal Bleeding	0.13±0.38	0.51±0.69	<0.0001
Change in Mayo Score	-4.95±2.02	-3.08±2.32	<0.0001
Change in Partial Mayo Score	-4.04±1.63	-2.83±2.07	<0.0001
Change in Stool Frequency	-1.31±0.90	-0.92±0.99	0.0003
Change in Rectal Bleeding	-1.30±0.89	-0.99±0.85	0.0012

a: Values are reported as mean ± SD.
b: P-values based on t-test.

Conclusions: Among subjects with moderately–severely active UC, those receiving IV UST induction had higher rates of EH, HH, and HEMH than those receiving PBO. Approximately 10% of subjects who did not achieve clinical response 8 weeks after IV UST achieved HEMH following a second (SC) dose. HH is associated with reductions in clinical and endoscopic disease activity as well as patient-reported symptoms.

DOP72

Increased risk of advanced neoplasia in inflammatory bowel disease patients with recurrent low-grade dysplasia

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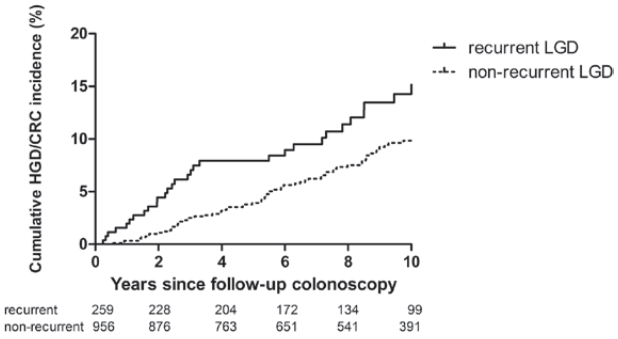
Background: A history of low-grade dysplasia (LGD) is a major risk factor for the development of high-grade dysplasia (HGD) and colorectal cancer (CRC) in inflammatory bowel disease (IBD) patients. Consequently, guidelines recommend an intensified surveillance programme for these patients. However, it is unknown how a second (recurrent) LGD impacts advanced neoplasia (HGD and/or CRC) risk. We aimed to assess the long-term advanced neoplasia risk in IBD patients with recurrent LGD and compared this to patients without subsequent dysplasia after initial LGD.

Methods: We identified all IBD patients with LGD from 1991 to 2005 in The Netherlands who received at least one follow-up colonoscopy in the subsequent 3 years, using the Dutch nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA). Follow-up data were collected until 2016. Kaplan–Meier curves were used to compare the cumulative advanced neoplasia incidence between patients with and without recurrent LGD at first colonoscopy after initial LGD. Patients were censored at the end of surveillance or colectomy.

Results: We identified 1215 IBD patients with colonic LGD and follow-up colonoscopy within 3 years (923 (76.0%) ulcerative colitis, 214 (17.6%) Crohn's disease, and 78 (6.4%) IBD unclassified). Mean time from initial LGD to first follow-up colonoscopy was 1.5 (±0.6) years in both patients with and without recurrent LGD. A total of 259 patients (21.3%) had recurrent LGD within 3 years, of whom 46 patients (17.8%, 31 CRC and 15 HGD) developed advanced neoplasia (vs. 10.9% in patients without recurrent LGD). Patients with recurrent LGD had a higher cumulative advanced neoplasia incidence (HR 1.70; 95% CI 1.20–2.41; p = 0.003; Figure 1). The cumulative advanced neoplasia incidence 2 years after follow-up surveillance colonoscopy was 4.4% in patients with dysplasia, vs. 1.4% in those without recurrent dysplasia.



Kaplan–Meier plot showing the cumulative advanced neoplasia incidence following first follow-up colonoscopy within 3 years after initial LGD, plotted separately for patients with and without recurrent LGD at follow-up colonoscopy.

Conclusions: Recurrent LGD at follow-up colonoscopy after initial LGD increased the advanced neoplasia risk (HR 1.70). Patients without LGD at follow-up colonoscopy after initial LGD had a cumulative advanced neoplasia incidence of 1.4% in the subsequent 2 years.

DOP Session 9 - Surgery and IBD

DOP73

Treatment of perianal fistulas in Crohn's disease, seton vs. anti-TNF vs. surgical closure following anti-TNF (PISA): a randomised controlled trial

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Background: Most patients with draining perianal Crohn's fistulas receive medical treatment with anti-TNF. So far, outcomes of this medical approach have not been directly compared with long-term seton drainage or surgical closure. The aim of this study was to identify the best treatment approach for perianal Crohn's disease. As closure rates were expected to be comparable based on our systematic review, we compared re-intervention rates among these three treatment arms. It was hypothesised seton drainage would result in fewer re-interventions compared with anti-TNF medication with or without subsequent surgical closure.

Methods: In this multi-centre randomised prospective trial, chronic seton drainage was compared with prolonged anti-TNF therapy and surgical closure following anti-TNF induction for the treatment of high perianal Crohn's fistula with a single internal opening. Patients with proctitis, rectovaginal fistulas, and patients who previously failed anti-TNF treatment were excluded. The primary outcome was the number of patients with fistula-related re-intervention(s), defined as surgical and/or (re)start anti-TNF within 1.5 year. Secondary outcomes were the perianal disease activity index (PDAI) and quality of life (QoL). Patients refusing randomisation due to a specific treatment preference were included in a parallel prospective PISA registry cohort.

Results: The study was stopped after inclusion of 44 of the 126 planned patients, based on futility at interim analysis (likelihood to show superiority of chronic seton treatment at the completion of the trial was less than 1%). A follow-up of minimally 6 months was awaited. Seton treatment was associated with the highest re-intervention rate within 1.5 year (10/15 vs. 6/15 anti-TNF and 3/14 surgical closure + anti-TNF patients, p = 0.02). No substantial differences in PDAI and QoL between the three treatment groups were observed. Interestingly, in the PISA prospective registry (n = 50), inferiority of chronic seton treatment could not be observed for any outcome measure.

Conclusions: The results imply that chronic seton treatment should not be recommended as the sole or superior treatment for perianal Crohn's fistulas. However, the statistical inferiority of seton treatment should be interpreted with caution, due to the crucial aspects of small numbers and as this inferiority could not be confirmed in the PISA registry data.

The PISA trial is registered at the Dutch National Trial Registry (NTR4137).

DOP74

Efficacy of ustekinumab in perianal Crohn's disease: the BioLAP multi-centre observational study

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Background: New therapeutic options for Crohn's disease (CD) patients with perianal lesions failing anti-tumour necrosis factor (TNF) therapy are needed. To date, no dedicated study with a large sample has evaluated the efficacy of ustekinumab on perianal CD (pCD). We assessed the efficacy of ustekinumab in pCD in a national multi-centre cohort and the predictive factors of success of the biological agent.

Methods: We conducted a French multi-centre, and observational study (Bio-LAP) including all patients with either active or inactive pCD (but with history of fistulizing and drained perianal lesion over the past 10 years) who received ustekinumab. In patients with active pCD at treatment initiation, the success of the biological agent was defined by clinical recovery at 6 months of treatment assessed by physician's appreciation without using additional medical or surgical treatment for perianal lesions. In patients with inactive pCD at treatment initiation, clinical recurrence of pCD was defined by the occurrence of perianal lesions and/or need of medical or surgical treatment.

Results: In total, 207 patients were screened. There were 75 (36.2%) males, the mean age at inclusion was 37.7 years, the mean BMI was 22 and the mean duration from CD diagnosis to initiation of treatment was 14.3 years. Of 207 (99%) patients, 205 have had at least 1 anti-TNF agent and a total of 197/207 (95.2%) patients had been exposed to thiopurine and/or methotrexate. Fifty-eight (28%) patients had previous exposure to vedolizumab. The mean number of prior perianal surgery was 2.8. The mean follow-up time was 66 weeks. Of 207(27%) patients, 56 discontinued therapy after a mean time of 363 days. In patients with active pCD at initiation, 88/148 (59.5%) patients had setons at initiation of therapy and ustekinumab success was reached in 56/148 (37.8%) patients. Among patients with setons at initiation, 29/88 (33%) patients had a successful seton ablation during follow-up. In multi-variate analysis, the only factor associated with treatment success was the absence of ustekinumab optimisation (OR 2.52; 95% CI 1.15–5.56; $p = 0.01$). Concomitant treatments (immunosuppressors and antibiotics), prior drainage or number of anti-TNF or prior biological agents were not predictors of success. In patients with inactive pCD at initiation, the mean follow-up time was 86 weeks, perianal disease recurred in 13/59 (22%) patients and 8/59 (13.6%) patients needed medical and/or surgical treatment for perianal disease. Mean time to recurrence was 25 weeks.

Conclusions: Ustekinumab appears as a potential effective therapeutic option in perianal refractory CD. Further studies are needed to precise the role of ustekinumab in relation to other biological therapies for the management of refractory pCD.

DOP75

Surgery and hospitalisations rates in inflammatory bowel disease patients in the Québec provincial database from 199–6 to 2015

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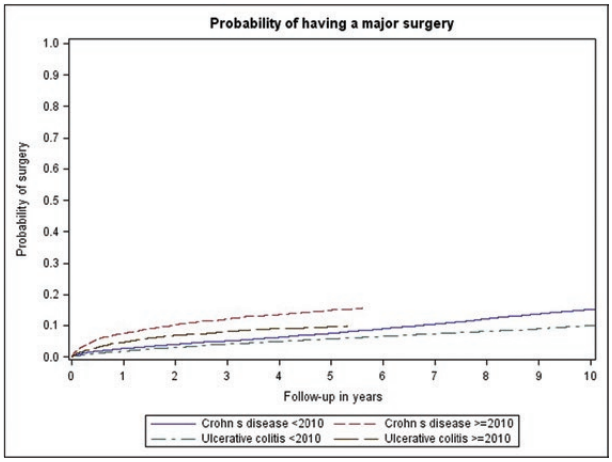
Background: Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are associated with high healthcare expenditures related to medications, hospitalisations, and surgeries. Our aim was to analyse disease outcomes and treatment algorithms in newly diagnosed IBD patients in Québec over the past 2 decades, comparing periods before and after routine public reimbursement of biologics.

Methods: Overall, 34 644 newly diagnosed IBD patients (CD: 20 644 or 59.5%; M:F CD: 3:4, UC: 1:1; CD <40 years old: 46% vs. UC<40 years old: 35%) were identified from the population-based health insurance database of Québec from 1996 to 2015. The primary and secondary outcomes included time to and probability of first hospitalisation and first major surgery, and medication exposures. Prescription data were collected from the public prescription database (RAMQ).

Results: Probability of major surgery increased after 2010 in CD (at 5 years after diagnosis: before and after 2010: 8% (SD: 0.2%) vs.15% (0.6%); $p < 0.0001$) and UC patients (6% (0.2%) vs. 10% (0.6%); $p < 0.0001$).



Probability of first major surgery

Hospitalisations rates remained unchanged, but were higher in CD compared with UC ($p < 0.0001$).

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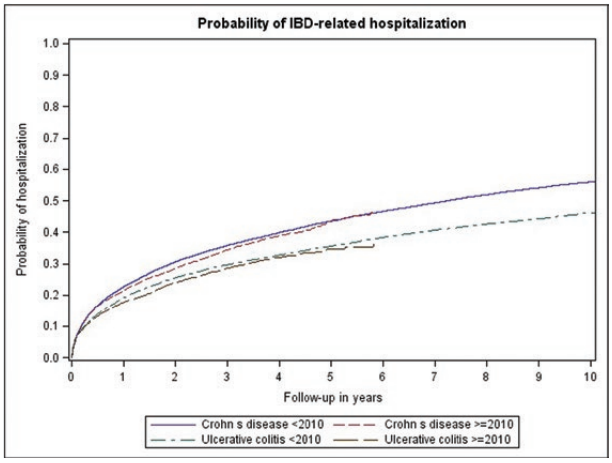

Probability of first hospitalisation

IBD patients on biologicals had overall lower probability of hospitalisations compared with other drug types (overall 5 years probability for all IBD patients using 5-ASA: 37% (0.6%); biologicals: 31% (1.8%), $p < 0.0001$). Biologicals were more commonly prescribed in CD after 2010 (4% (0.2%) vs. 16% (0.6%), $p < 0.0001$), especially in patients less than 40 years old at diagnosis. Thiopurine exposure increased in IBD patients after 2010 (CD: 21% (0.4%) vs. 24% (0.6%) $p < 0.0001$; UC: 13% (0.4%) vs. 16% (0.7%), $p < 0.0001$), while methotrexate use remained overall low (overall 5 years probability in CD: 4% (0.1%) ;UC: 1% (0.1%); $p < 0.0001$). Corticosteroid exposure was unchanged before and after 2010 (CD: 31% (0.4%) vs. 30% (0.7%) $p = 0.46$; UC: 31% (0.5%) vs. 34% (0.9%); $p = 0.03$). 5-ASA use was higher in UC (40% (0.4%), $p < 0.001$), while in CD it became lower after 2010 (33% (0.4%) vs. 21% (0.6%), $p < 0.0001$).

Conclusions: The probability of first hospitalisation remained unchanged whilst the probability of first major surgery was increased despite the higher and earlier use of biological therapies in this large population-based inception cohort from Québec. Overall, there was a slight increase in the use of thiopurines and methotrexate, while the use of corticosteroids was unchanged.

DOP76

Prevalence and healthcare costs of perianal fistulas in Crohn's disease in a nationwide cohort

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Background: Data on the prevalence of perianal fistulas in Crohn's disease (pCF) and the associated healthcare costs remain sparse. This study aimed to determine the prevalence of pCF in a nationwide cohort. Secondary outcomes included the use of biologicals, number of surgical interventions, and direct healthcare costs related to pCF.

Methods: All patients registered in the Danish National Patient Registry as having Crohn's disease (CD) between 2010 and 2016 were identified of whom the subpopulation with a pCF diagnosis (complex and simple) or a pCF-related surgical procedure were included. Data on in- and out-patient services were retrieved from the National Patient Registry, which includes data on all patient contacts, including diagnoses as well as diagnostic and treatment procedures. The database uses international classification systems, for instance, the ICD-10. Data were linked with the Danish Case Mix System (Diagnose-Related Groups) to assign costs to outpatient and inpatient services in pCF cases.

Results: In total, 17 789 patients were identified as having CD in the study period. The prevalence of pCF ranged from 612 (5.1 fistula patients per 100 patients with CD) to 544 (3.1 fistula patients per 100 patients with CD) during the study period. Furthermore, the number of incident perianal fistula cases decreased from 303 cases in 2010 to 144 cases in 2016. In total, 1773 (10%) patients were identified with an incident pCF in the study period of whom 49% were female. Mean age was 33.4 years and mean duration of CD prior to pCF was 366 days. Biological treatment was administered to 46.9% of the patients; of whom, 25.9% were in biological treatment prior to the diagnosis of pCF. In total, 35% were subjected to surgical intervention. The mean number of pCF-related surgical procedures per year was 1.4 per patient. During the study period 17 (0.096%) patients had a stoma performed, whereas 8 (0.045%) had reversal of their stoma. Mean cost from 2010 to 2015 was €21 708 per patient (IQR: €2501–28 930). In 2016, the total hospital-associated costs for diagnosis and treatment of pCF was €2.3 million, with biologicals being the major expenditure (€911 200) followed by surgical interventions (€723 600). Healthcare costs for treatment of pCF decreased during the study period mainly due to lowered prices on biologicals.

Conclusions: In a Danish nationwide cohort of patients with CD, the prevalence of perianal fistulas decreased in the period from 2010 to 2016. The reason for this needs further elucidation. Only half of the incident cases received biologicals, yet biological treatment was the main expenditure for the entire study population. Healthcare costs for pCF decreased during the study period, but are still high compared with non-pCF IBD patients.

DOP77

The effectiveness of combination therapy mesenchymal stromal cells and certolizumab pegol in perianal lesions in Crohn's disease

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Background: Perianal fistulas are common types of fistulas in Crohn's disease (CD). Mesenchymal stromal cells (MSC), which have immunomodulatory properties and high regenerative potential, are currently also used for the treatment of fistula CD. The objective of this study was to compare the effectiveness of combined therapy (local and systemic administration) of bone marrow MSC, the effectiveness of combined therapy of MSC (local administration), and certolizumab pegol (CZP) according to the scheme and monotherapy of CZP according to the scheme of the frequency of healing of simple perianal fistulas in CD.

Methods: Fifty-four patients with CD with perianal lesions were divided into three groups depending on the method of therapy. The

first group of patients aged 19 to 58 years (Me-29) (n = 18) received the culture of MSC systematically according to the scheme and locally: 40 million MSC—4 injection points of 1 ml of physiological solution containing 10 million MSC were administered along the perimeter of the fistula. Then, after 4 and 8 weeks, 40 million MSC were re-introduced into the fistula area. The second group of patients with CD (n = 18) aged 20 to 68 years (Me-36) received MSC locally and anticytokine therapy with CP according to the scheme. The third group of patients with CD (n = 18) aged 20 to 62 years (Me-28) received anticytokine therapy for CZP according to the scheme. The dynamics evaluated the complete closure of the external opening of the fistula. Ano-and rectosigmoscopy was performed 2, 6, and 12 months after the start of therapy.

Results: After 2 months in the first group of patients the healing of simple fistulas was observed in 7/18 (38.9%), in the second group the healing of simple fistulas in 14/18 (77.8%) (OR-5.5; 95% CI 1.28–23.7; p = 0.043 in comparison with the first group). In the third group, 6/18 patients (33.3%) (OR 0.26; 95% CI 0.07–0.97; p = 0.019 in comparison with the first group). After 6 months in the first group receiving MSC, the healing of simple fistulas persisted in 6/18 (33.3%), in group second 14/18 (77.8%) (OR-7.0; 95% CI 1.59–30.8; p = 0.019 in comparison with the first group). In the third group, in 5/18 patients (27.8%) (OR 9.1; 95% CI 1.99–41.45; p = 0.008 in comparison with the second group). After 12 months in the first group receiving MSCS, the healing of simple fistulas persisted in 8/18 (44.4%), in the second group-in 15/18 (83.3%) (OR 6.2; 95% CI 1.33–29.43; p = 0.038 in comparison with the first group). In the third group, in 7/18 patients (38.9%) (OR 7.857; 95% CI 1.65–37.4; p = 0.017 in comparison with the first group).

Conclusions: Combined cell and anti-cytokine therapy with CZP of CD with perianal lesions promotes more frequent and prolonged closure of simple fistulas, compared with MSC monotherapy and CZP monotherapy.

DOP78

Efficacy of vedolizumab in perianal Crohn's disease: the BioLAP multi-centre observational study

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Background: New therapeutic options for Crohn's disease (CD) patients with perianal lesions failing anti-tumour necrosis factor (TNF) therapy are needed. To date, no dedicated study with a large sample has evaluated the efficacy of vedolizumab on perianal CD (pCD). We assessed the efficacy of vedolizumab in pCD in a multicentre cohort and the predictive factors of success of the biological agent.

Methods: We conducted a French multi-centre, and observational study (Bio-LAP) including all patients with either active or inactive pCD (but with history of fistulizing and drained perianal lesion over the past 10 years) who received vedolizumab. In patients with active pCD at treatment initiation, the success of the biological agent was defined by clinical recovery at 6 months of treatment assessed by physician's appreciation without using additional medical or surgical treatment for perianal lesions. In patients with inactive pCD at treatment initiation, clinical recurrence of pCD was defined by the occurrence of perianal lesions and/or need of medical or surgical treatment.

Results: In total, 151 patients were screened. There were 49 (32.5%) males, the mean age at inclusion was 39.5 years, the mean BMI was 22.4, the mean duration from CD diagnosis to initiation of treatment was 14.9 years. 149/151 (98.7%) have had at least 1 anti-TNF agent, a total of 143/151 (94.7%) patients had been exposed to thiopurine and/or methotrexate. Ten (6.6%) patients had previous exposure to ustekinumab. The mean number of prior perianal surgery was 2.4. The mean follow-up time was 86 weeks. Ninety-eight patients (64.9%) discontinued therapy after a mean time of 284 days. In patients with active pCD at initiation, 61/102 (59.8%) patients had setons at initiation and vedolizumab success was reached in 23/102 (22.5%) patients. Among patients with setons at initiation, 9/61 (15%) patients had a successful seton ablation during follow-up. In multi-variate analysis, factors associated with success were the number of prior biological agents (3 or more, OR: 0.13; 95% CI: 0.02–1.09; p = 0.018) and antibiotics at initiation (no antibiotics, OR: 4.12; 95% CI: 1.06–15.98; p = 0.024). In patients with inactive pCD at initiation, the mean follow-up time was 131 weeks, perianal disease recurred in 15/49 (30.6%) patients and 11/49 (22.4%) patients needed medical and/or surgical treatment for perianal disease. Mean time to recurrence was 26 weeks.

Conclusions: Numerous treatment cessations and perianal disease recurrences under vedolizumab raise the question of the efficacy of anti-integrins at anal canal site. This study warrants further evaluation in dedicated prospective clinical studies to precise the role of vedolizumab in relation to other biological therapies for the management of refractory pCD.

DOP79

Effect of vedolizumab on surgical rates in IBD: post hoc analysis from the GEMINI trials

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Background: Vedolizumab (VDZ) is a safe and effective treatment for moderately to severely active ulcerative colitis (UC) and Crohn's disease (CD); however, effects on surgical rates have not yet been evaluated. This study aimed (1) to compare the surgical incidence

rates of VDZ and placebo (PLA) in GEMINI I (UC; NCT00783718) and II (CD; NCT00783692); and (2) to describe the surgical incidence rates through year 5 from the GEMINI LTS trial (UC and CD; NCT00790933).

Methods: Data were pooled from Week 6 induction VDZ responders who were randomised to VDZ or PLA maintenance (intent-to-treat [ITT] maintenance populations) from GEMINI I[1] and II,[2] and from patients receiving VDZ in the GEMINI LTS trial.[3,4] Using the Kaplan–Meier product-limit method, we estimated 'time to first surgery' through 1 year (VDZ and PLA groups from GEMINI I and II) and 5 years (VDZ1 and VDZ2 groups from GEMINI LTS. VDZ1 = VDZ throughout; VDZ2 = PLA from Week 6 to 1 year, then VDZ for the LTS study). Patients without surgery were censored at the last follow-up date through 1 year and 5 years. The log-rank test was used for comparisons between groups.

Results: The analysis included 834 patients in total. Mean ages were 40.0 and 35.7 years for patients with UC and CD, respectively; proportions of prior tumour necrosis factor antagonist failure were 39.9 and 54.9%, and mean disease duration times were 7.2 and 8.6 years. Figure 1 shows cumulative surgical incidence rates for the study groups, and the log-rank comparisons at 1 year (VDZ and PLA groups) and 5 years (VDZ1 and VDZ2 groups).

Conclusions: In this population of patients with moderately to severely active UC or CD, surgery rates within the first year of observation were lower in patients assigned to VDZ than those who received PLA with a significant difference observed in UC. For patients who continued treatment for up to 5 years, VDZ provided long-term benefit in both diseases with low rates of surgical intervention. The post hoc nature of the analysis and the small number of surgical events require further real-world evaluation of the ability of VDZ to reduce surgical rates in patients with UC and CD.

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DOP80

Oral curcumin is not more effective than placebo to prevent endoscopic postoperative recurrence in patients with Crohn's disease treated with concomitant thiopurines: the POPCUR trial

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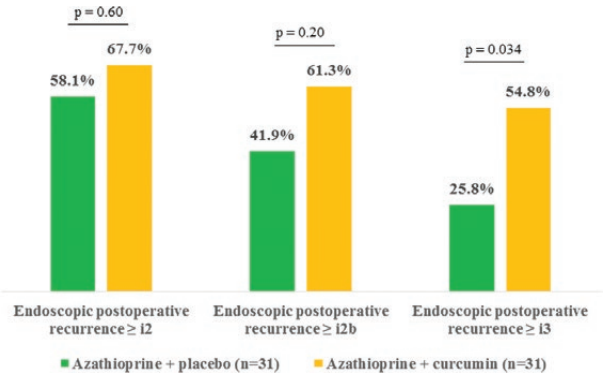
Background: Postoperative recurrence is a major concern in patients with Crohn's disease (CD). Curcumin exhibited anti-inflammatory and anti-oxidative properties in cellular and rodent models. Recently, a randomised controlled trial demonstrated that oral curcumin was more effective than placebo to induce clinical and endoscopic remission in patients with ulcerative colitis failing to mesalamine.[1] We aimed to assess the efficacy of oral curcumin compared with placebo to prevent endoscopic POR in patients with CD receiving concomitant thiopurines therapy.

Methods: We conducted a double-blind, randomised, placebo-controlled trial in eight IBD centres. All patients with CD (> 18 years old) undergoing bowel resection were consecutively enrolled within 15 days after the surgery or the closure of diverting stoma. All macroscopic lesions had to be removed and the anastomosis had to be reached by colonoscopy. The patients were randomised to be treated with azathioprine 2–2.5 mg/kg, and either placebo (placebo group) or oral curcumin (3 g/day) (curcumin group). The primary endpoint was endoscopic POR at 6 months (M6), defined as Rutgeerts' index ≥ i2a. Secondary endpoints were severe endoscopic POR (≥ i3), clinical POR (CDAI > 150), quality of life (IBDQ) and safety. An intermediary analysis was planned after the enrolment of 50% of the patients (n = 62 patients).

Results: Overall, 62 patients were enrolled (mean age 36.3 ± 12.0 years, mean CD duration 8.1 ans ± 8.0 years, 67.2% female genders, 37.8% smokers, 8.2% with perianal lesions, 45.9% with structuring CD, 36.1% with fistulizing CD, 45.9% with prior bowel resection, 18.0% of anti-TNF naïve patients). In intermediary analysis (intent-to-treat), curcumin was not more effective than placebo to prevent endoscopic POR at M6: 67.7% (21/31) vs. 58.1% (18/31) (p = 0.60), in curcumin and placebo groups, respectively.



The rate of severe endoscopic POR was significantly higher in patients treated with curcumin (17/31, 54.8%) compared with placebo (8/31, 25.8%) (p = 0.02). The rate of clinical POR was not different between the two groups: 38.7% (12/31) in curcumin group vs. 45.2% (14/31) in placebo group (p = 0.80). IBDQ was similar between the two groups (178.5 in the curcumin group vs. 181.5 in the placebo group; p = 0.63). The rate of adverse events was not different between the two groups.

Conclusions: Oral curcumin was not more effective than placebo to prevent endoscopic postoperative recurrence (POR) in patients with CD receiving concomitant thiopurines therapy.

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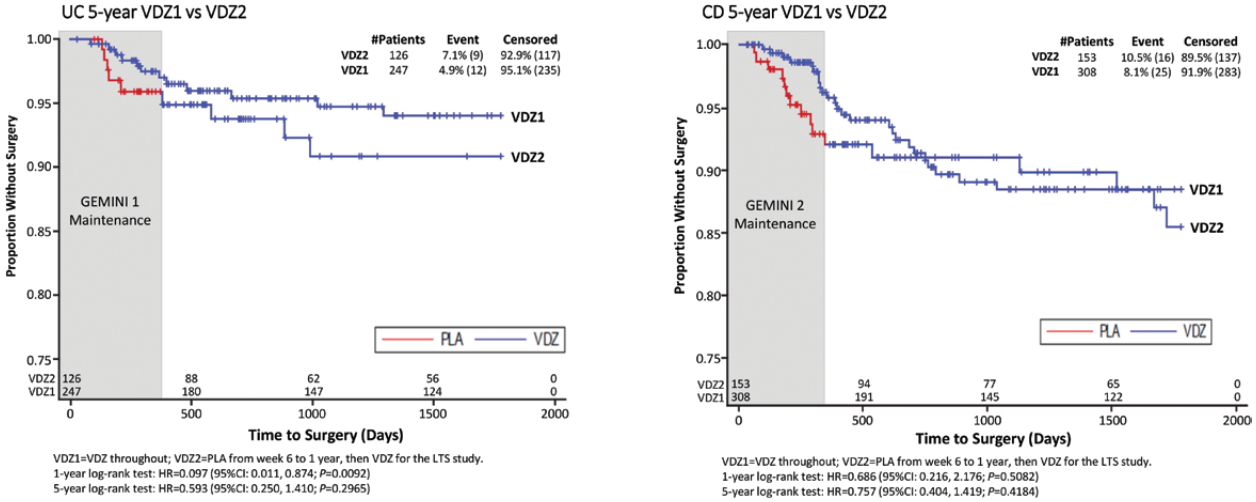

For the 1-year comparison: cut-off date was week 66 (final safety visit) for those who did not proceed to enrol in the LTS study, and the date of the 'first LTS dose' for those who did.
For the 5-year comparison: cut-off date was 2 weeks after the last safety assessment in the 5-year period.

Abstract DOP79 – Figure 1. Kaplan–Meier surgery rate estimates throughout 5 years in the GEMINI maintenance studies

DOP81

Utility of a simple blood test for mucosal healing monitoring is accurate in post-operative Crohn's disease

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Background: Crohn's disease (CD) recurs after intestinal resection. Ileo-colonoscopy is the gold standard for monitoring for recurrence but is invasive and cannot be performed frequently. A simple blood test for monitoring for recurrence would be valuable. A serologic panel of 13 markers, with a computed score (Mucosal Healing Index, MHI) has been validated in CD patients for monitoring mucosal healing in the non-operative setting. We explored the utility of MHI in the post-operative setting where there is a lower disease burden.
Methods: Patients in the Post-Operative Crohn Endoscopic Recurrence (POCER) Study[1] who underwent intestinal resection and colonoscopic assessment at 6 and 18 months provided serum (preoperative, 6, 12, and 18 months). Mucosal healing markers (Monitr™ panel; measuring CEACAM, VCAM, CRP, SAA, Ang-1, Ang-2, MMP-1, -2, -3, -9, EMMPRIN, TGF-α, IL-7) were used with proprietary calculation to derive a mucosal healing index. Endoscopic disease was assessed using Rutgeerts Score (i0-i4; recurrence ≥i2). Assay performance and cut-offs were assessed by calculating the AUROC and test characteristics (sensitivity, specificity, PPV and NPV).
Results: In total, 132 (46% male; median age 36) patients provided 439 samples for assessment, of which 95 samples had matched serum and endoscopy at 6 months and 107 at 18 months. At both 6 and 18 months, the median MHI was lower in those patients in remission (6 months: <i2 MHI 21.5 vs. ≥i2 MHI 29.3; p = 0.037, 18 months <i2 MHI 22.3 vs. ≥i2 MHI 26.7; p = 0.083). The correlation between the MHI and the Rutgeerts score at 6 and 18 months was significant but weak (r = 0.24; p = 0.0004). AUROC for the discrimination between mucosal normality (i0) and severe recurrence (i3–4) was 0.75 (95% CI: 0.64–0.87) with diagnostic performance shown below at various MHI cut-offs. MHI cut-off of ≤20 has a sensitivity of 87.5% to rule out severe recurrence while a cut-off of 40 has a 93% specificity to rule it in.

Table 1. Test performance of the MHI in post-operative Crohn's disease recurrence.

COMBINED 6 & 18 MONTH OUTCOMES										
	i0-i1 vs i2-i4 Remission vs Recurrence n = 202 AUROC = 0.617					i0 vs i3-i4 Normality vs Severe Recurrence n = 81 AUROC = 0.752				
MHI Cut-off	Sens	Spec	PPV	NPV	Accuracy	Sens	Spec	PPV	NPV	Accuracy
20	68.9	41.4	40.5	69.7	51.5	87.5	47.4	41.2	90.0	59.3
30	50.0	72.7	51.4	71.5	64.4	58.3	79.0	53.9	81.8	72.8
40	18.9	87.5	46.7	65.1	62.4	25.0	93.0	60.0	74.7	72.8

Conclusions: A non-invasive multi-marker serum test (MHI) has sufficient accuracy to be a useful adjunctive test for monitoring of post-operative Crohn's disease recurrence.

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DOP Session 10 - Clinical Epidemiology

DOP82

Direct and indirect costs of inflammatory bowel disease in the biological era; 10 years of follow-up in a Danish population-based inception cohort

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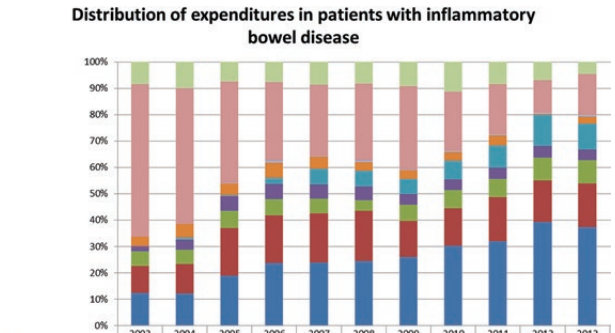
Background: Crohn's disease (CD) and ulcerative colitis (UC) carries a high burden on healthcare resources. To date, no study has assessed the combined direct and indirect cost of inflammatory bowel disease (IBD) in a population-based setting. Our aim was to assess this in a population-based inception cohort with 10 years of follow-up.

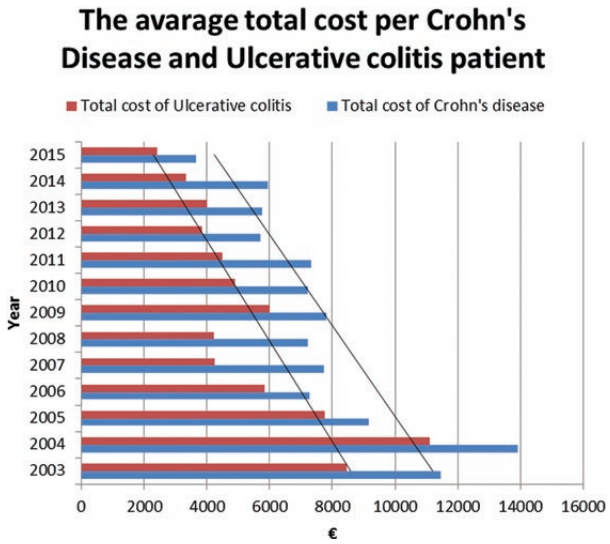
Methods: All incident patients diagnosed with CD or UC between 2003 and 2004 in a well-defined Copenhagen area, were followed prospectively until 2015. Information regarding direct and indirect costs was retrieved from the Danish national registries. Data were compared with a control population matched by age, sex and municipality with a ratio of 1:20 (10259). Using multiple linear regression models, associations between the total cost and multiple variables were assessed.

Results: A total of 513 (CD: 213 [42%], UC: 300 [58%]) IBD patients were included. No significant differences were found in indirect costs between CD, UC, and the control population regarding paid sick leave, unemployment benefits or loss of tax income. Costs for CD patients were significantly higher than UC regarding all direct expenditures (except for 5-ASA), but no differences were found in diagnostic expenses. The expenses for biologics were, respectively, €1.6 and 0.3 million for CD and UC. The total costs accounted for €42.6€ million. Figure 1 illustrates the distribution of all expenses; Figure 2 illustrates the total costs per patient each year. Subgroup analyses only revealed significant increased direct expenses in patients with extensive colitis (Proctitis: €2273 [1341–4092], left-sided: €3606 [2354–5311], extensive: €4093 [2313–6057], $p < 0.001$). Using multi-variable linear regression, no variables were significantly associated with increased total costs in CD or in UC patients.



	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Diagnostic procedures	8	10	7	8	9	8	9	11	8	7	5
Hospitalisations	58	51	39	30	27	29	32	22	19	12	15
Minor surgery	0	0	0	1	0	1	0	0	0	1	1
Major Surgery	4	5	4	6	5	3	3	3	4	0	3
Biologics	0	1	1	2	6	6	6	7	9	12	10
Conventional medicine	2	4	5	6	5	5	4	4	4	4	4
Loss in taxes	6	5	7	6	6	4	6	7	7	9	9
Paid sick-leaves	10	11	18	18	19	19	14	14	17	16	16
Social benefits	13	12	19	24	24	25	26	30	32	39	38

Abstract DOP82 – Figure 1. Distribution of costs per year in patients with inflammatory bowel disease. Conventional medicine: 5-aminosalicylic acid, topical steroids, corticosteroids and immunosuppressants.



Abstract DOP82 – Figure 2. The average total cost per Crohn's disease and ulcerative colitis patient; including paid sick-leave, social benefits, lost tax income, diagnostic procedures, surgery, hospitalisation, and medication.

Conclusions: In this prospective population-based cohort, direct costs for IBD remain high. However, indirect costs (sick leave, unemployment and loss of tax-income etc.) did not surpass the control population. Total costs were mainly driven by hospitalisation, but over time indirect costs accounted for a higher percentage; though also decreasing over years.

DOP83

Association of FUT2 and ABO with Crohn's disease in Koreans

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Background: Fucosyltransferase 2 (FUT2) at 19q13 is a well-established susceptibility locus for Crohn's disease (CD) in Caucasians. FUT2 encodes α-1,2-fucosyltransferase that is responsible for the secretion of the ABO antigens in both gastrointestinal mucosa and secretory glands. Given CD is thought to arise by dysregulated mucosal immune responses to the gut flora and both ABO blood group and the FUT2 secretor status affect the composition of the gut microbiota, the goal of this study was to evaluate associations of variants of FUT2 and ABO with Korean patients with CD.

Methods: Three single-nucleotide polymorphisms from the FUT2 and ABO genes were genotyped in 1735 patients with CD and 8074 healthy controls. The influences of the FUT2 secretor status and ABO blood group on the cumulative probabilities of intestinal resection were assessed.

Results: The FUT2 non-secretor allele showed genome-wide significant association with CD in Koreans (rs1047781, OR = 1.30, $p_{combined} = 3.52 \times 10^{-12}$). The ABO locus showed genome-wide significant association with CD in Asians ($p_{meta} = 2.35 \times 10^{-8}$). Compared with the O group, moderate association was observed with the A and B groups (OR = 1.40, $p = 2.26 \times 10^{-6}$ and OR = 1.32, $p = 1.92 \times 10^{-4}$, respectively). Following stratification on the basis of FUT2 genotype, carriers of the secretor O blood group were significantly protective against CD compared with the secretor non-O blood group (OR = 0.63, 95% CI = 0.54–0.73, $p = 2.86 \times 10^{-9}$, Figure 1).

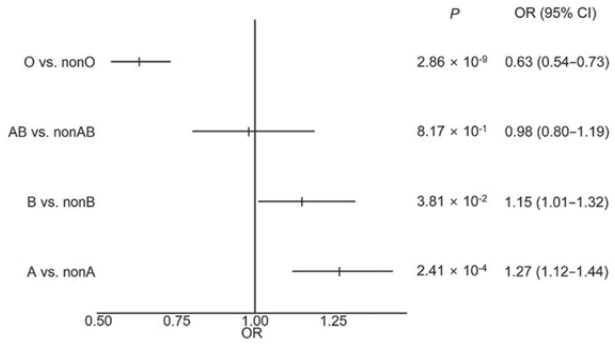

Figure 1. Forest plot illustrates the different odds ratios and 95% confidential interval of specific blood groups between case and controls with secretor status.

The cumulative probability of intestinal resection was significantly higher in patients with non-secretor status compared with those with secretor status: 38.4% vs. 33.3% at 10 years, 44.7% vs. 39.5% at 20 years, and 45.3% vs. 39.6% at 25 years ($p = 0.014$, Figure 2).

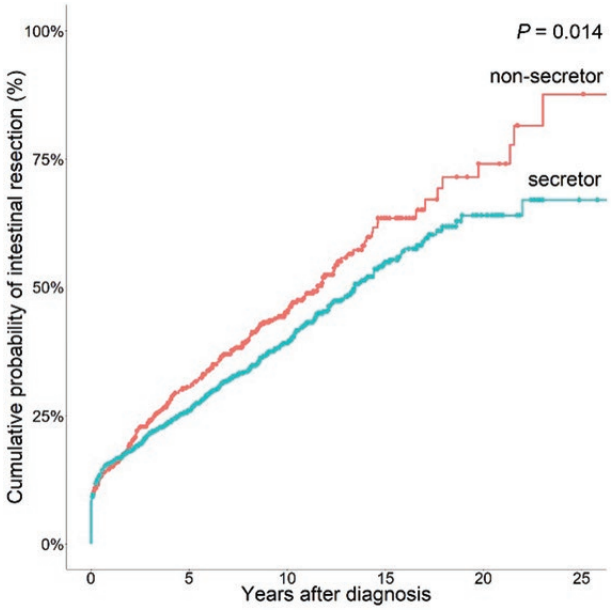

Figure 2. Kaplan–Meier curve for comparison of cumulative probability of intestinal resection between Crohn's disease patients with secretor vs. non-secretor status.

Conclusions: Our data show that both FUT2 and ABO loci show genome-wide significant association with CD, the FUT2 non-secretor status affects 25-year clinical outcomes, and blood group O and secretor status are protective factor against CD in Asians.

DOP84

Nationwide incidence and prevalence of paediatric inflammatory bowel disease in Scotland 2015–2017 demonstrates the highest paediatric prevalence rate recorded worldwide.

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Background: Robust epidemiological data on paediatric inflammatory bowel disease (PIBD; IBD diagnosed <16 years of age) is vital to organising current healthcare provision and planning future service design. Historically, Scotland has the highest incidence of PIBD in the UK and one of the highest worldwide, however data on prevalence is lacking. We aimed to calculate an updated incidence rate as well as both point and period prevalence rates of PIBD in Scottish children between 2015 and 2017.

Methods: Incident and prevalent cases of PIBD were prospectively recorded by the three Scottish regional paediatric gastroenterology networks covering all paediatric units nationwide. PIBD was defined as children <16 years of age with Crohn's disease (CD), ulcerative colitis (UC) or Inflammatory Bowel Disease Unclassified (IBDU) according to internationally accepted diagnostic criteria. Incidence rate for the period 2015–2017, as well as point (30th June each year) and period prevalence (calendar year) were calculated against age-specific population data for Scotland. A relevant literature review of PIBD prevalence rates to 12.2017 was performed for comparison.

Results: In total, 330 patients with PIBD were diagnosed in Scotland within the 3-year period providing an overall incidence of 12.0/100 000/year. The number of prevalent patients per year ranged from 523 to 541 with differences in rates for both gender and age: male 68.3 vs. female 47.4/100 000/year; pre-school age (0–5 years) 5.8, primary school age (6–10 years) 39.7 and secondary school age (11–15 years) 143.1/100 000/year. The highest point prevalence was 46.3/100 000/year (95% CI 42.0–50.9) at 30 June 2017 and the highest period prevalence was 58.9/100 000/year (95% CI 54.1–64.2) between 1 January 2016 and 31 December 2016. Breakdown of prevalent cases according to disease subtype was CD 39.5 (68%), UC 12.5 (22%) and IBDU 6.1/100 000/year (10%). No major differences in prevalence rates across regions were noted, however different practices in transition to adult services are evident with 22/139 (16%) of patients being managed by PIBD services in North of Scotland >16 years of age; in contrast to 56/156 (36%) in South-East Scotland and 100/308 (32%) in West of Scotland.

Conclusions: The PIBD prevalence rate in Scotland is higher than any other cohort (aged <16 years) published in the worldwide literature. These prevalence rates are in keeping with the high incidence rate, which continues to rise, and the chronic nature of this disease. Given that the true case load within paediatric services includes patients >16 years, who are often not transitioned until they have completed schooling, these data urgently need to be explored across the UK as if replicated would have significant implications for the PIBD workforce overall.

DOP85

Rising depression and antidepressant use amongst inflammatory bowel disease patients

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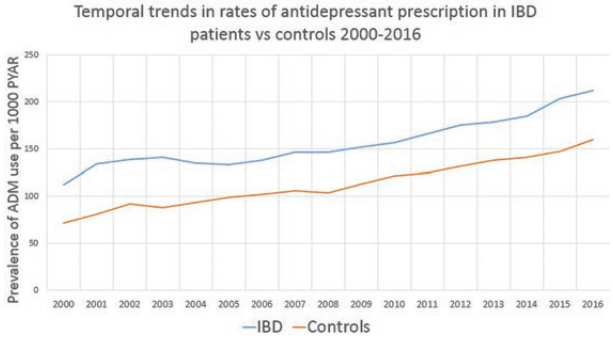
Background: Depression and the use of antidepressant medication (ADM) has risen substantially in recent years in the general population and is thought to be more common in those with chronic conditions.
Aims: To evaluate changes in depression and ADM use amongst patients with inflammatory bowel disease (IBD) compared with the general population.
Methods: Using the Clinical Practice Research Datalink (CPRD), a nationally representative research database comprising 8% of the UK population, we identified cases of IBD diagnosed from 1999 to 2016. A non-IBD control group was matched 1:1 for age and sex with IBD patients. We defined prevalent depression in patients with a code for depression or depressive symptoms in that calendar year or patients receiving an ADM in that year as well as having a code for diagnostic depression or depressive symptoms previously.[1,2] Medical record codes were used to determine ADM use, including selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants (TCA). We used linear regression to analyse temporal trends.
Results: We identified 9900 cases of ulcerative colitis, 4131 cases of Crohn's Disease and 14 031 controls. Prevalence of depression in IBD patients doubled from 63 to 137 per 1000 patient-years at risk (PYAR) between 2000 and 2016 ($p < 0.001$). IBD patients were significantly more likely to have depression than controls (14% vs. 10%, OR 1.43, 95% CI 1.19–1.72, $p < 0.001$). Prevalence of ADM use among IBD patients almost doubled between 2000 and 2016 (112 to 212 per 1000 PYAR, $p < 0.001$). Similar trends were seen for both SSRIs (61 to 134, $p < 0.001$) and TCAs (45 to 78, $p < 0.001$). Eighty-three per cent of amitriptyline prescriptions were for low-dose amitriptyline (≤30 mg/day).



Antidepressant use has increased significantly in the IBD and general population.

Conclusions: Patients with IBD are at 40% higher risk of depression compared with the general population and 1 in 5 patients are now using ADMs. Rates of depression have doubled between 2000 and 2016 and are mirrored by SSRI prescription. The rise in TCA use is largely accounted for by an increase in low-dose amitriptyline prescription, likely being used for the management of abdominal pain. Clinicians need to be vigilant to the risk of psychiatric co-morbidities amongst patients with IBD.

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DOP86

Risk for development of inflammatory bowel disease under inhibition of interleukin 17 in psoriasis, psoriatic arthritis, ankylosing spondylitis, and rheumatoid arthritis: a review and meta-analysis

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Background: Cases of inflammatory bowel disease during anti-interleukin 17 treatment have been reported from trials in psoriasis, psoriatic arthritis, and ankylosing spondylitis . The aim of this study was to assess the risk of IL-17 inhibition for development of inflammatory bowel disease.
Methods: We conducted a systematic review and meta-analysis (PROSPERO CRD42018109276) evaluating the risk of development of inflammatory bowel disease during treatment with secukinumab, ixekizumab or brodalumab in patients with psoriasis, psoriatic arthritis, ankylosing spondylitis, and rheumatoid arthritis. Data sources included published trials on PubMed and results of yet unpublished studies on clinicaltrials.gov between 2010 and 2018. We calculated incident cases of inflammatory bowel disease overall, and sub-analyses for specific indications and drugs as well as a 'worst-case scenario' (all unknown cases calculated as new diagnosis).
Results: Sixty-six studies were included for analysis. Data of 14 390 patients exposed to anti-IL-17 treatment have been evaluated during induction treatment and 19 380 patients were analysed for the entire treatment period. During induction treatment 11 incident cases of inflammatory bowel disease (worst-case scenario) were identified. Overall (entire treatment period) 33 new cases of inflammatory bowel disease were diagnosed (worst-case scenario) under anti-IL-17 treatment. In the meta-analysis we observed a pooled incidence rate of zero events for the worst-case scenario and for all sub-analyses.
Conclusions: Risk for development of inflammatory bowel disease in patients treated with interleukin 17 antagonists was not increased. Prospective trials evaluating the risk for inflammatory bowel disease in patients receiving therapy directed against interleukin 17 are warranted.

DOP87

Multi-parameter datasets are required to identify the true prevalence of IBD: The Lothian IBD Registry (LIBDR)

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Background: A recent systematic review reports stabilising or falling IBD incidence in Western countries with an overall prevalence in excess of 0.3%.[1] However, the true prevalence may be under-reported due to incomplete ascertainment of cases. We therefore conducted an extensive multi-parameter search strategy, manually confirming all diagnoses through electronic patient record (EPR) review, to provide a robust point prevalence estimate for Lothian assessing the ability of data sources to identify true positives.

Methods: Lothian is a well-defined geographical area in Scotland of 889 450 people served by a single health board. All Scottish residents have a unique community health index (CHI) number for identification/linkage purposes. All regional pathology is coded for IBD in a single centre (1988–); all secondary care utilise a single EPR system for all patient interactions, all primary care prescribing is recorded centrally (2003–) as is secondary care prescribing of IBD biological drugs (2009–). We identified patients from the following sources; inpatient IBD codes (K50/51/52) (*n* = 15 879), IBD pathology codes (*n* = 7313), IBD biological prescriptions (*n* = 842), primary care 5'ASA prescriptions (*n* = 5079) and an existing calprotectin database (*n* = 7129) to identify 'possible' IBD cases to 31/08/18 (Figure 1A). Eight IBD physicians then manually screened the EPRs for all 'possible' cases to identify 'true' cases as per Lennard–Jones criteria, cross-referenced to all GI outpatient attendances in 2017 to assess completeness of data. In total, 24 188 'possible' IBD cases were identified, manual review of patient EPRs revealed 14 102 non-IBD diagnosis (Figure 1A).

Results: The point prevalence of IBD in Lothian on 31/8/18 was 0.78% (CD; 283/100 000, UC; 429/100 000). Age (median, IQR) of the cohort was 49.3 (35.0–62.6) and 52.8 (39.6–66.2) years, age at diagnosis was 31.3 (21.7–48.9) and 38.1 (26.9–52.3) years and disease duration was 12.0 (6.1–20.9) and 11.2 (5.9–19.0) years for CD and UC, respectively. Age-group prevalence data for UC and CD is reported in Figure 1B. Pathology coding identified the most cases with >99% true positives and 72% of LIBDR patients overall. The inclusion of ICD K52 coding (IBDU, colitis unspecified etc.) reduced the accuracy of in-patient coding from 75 to 27% but in-patient coding overall only identified 55% of LIBDR patients (Figure 1C).

Conclusions: We report a rigorously validated IBD cohort with all age point-prevalence of 0.78% on 31/8/18, one of the highest in Northern Europe.

Reference

1. Ng SC. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2018;10114:2769–2778.

DOP88

Thiopurine and allopurinol combination therapy and the risk of adverse outcomes and step-up medical therapy in inflammatory bowel disease patients: a nationwide Danish cohort study

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Background: Thiopurine and allopurinol combination therapy is associated with clinical remission in patients with inflammatory bowel diseases (IBDs), but its influence on adverse outcomes, ie, IBD-related surgery, IBD-related hospitalisation, and death, and need for biological treatment is unclear. We compared these outcomes in patients with IBD treated with thiopurine and allopurinol and patients with IBD treated with thiopurine monotherapy.

Methods: We established a nationwide cohort of patients with an IBD diagnosis who had been prescribed thiopurine therapy, 1999–2014, using Danish registry data. The primary outcome was a composite of any adverse outcome or need for biological treatment: IBD-related hospitalisation, IBD-related surgery, biological therapy initiation, or death, whichever came first. Poisson regression analyses were used to calculate incidence rate ratios (IRR) with 95% confidence intervals (CI) comparing patients exposed to allopurinol-co-therapy and patients exposed to thiopurine monotherapy. Exposure was analysed as a time-varying variable and IRRs were adjusted for IBD subtype, sex, age at treatment, calendar year, and age at diagnosis.

Results: There were 10 367 patients with IBD (Crohn's disease [CD] *n* = 5484, ulcerative colitis [UC] *n* = 4883) who were prescribed thiopurines, and of these 217 were exposed to allopurinol co-therapy. We observed 40 incident outcomes in patients exposed to allopurinol co-therapy among 129 person-years (PY) (IR = 310.1 per 1000 PY). In patients exposed to thiopurine monotherapy, we observed 4745 outcomes among 24 585 PY (IR = 193.0 per 1000 PY). The adjusted IRR of an adverse outcome was not significantly different in the two groups of patients (IRR 1.26 [95% CI 0.92, 1.73]). The results did not differ when analysed in strata by IBD subtype (IRR = 1.25 (95% CI 0.78, 2.02) for CD, IRR = 1.23 [95% CI 0.82, 1.86] for UC).

Conclusions: Thiopurine and allopurinol exposed IBD patients did not have a statistically significant different risk of surgery, hospitalisation, biological therapy initiation, and death, when compared with IBD patients exposed to thiopurine monotherapy. Even though allopurinol co-therapy seems to improve clinical remission in IBD patients in previous studies, our study does not suggest an association with subsequent clinical outcomes.

DOP89

Final growth in paediatric Crohn's disease is impaired also in the era of biologics: a population-based analysis from the epiIRN administrative cohort

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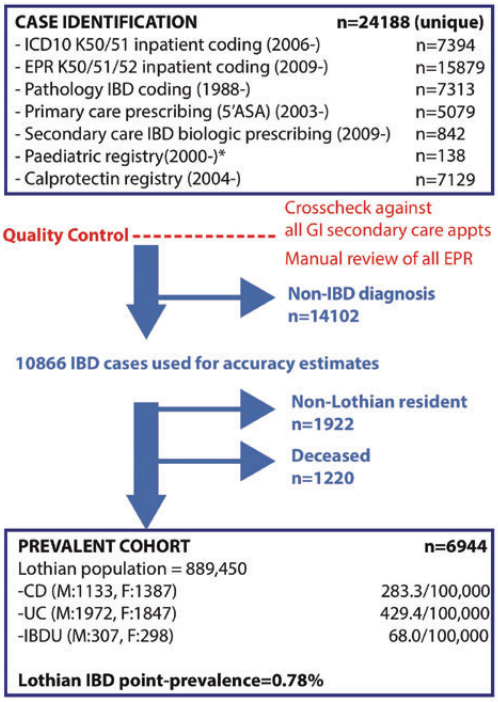
Background: The diagnosis of Crohn's disease (CD) during childhood is associated with a high rate of growth impairment. The contemporary rate of impaired final height is, however, less known in the era of biologics. We aimed to explore the final height of children diagnosed with IBD before the age of 12 years and during the biologics era.

Methods: New paediatric CD cases were identified within the epiIRN database, a validated registry of all IBD patients in the Israeli national health maintenance organisations (HMOs), covering 98% of the Israeli population. Height and height velocity measurements were retrieved from the electronic charts and transformed into age- and sex-matched z-scores according to the WHO reference standards.

Results: In total, 1365 children were diagnosed with IBD under the age of 12 years during 2005–2017; 902 had CD of whom 346 reached the age of 18 years by time of analysis (55.5% males, mean age at diagnosis 9.7 ± 1.8). The height difference between CD children and the reference standards steadily decreased over the years: from Δ5.7 cm (z score=–0.83 95% CI [–0.92, –0.74]) at age 12 to Δ3 cm (z=–0.45 [–0.54, –0.36]) at age 18 years in females, and from Δ 2.4 cm (z=–0.33 [–0.4, –0.27]) to Δ3.92 cm (z=–0.52 [–0.6, –0.45]) in males. Similarly, the rate of females with height <1 and <2 SD of the general population mean decreased from 40.3% and 13% at age 12 years to 25.1% and 6.9% at 18 years, respectively. The corresponding rates of <1 and <2 SD in males were 27.3% and 4.9% at age 12 years and 27.30% and 6.82% at age 18. Eventually, both males and females with CD were significantly shorter at the age of 18 years than the general population (173.2 ± 7.6 cm vs. 176.1 ± 7.5 and 160 ± 11.5 vs. 163 ± 6.6, respectively; $p < 0.0001$). The final height of 463 children with UC at the age of 18 years was similar to the general population (z-score of females –0.0048 95% CI [–0.2, 0.19] and of males –0.1347 [–0.39, 0.122]).

A



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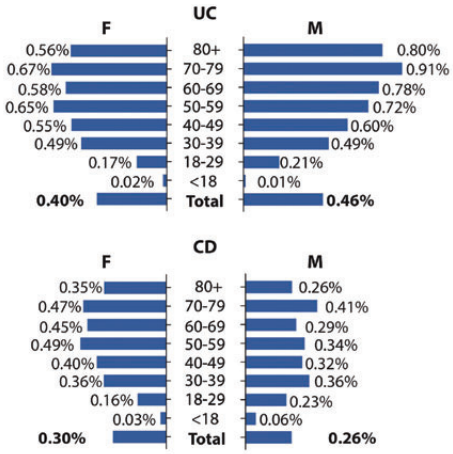
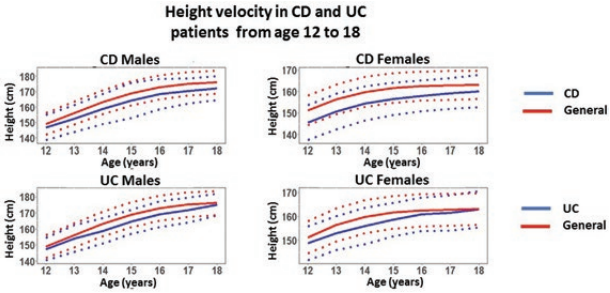


C

Data Source / n	True Positives n (%)	False positives n (%)	% of total IBD patients identified
ICD10 coding n=7394	5525 (75%)	1186 (25%)	55%
EPR coding n=15879	4254 (27%)	11625 (73%)	42%
Pathology coding n=7313	7232 (99%)	81 (1%)	72%
Primary care prescribing n=7313	5079 (84%)	956 (16%)	50%
Secondary care prescribing n=842	842 (100%)	0 (0%)	8%
Paediatric registry n=138	138 (100%)	0 (0%)	1%
Calprotectin registry n=7129	7097 (99%)	32 (1%)	70%

Abstract DOP87 – Figure 1. The Lothian IBD registry (LIBDR). (A) Flow chart of LIBDR data sources, screening methodology, and prevalent cohort details, using mid-2017 population estimates (National Records of Scotland). (B) LIBDR-based prevelance by sex and age for UC and CD, using mid-2017 population estimates (National Records of Scotland). (C) Accuracy of data sources used to identify true positives and total LIBDR patients before excluding non-resident/deceased (n = 100866). *The paediatric registry has prospectively recorded prevelant IBD cases from 2000–, for which we display the point-prevalence case number on 31 August 2018.



Height velocity in CD and UC patients from age 12 to 18.

Conclusions: This population-based analysis shows that 25.1% of females and 27.3% of males diagnosed with CD in the biologics era do not attain normal final adult height while 6.9% of females and 6.8% of males have a substantially reduced height. This study was supported by a grant from the Leona M. and Harry B. Helmsley Charitable Trust.

DOP90

The impact of spondyloarthritis and joint symptoms on health-related quality of life and fatigue in IBD: results after 20 years of follow-up in the IBSEN study

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Background: Patients with inflammatory bowel disease (IBD) often suffer from musculoskeletal manifestations. Health-related quality of life (HRQoL) and fatigue are known to be associated with IBD activity as well as musculoskeletal complaints. The aim was to determine whether spondyloarthritis or joint symptoms were associated with HRQoL or fatigue after 20 years of disease in the IBSEN cohort.

Methods: Four hundred and seventy incident IBD patients were followed prospectively for 20 years (the IBSEN cohort) with clinical examinations and questionnaires. At the 20-year follow-up, the patients answered detailed questionnaires regarding rheumatological diagnoses and symptoms, intestinal symptoms, as well as HRQoL (the 36-item Short Form Health Survey (SF-36) and the Norwegian version of the inflammatory bowel disease questionnaire (N-IBDQ)) and fatigue (the Fatigue Questionnaire (FQ)). Linear regression analyses were used to evaluate possible associations between spondyloarthritis or joint symptoms and HRQoL or fatigue. Sex, IBD diagnosis and age were included in all the multivariate regression models, in addition to other clinically relevant confounders.

Results: In total, 441 patients (93.8%) completed the questionnaires at the 20-year follow-up. The criteria for spondyloarthritis (axial or peripheral) were fulfilled in 158 patients (35.8%), daily back pain during the previous 3 months was reported by 79 patients (18.7%) and daily joint pain by 178 patients (42.5%). In multiple regression analyses, the variables back pain and joint pain were both independently associated with lower scores in all SF-36 domains and N-IBDQ total score, and with a higher total FQ score. Spondyloarthritis was not associated with reduced scores in any of the SF-36 domains, N-IBDQ total score or higher FQ scores, when adjusted for possible confounders.

Conclusions: Ongoing joint pain and back pain were both associated with poorer HRQoL and more fatigue in IBD patients 20 years after diagnosis, while spondyloarthritis did not impact HRQoL or fatigue negatively in this cohort.

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Poster presentations

Poster presentations

Basic science

P001

Multi-omic data integration assisted identification of molecular features contributing to disease heterogeneity in Crohn's disease

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Background: The disease behaviour of Crohn's disease is heterogeneous as evidenced by inflammatory, fibrostenotic or penetrating sub-types. Biomarkers that predict these sub-types at diagnosis, and biological mechanisms explaining the difference between them are lacking. Dysregulated CD4+ cell populations in CD patients have been associated with disease activity variation. We aim to identify discriminative features, from the integrative analysis of gene expression from blood-derived, sorted PBMC (CD4+ monocytes and CD14+ T cells) and genetic risk burden, which explain CD behavioural heterogeneity.
Methods: Sorted populations of circulating CD14+ and CD4+ cells were isolated from the blood of 29 patients with active CD (35% male; median [IQR] disease duration 21.5 [14.0–27.3] years; 24% inflammatory (B1), 48% stenosing (B2) and 28% penetrating disease (B3)). RNA was extracted from the CD14+/CD4+ cells and sequenced. The genetic risk burden was calculated for known CD GWAS variants using Immunochip genotyping data. We integrated the three above-described -omic data using Multi-Omics Factor Analysis (MOFA). Features were selected from the strongest -omic layers of the explanatory Latent Factors (LFs). To obtain the strongest features, we further selected the top 20% using the multivariate filter RRelief.
Results: Nine Latent Factors (LFs) were identified to contribute at least 2% of the total variance. One of the nine LFs explained disease behaviour (r = 0.45, p = 0.01). Clustering of the samples along the explanatory LF achieved meaningful separation of the samples as evidenced by the enrichment of sub-types in the clusters. We identified gene expression of CD4+ cells as the strongest -omic layer in the explanatory LF. Post feature extraction and selection, we identified a panel of 86 genes expressed in CD4+ cells distinguishing the three sub-types. The RRelief selected top 20% gene-set was enriched with immune cell and interleukin signalling in addition to particular genes encoding HLA antigens and those related to chaperones.
Conclusions: Using multi-omic data integration, we identified gene expression signatures from CD4+ T cells which could explain CD subtypes. Even though HLA loci has been linked to CD susceptibility and CD described as a 'chaperonopathy', we present the novel finding that the expression of distinct HLA genes and those associated with chaperones in CD4+ cells could be used as potential biomarkers to distinguish CD subtypes. It can lead to surrogate biomarkers in whole blood without the need for additional sample processing. Verification using newly diagnosed cohorts can validate our findings and predict disease trajectories as well as formulate personalised therapies.

P002

Endoscopic placement of a drug-eluting platform with monoclonal antibodies in an animal model of experimental colitis by TNBS: effect on disease outcome and anti-drug antibodies (ADA's) formation

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Background: Biological treatments with monoclonal antibodies (mAb's) are widely used in inflammatory bowel disease (IBD) in patients with a mild–severe affectation who fail to meet primary endpoints or are intolerant to conventional therapy. These drugs target pro- inflammatory cytokines or other type of molecules with an important role in IBD. mAb's are big and complex proteins with a risk of developing an immunogenicity reaction which account for the absence or loss of response in patients through time. Our group has developed a drug-eluting platform capable of being endoscopically administered to treat locally inflammatory lesions with a lower drug dose than the systemic path. We aimed to determine the efficacy of this platform and the anti-drug antibodies (ADA) levels though the placement of our drug-eluting platform vs. submucosal injection of therapy in an experimental colitis animal model by TNBS.
Methods: Two studies were done: Acute experimental colitis (1 round of TNBS application). Five groups: Sham, Control (non-treated animals), Platform, Platform + Infliximab (1 mg/ml), Platform + Vedolizumab (1 mg/ml). Chronic experimental colitis (4 rounds of

TNBS application). Two groups: Platform + Infliximab (1 mg/ml), s.c. Infliximab (5 mg/kg). Clinical and histological evaluations were done in both studies (ponderal evolution, bacterial translocation to liver, colon weight as a marker of oedema and inflammation, inflammatory cell infiltrate and intestinal architecture). ADAs levels were determined in the chronic model.

Results: On the acute model, treatment with our drug-eluting platform significantly improved clinical evaluations (ponderal evolution), macroscopic (colon weight), and histological tissue evaluations. On the chronic model, both drug-eluting platform and subcutaneous administration showed a similar fashion in resolving the disease, but the formation of ADA's was significantly diminished with our drug-eluting platform (0.9 vs. 1.97 µg/ml-c, p = 0.0025) at day of euthanasia (Day 28).

Conclusions: Endoscopic placement of drug-eluting platforms opens a new possibility for therapeutic endoscopy. We have been able to reduce the formation of ADA's when a biological therapy is used. This could be of great importance for the future management of patients with IBD and other pathologies where mAb's are used.

P003

C86/CD16 macrophages may act as a source of WNT2b in intestinal tissue from B3 Crohn's disease patients

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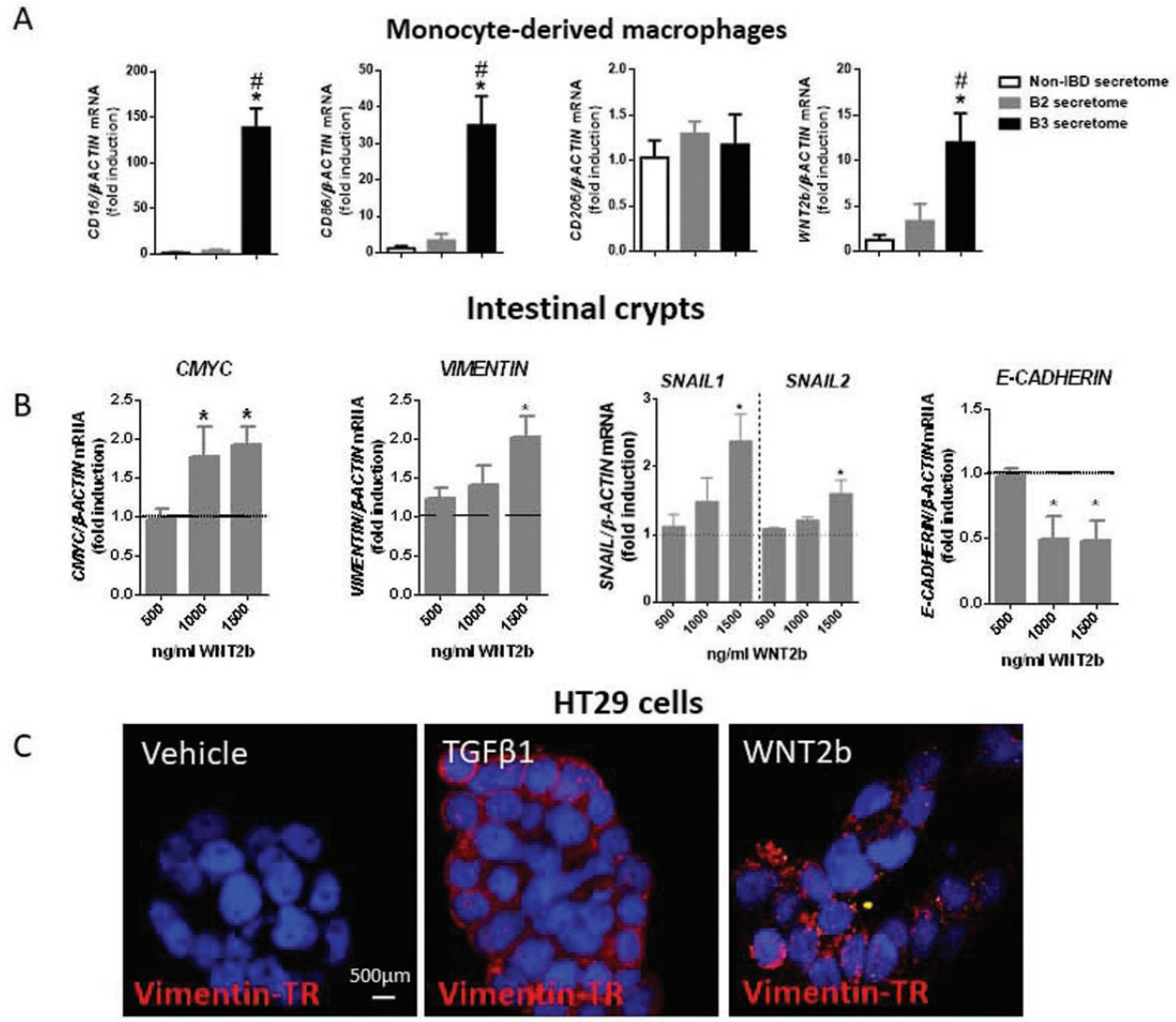

Abstract P002 – WNT2b induces EMT. (A and B) Relative mRNA expression vs. β-ACTIN and represented as fold induction vs. vehicle-treated. (C) Images showing VIMENTIN and nuclear staining in HT29 cells.

Background: Macrophages contribute to fibrosis through the release of different mediators and the pattern of secretion may vary according to their phenotype. The expression of WNT ligands has been related with the macrophage phenotype and strong evidence identifies the WNT signalling pathway as an emerging modulator of fibrosis.
Methods: The aim of the present study was to analyse the pattern of expression of macrophages and the expression of WNT ligands in surgical resections from Crohn's disease (CD, $n = 43$) patients which were categorised according to Montreal classification (B2 or B3; unaffected mucosa of patients with colorectal cancer was used as control). mRNA was isolated from intestinal samples and the expression of macrophage markers and WNT2b was analysed by RT-PCR. The number of macrophages positive for the different markers (CD206, CD86, CD16, and WNT2b) was determined by flow cytometry. PBMCS were isolated from healthy donors and treated during 5 days with secretomes, from control, B2 or B3 surgical resections; the mRNA expression of macrophage markers and WNT2b was determined by RT-PCR. Intestinal crypts were isolated from control samples and were incubated for 24 h with WNT2b and the expression of EMT genes was analysed by RT-PCR. HT29 were treated for 7 days with WNT2b or TGFβ1 and immunofluorescence was performed. Results are expressed as mean ± SEM ($n \geq 5$). Statistical analysis was performed by ANOVA + Newman–Keuls test. $^{*}p < 0.05$ significant differences vs. Non-IBD group or vehicle, $\#p < 0.05$ vs. B2-CD group.
Results: The expression of WNT2b was significantly higher in intestinal samples from B3 CD patients (2.3 ± 0.4) than in controls (1.1 ± 0.1) or B2 patients (0.7 ± 0.1). The number of CD16 or CD86-positive macrophages was significantly higher in intestinal tissue from B3 CD patients (69.7 ± 24.4% and 88.8 ± 18.4%, respectively) than in that from B2 CD patients (36.12 ± 5.8% and 30.58 ± 10.9%, respectively). A high percentage of CD16 positive macrophages in intestinal tissue from B3 CD patients were also positive for WNT2b (24.7 ± 8.8%). The mRNA expression of CD16, CD86, and WNT2b was significantly higher in PBMCS treated with B3-secretomes than in those treated with B2- or control secretomes (A). Exogenous administration of WNT2b to intestinal crypts induced the mRNA expression of EMT genes (B). WNT2b and TGFβ1-induced VIMENTIN expression in HT29 cells (C).
Conclusions: A macrophage phenotype expressing CD86/CD16 may act as a source of WNT2b in intestinal tissue from CD patients with a penetrating (B3) behaviour. WNT2b induces EMT in intestinal crypts and HT29 cells.

P004

IL-22 affects barrier function and cell polarity by MAPK/PI3 kinase signal transduction

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Background: Polarity in intestinal epithelial cells (IECs) is crucial to the barrier function. IL-22 is a cytokine that has been related to directly affect the integrity of the epithelial layer. IL-22 receptor/signalling complex is found mainly in epithelial cells membranes. The activated complex leads to the activation of various cellular signalling pathways including STAT-3, MAPK and PI3K/AKT. The effect of IL-22 on epithelial cells concerning cell polarity and barrier defect is not clearly understood. Therefore, this study aimed to understand the mechanism underlying the development of dyspolar epithelia and barrier defect caused by IL-22.
Methods: To investigate the role of IL-22, we exposed various intestinal epithelial cell lines (Caco-2, T84 and HT29/B6) with IL-22. Single IECs implanted in Matrigel were grown to 3-dimensional cysts +/– IL-22 and analysed by confocal microscopy. The integrity of the barrier was monitored by measurements of transepithelial resistance (TER). Calcium switch experiments (Ussing chamber) was used to evaluate tight junction (TJ) assembly. To evaluate cell motility wound healing and invasion assays were performed. Intracellular localisation of immunostained proteins related to TJ (JAM and ZO-1) was investigated using confocal microscopy. Activated signal transduction pathways were identified in phosphoblots and inhibitors of STAT-3, MAPK/ERK, and PI3K pathways were applied to uncover the signal transduction of barrier and polarity effects.
Results: IL-22 treatment reduced TER, altered distribution of TJ proteins and caused multi-lumen cysts, suggesting disturbed cell polarity and secondary to that disturbance of barrier function of IECs. In addition, invasion and migration were increased after IL-22 treatment. It was, furthermore, observed that IL-22 treatment induced STAT-3, ERK, and AKT phosphorylation, which were associated with the observed IL-22 effects. Interestingly, only blocking of PI3K/AKT and MAPK pathways rescued barrier effects of IL-22 exposure, while STAT-3 primarily caused effects on cell viability.
Conclusions: IL-22 treatment alters cell polarity and has an effect in barrier function in IECs. Altogether, our data suggest that this effect is associated with the activation of PI3-kinase and ERK-pathways rather than STAT-3 pathways

P005

Persistent transcriptional reprogramming in the choroid plexus during chronic colitis: towards understanding persistent fatigue in patients with quiescent inflammatory bowel disease?

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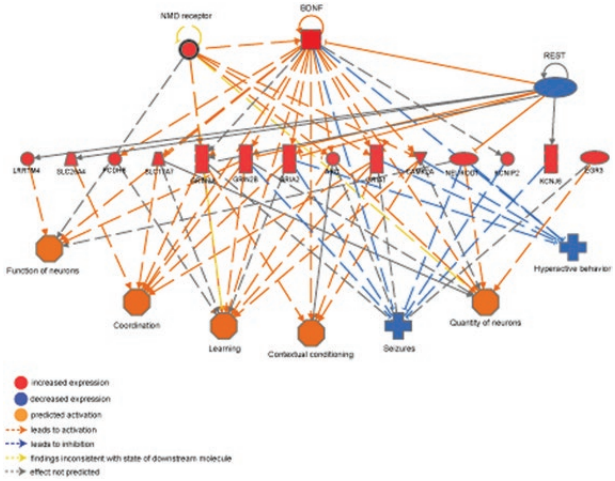
Background: Neurobehavioural comorbidities such as depression, anxiety, and fatigue are correlated with disease activity in patients with inflammatory bowel diseases (IBD). The persistence of fatigue during disease remission, however, remains a clinical challenge, and lacks any scientific basis. In the present study, we described behavioural changes in mice with extinguished chronic colitis, and mapped the transcriptional profiles at the blood–cerebrospinal fluid barrier, constituted by the choroid plexus.
Methods: Chronic gut inflammation was induced in C57BL/6J mice by repeated administration of dextran sodium sulphate (DSS). Following a recovery period of 3 weeks, mice were subjected to behavioural tests, and the choroid plexus tissue was analysed by RNA sequencing.

Results: The DSS treatment resulted in chronic colitis, characterised by clinical recovery but persistent structural damage in the colon, mimicking IBD in remission. Colitic mice exhibited reduced movements in the open field test, and performed worse on the inverted grid test, whereas anxiety behaviour was not observed. In forced behavioural tests, including the forced swim test and rotarod performance test, colitic mice performed similar as healthy mice. Chronic gut inflammation was associated with major transcriptional alterations in choroid plexus tissue, converging to an enrichment of genes associated with behaviour, mainly those involved in excitatory glutamate receptor activation.



IPA analysis of the RNA sequencing dataset of the choroid plexus demonstrated changes in top regulator effect networks linked with cognition and behaviour, inducing genes coding for subunits of ionotropic glutamate receptors.

Conclusions: Chronic gut inflammation in the absence of active disease was associated with locomotor dysfunction and muscle fatigue in mice, which fits with self-reported fatigue parameters in IBD patients. Transcriptional adaptations in the choroid plexus indicate increased glutamate signalling. These data provide a scientific basis towards understanding persistent fatigue in quiescent IBD patients.

P006

Loss of protein tyrosine phosphatase non-receptor type 23 (PTPN23) in intestinal epithelial cells induces inflammation and epithelial hyperproliferation

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Background: Colorectal carcinoma (CRC) is still a mayor complication in patients with inflammatory bowel disease (IBD) with colonic involvement. Colitis-associated cancer patients have a worse prognosis than those with spontaneous CRC, and are frequently diagnosed at an advance stage. Protein tyrosine phosphatase non-receptor type 23 (PTPN23) regulates signal transduction events involved in cell differentiation, proliferation, apoptosis, migration and invasion. Although PTPN23 is involved in some epithelial cancers, it is unknown whether PTPN23 affects intestinal epithelial cells (IEC) homeostasis and/or malignant transformation. Here we aim to identify a role for PTPN23 in the pathogenesis of IBD and CRC.

Methods: To investigate the role of PTPN23 in IBD and CRC, we generated mice specifically lacking PTPN23 in IEC. For this aim, mice homozygous for a LoxP flanked PTPN23 gene ($PTPN23^{fl/fl}$), were crossed with mice heterozygous for the $PTPN23^{fl}$ gene expressing Cre under the Villin Promoter ($PTPN23^{fl/WT}$ $VillinCre^{+/-}$ mice). $PTPN23^{fl/fl}$ $VillinCre^{+/-}$ (KO) and control littermates were analysed at the age of 6 weeks. Additionally, PTPN23 expression was examined in patients with IBD and CRC by immunohistochemistry.

Results: PTPN23 KO mice were born at a reduced frequency. Those that were born and did survive until weaning, were significantly smaller, featured less weight and developed severe diarrhoea. Kaplan Meier survival curve demonstrated that all of them died spontaneously within 140 days after birth. Interestingly, PTPN23 KO mice presented severe splenomegaly, but elongated small intestine and colon compared with their WT littermates. Histologically, PTPN23 KO mice showed epithelial cell hyperplasia, with an increase of Ki67+ epithelial and immune cells through the epithelium. In human, PTPN23 was highly expressed in colon tissue derived from patients with IBD and CRC primary tumours compared with healthy regions from the same patients. Aside from high expression in cancerous epithelial cells, we also observed high PTPN23 staining in immune cells within the lamina propria, indicating an important role for PTPN23 in haematopoietic cells as well. In contrast to primary CRC tissue, PTPN23 expression was almost completely lost in liver and lung metastases of the same CRC patients.

Conclusions: Our results suggest that PTPN23 plays an important role in IEC proliferation and inflammation. The development of this novel mouse model lacking PTPN23 specifically in IEC will allow unravelling mechanism involved in intestinal inflammation and cancer. Given the strong inflammatory phenotype observed in mice lacking PTPN23 in IEC, PTPN23 represents an interesting target in the treatment of IBD and CRC.

P007

Faecal protease activity as a predictor marker of disease recurrence in patients with Crohn's disease following ileocecectomy

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Background: Up to 90% of Crohn's disease (CD) patients who undergo intestinal resection will suffer from endoscopic disease recurrence within 1 year. Some evidence suggests that increased intestinal permeability caused by disruption of the epithelial barrier may be the first step towards exposure of the immune system to

enteric microbial antigens and to disease exacerbation. We examined whether increased faecal proteolytic activity predates endoscopic disease and whether it correlates with disease activity as reflected by faecal calprotectin level in CD patients post ileocecectomy resection.
Methods: CD patients who underwent ileocecectomy were prospectively recruited between 2010–2017 at the Tel Aviv Medical Center (TLVMC). Inclusion criteria were: clinical remission (CDAI <150) at 45 days post-surgery (Week 0), no residual disease and a non-stricturing-non-penetrating disease phenotype. Patients were evaluated at Weeks 0, 12, 24, 36, and 48 for faecal calprotectin level (CLP), faecal protease activity (PA) and disease activity was also assessed using the CDAI. Faecal PA was assessed using an FITC-casein florescence assay. All patients underwent scheduled colonoscopies at Weeks 24 and 48 to assess for disease recurrence. A Rutgeerts score of ≥i2 was considered as disease recurrence.
Results: Endoscopic evaluation of disease activity was documented in 33 patients at Week 24 and in 26 patients at Week 48 post screening. Thirteen patients had endoscopic recurrence at Week 24. Seven patients had endoscopic recurrence at Week 48. CLP levels at Week 12 were significantly higher in patients who suffered from disease recurrence at Week 24 (141.2 ± 147.4 vs. 398.0 ± 283.6, $p = 0.032$). CLP at Week 24 was significantly higher among patients with endoscopic disease recurrence at Week 48, compared with those who remained in remission (912.0 ± 1039.0 vs. 116.7 ± 84.8, $p = 0.028$). PA was not significantly higher in patients who suffered from endoscopic recurrence, was not elevated prior to disease recurrence and did not correlate with CLP levels at the various time points.
Conclusions: Faecal PA is not associated with CD activity in post-operative patients in contrast to faecal calprotectin level which is associated with post-operative CD recurrence and may be used to non-invasively monitor disease activity. Monitoring mucosal inflammation with better non-invasive techniques is crucial to limit disease progression and complications.

P008

Proteomic markers of response to anti-TNF drugs in patients with Crohn's disease

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Background: Therapy with anti-TNF has improved notably the management of Crohn's disease (CD).[1] However, 25–40% of patients treated with these drugs lose response long-term.[2] In addition, these treatments are expensive and not without risk of adverse events. Therefore, it is essential to identify reliable markers that will select those patients who can benefit of anti-TNF drugs, thus improving their efficacy and safety
Methods: A consecutive cohort of CD patients, who were naïve to anti-TNF therapy, were enrolled and followed up during 12 months. Demographic, analytical, nutritional and physiopathology were recorded. Patients were stratified according to clinical response as follows: (a) Non-primary response (NPR) at 12 weeks post-treatment; (b) loss of response (LR) within 12 months; (c) sustained clinical response (SCR). In addition, plasma samples were collected previously to anti-TNF treatment and further analysed by SWATH proteomics,[3] to identify potential biomarkers of response to anti-TNF. Anova or Kruskal–Wallis tests were used for analysis, according to data distribution. Functional pathways of identified biomarkers was analysed by DAVID Bioinformatics Resources 6.7.[4]
Results: In total, 54 CD patients were included. Most of them (77.3%) showed an SCR. However, 4.5% of patients had NPR and 18.2% LR. Patients with recent diagnosis of CD (<12 months) were less likely to achieve SCD. Indeed, the interval from diagnosis to anti-TNF therapy was shorter in patients NPR (0 ± 0) as compared with LR (9.9 ± 5.9 years) and SCR (6.32 ± 8.0 years) ($p = 0.04$). Increased blood leucocytes count before treatment was also associated with NPR (NPR: 13.7 ± 2.1 vs. LR: 8.4 ± 2.3 and SCR: 7.6 ± 2.9) ($p = 0.018$). In addition, we have identified the overweight as a factor of losing response during the first year of treatment (BMI: NPR: 24.5 ± 7.5, LR: 27.6 ± 4.6 vs. SCR: 23.4 ± 3.6) ($p = 0.036$). As potential biomarkers of primary response we have identified 18 proteins up-regulated, related to hemostasis and metabolism of carbohydrates, all of them with $p \leq 0.009$ and a fold change ≥ 2.4. Seventeen of these proteins are regulated by acetylation. In addition, 4 proteins were potential biomarkers of loss of response ($p \leq 0.05$ and fold change from 0.5 to 1.4). Two of them related to lipids metabolism.
Conclusions: Early need for anti-TNF and increased blood leucocytes count, probably related to a more severe disease, are associated with NPR. Overweight is associated with secondary loss of response to anti-TNF. In addition, hemostasis, metabolism of carbohydrates and lipids may be involved in the response to anti-TNF in CD.
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P009

Fluorescence mediated tomography detects and quantifies early intestinal neutrophil infiltration in experimental colitis

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Background: Recruitment, infiltration, and activation of inflammatory cells are crucial steps in the pathogenesis of IBD. The aim of this study was the visualisation of these processes *in vivo* and documentation of the kinetics of infiltration in experimental colitis.

Methods: Colitis was induced in C57BL/6 WT mice fed with 2.5% (w/v) dextran sodium sulphate (DSS) in their drinking water. Animals were monitored for weight loss and presence of blood in the stools by hemoccult testing. Intestinal neutrophil infiltration was measured by targeted fluorescence mediated tomography (FMT) after injection of a neutrophil-specific fluorescence labelled (Cyanine7, $\lambda_{excitation}$: 750 nm, $\lambda_{emission}$: 776 nm) rat-anti-mouse Gr1 antibody or unspecific isotype control. FMT examinations and additional white light and fluorescence endoscopy were performed before (Day 0) and during (Day 5) colitis induction as well as at the end of the experiment (Day 10). Distribution of inflammatory cells in peripheral blood samples was determined by FACS staining for CD11b and Ly6C. *Post mortem*, intestinal neutrophil infiltration was quantified by immunohistochemistry for Gr1 and ELISA measurements of tissue myeloperoxidase (MPO) levels.

Results: Colitic animals showed decreasing body weight and faecal occult blood. FMT revealed a significantly increased level of fluorescence only 5 days after colitis induction when compared with pre-experiment healthy conditions (738.6 pmol tracer vs. 73.2 pmol tracer; $p < 0.05$) while neither clinical parameters nor endoscopy detected significant changes at this early time. Confirmatory, FACS analysis revealed a significant increase in inflammatory $CD11b^{high}Ly6C^{high}$ monocytes ($p < 0.05$). At the end of the experiment, white light endoscopy showed significant colonic inflammation with confirmatory neutrophil infiltration in colon tissue indicated by significant tracer accumulation in FMT and fluorescence endoscopy (compared with pre experiment healthy conditions, $p < 0.05$) as well as increased numbers of Gr1 positive cells and elevated MPO levels in *post mortem* analysis of colonic tissue (compared with healthy control mice, $p < 0.05$).

Conclusions: Gr1-targeted FMT can detect early colonic infiltration of inflammatory neutrophils before clinical symptoms or endoscopic alterations occur. *In vivo* FMT and fluorescence endoscopy allow repetitive monitoring of inflammatory activity and kinetics of leucocyte emigration and can be employed in various models of inflammation providing a valuable non-invasive tool to visualise and quantify the accumulation of inflammatory cells or other desirable targets.

P010

Synergy of Notch signalling and TNF-α in the inflamed intestinal epithelia of IBD patients leads to up-regulation of UBD, a ubiquitin-like protein

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Background: It is well recognised that the intestinal epithelium of inflammatory bowel disease (IBD) patients is exposed to pro-inflammatory cytokines, most notably TNF-α. We have shown previously that the Notch signalling pathway is also up-regulated in such an epithelium, contributing to intestinal epithelial cell (IEC) proliferation and regeneration. We aimed to reproduce such environment *in vitro* and explore the gene regulation involved.

Methods: The human colonic epithelial cell line LS174T tet-on NICD cells where the Notch intracellular domain (NICD) could be induced with doxycycline (Dox) was treated with TNF-α to study the effect of TNF-α-induced NFkB pathway on the Notch signalling pathway and vice versa. Microarray analysis was performed on LS174T tet-on NICD cells while co-stimulating with Dox and TNF-α. The expression of ubiquitin D (UBD) was analysed by quantitative RT-PCR and western blot. UBD transcription was analysed using luciferase and ChIP assays. Intestinal tissues from IBD patients undergoing surgery were immunostained to compare the distribution of UBD expression in inflamed and uninflamed states. Human intestinal organoid lines were established from biopsies taken from non-IBD and UC patients undergoing screening endoscopy. Endoscopic biopsy samples from IBD patients were immunostained to compare UBD expression before and after infliximab (IFX) treatment.

Results: We found that Notch signalling and TNF-α-induced NFkB signalling are reciprocally regulated to promote expression of a specific gene subset in human IEC cell lines. Microarray analysis identified UBD to be one of the most highly up-regulated genes due to synergy of Notch and TNF-α. The synergistic expression of UBD was regulated at the transcriptional level, where NFkB was found to bind to regions within the UBD promoter and 5'UTR, which was further enhanced by Notch activation. UBD protein was found to have an extremely short half-life due to post-translational, proteasomal degradation. In uninflamed intestinal tissues from IBD patients, UBD expression was limited to IECs residing at the crypt bottom. In contrast, UBD-expressing IECs were seen throughout the crypt in inflamed tissues, indicating substantial induction by the local inflammatory environment. Analysis using patient-derived organoids confirmed conserved Notch- and TNF-α-dependent expression of UBD. Notably, post-infliximab (IFX) down-regulation of UBD reflected favourable outcome in IBD patients.

Conclusions: We propose that UBD is a novel inflammatory-phase protein expressed in IECs, with a highly rapid responsiveness to anti-TNF-α treatment.

P011

Signalling and transcriptional network propagation uncovers novel ulcerative colitis pathogenetic pathways from single-nucleotide polymorphisms

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Background: ulcerative colitis (UC) is a complex disease with poorly understood pathogenesis. In recent years, enormous genome-wide association studies have identified 242 single-nucleotide polymorphisms (SNPs) which cause UC susceptibility. However, their exact functions and effects remain unknown. To help discover novel pathogenic pathways in UC, we developed network biology approaches to study these SNPs in the context of their signalling and regulatory landscapes.
Methods: We used immunochip profiles of 941 UC patients and focussed on UC-associated SNPs which altered miRNA target sites or transcription factor (TF) binding sites. We identified the SNP affected proteins, and mapped them to a comprehensively curated signalling database, OmniPath (http://omnipathdb.org/), to uncover their known interactions. We run a simulation using an approach called random walks to link the effect of the SNP affected proteins to TFs. We calculated how many signals reached each TF from the SNP affected proteins in each patient. Afterwards, we connected the TFs to their target genes, using a manually curated TF-target gene dataset we developed in-house (TFlink) and the Gene Transcription Regulation Database. Following a randomised control, we kept those genes that were significantly affected in more than 50% in the analysed patients.
Results: We found 24 genes with putative links to UC. The 24 genes linked the immune-related kinase LYN and STAT4 to the immune-based pathogenesis of UC. UC SNPs affected CSKA1, CSKA2, and PKCA kinases. These kinases regulate major parts of cellular signalling networks, indicating their key role in pathogenic rewiring. Furthermore, we identified TFs involved in myofibroblast development including MYOD1 and MEF2A and MEF2D. We also identified EPCAM and ACTN4A which are involved in the focal adhesion complex, which is regulated indirectly by LYN. The involvement of these genes suggests a defected wound healing mechanism in the colon as a key player in UC pathogenesis.
Conclusions: Our findings suggest that the SNPs in UC can affect, via their signalling interactions, a wide variety of cellular functions with known pathogenic relevance. The functions of the affected genes indicate the focal adhesion complex and the myofibroblast development to be involved in UC pathogenesis. The described effects suggest novel pathogenetic pathways involved in UC which may be used to illuminate potential novel therapeutic intervention points.

P012

IL22 expression in intestinal immune cells is not augmented by AHR activation in health or Crohn's disease

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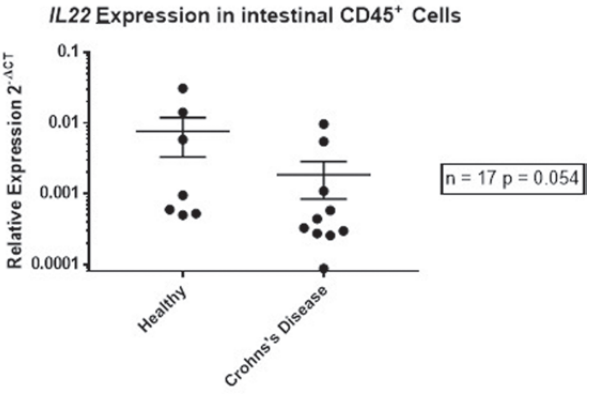
Background: IL-22 produced by mucosal immune cells plays an important role in maintenance of the intestinal barrier; production is increased in response to intestinal injury. The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor that responds to specific dietary and bacterial ligands. In mice, activation of AHR is critical for the expression of *IL22*. In diverse models of colitis, genetic deletion of AHR or low AHR ligand availability leads to reduced IL-22 activity and increased disease severity. Although enhancing IL-22 release by activating AHR is an attractive therapeutic approach it is unclear if this would reduce inflammation in the human IBD. In this study, we determine activation of AHR *in vivo* using quantitative measurement of *CYP1A1* expression, which closely correlates with AHR activation, and examine the impact of AHR blockade or activation on *IL22* expression in health and Crohn's disease.
Methods: CD45+ cells isolated from endoscopic biopsies using antibody labelling and immunomagnetic sorting, were cultured with AHR ligand (FICZ 10 nM) or antagonist (CH-223191 100 μM). Whole biopsies were also immediately homogenised in RLT buffer and expression of *AHR, CYP1A1*, and *IL22* determined by qRT-PCR.
Results: Whole biopsies and CD45+ intestinal immune cells expressed both *AHR* and *CYP1A1 ex vivo* suggesting the presence of a functional AHR signalling pathway; *AHR and CYP1A1* expression was higher in CD. *IL22* expression was also detectable *ex vivo* but did not correlate with *CYP1A1* expression and was lower in CD.



AHR signalling was significantly inhibited by antagonist but was minimally enhanced by agonist. However, *IL22* expression *in vitro* by CD45+ cells was not significantly affected by either AHR antagonist or agonist. Baseline AHR activation or response to agonist did not correlate with *IL22* expression in response to agonist. However, the degree to which *CYPY1A1* expression was inhibited by antagonist, a potential surrogate for *in situ* activation, did correlate with baseline *IL22* expression in the same tissue suggesting a more complex relationship.
Conclusions: In humans the AHR pathway is activated *in vivo* in both health and Crohn's disease. Resting *IL22* expression is lower in CD compared with health. However, the expression of *IL22* in intestinal immune cells was not augmented in vitro by AHR ligand in either health or disease, perhaps because the pathway is already near maximally activated. This suggests the relationship between AHR and IL22 is complex and simply supplementing AHR ligand intake may not be helpful in IBD.

P013

Novel immunomodulatory role of food bioactive peptide lunasin in the healthy human intestinal mucosa

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Background: The gastrointestinal mucosa represents the main interface between dietary components and the organism. Lunasin is a 43-amino acid peptide naturally present in soybean protein with a variety of biological functions demonstrated by in vitro assays, cell cultures and animal models. Nevertheless, its physiological relevance in human primary intestinal cells remains elusive.
Methods: Peptide was obtained by chemical synthesis. Human colonic biopsies were obtained from healthy controls and conditioned with peptide lunasin (5, 50, and 200 μM), both in the presence and absence of pro-inflammatory lipopolysaccharide (LPS, 100 ng/ml). Peptide integrity during overnight culture was monitored by liquid chromatography coupled to tandem mass spectrometry (HPLC-MS/MS). After culture, the relative gene expression of colonic biopsies as well as the intestinal cytokine milieu in culture supernatants were characterised.
Results: HPLC-MS/MS analysis showed that lunasin maintained its stability during biopsy culture up to 90%. Lunasin was bioactive in the human mucosa inducing IL-1β, TNF-α, IL-17A, CCL2, and PGE2/COX-2 gene expression, typically in a dose-dependent manner. Moreover, lunasin also enhanced mucosal expression of tolerogenic cytokines IL-10 and TGFβ and down-regulated the expression of iNOS and subunit p65 from NF-κB. LPS induced a pro-inflammatory immune response which was, however, partially abrogated in the presence of lunasin as it down-regulated pro-inflammatory IL-17A and IFN-γ, and enhanced mucosal gene expression of regulatory IL-10 and TGFβ. Moreover, results were further validated at the protein level as IL-1β, TNF-α, and IL-10 secretion were enhanced while IL-6, CCL2, and IFN-γ production were abrogated by lunasin. Indeed, the latter cytokine was also neutralised in the presence of LPS.
Conclusions: Food-derived peptide lunasin is biologically active in the human intestinal mucosa determined by changes on the global cytokine milieu both at the messenger and protein levels. Lunasin displayed its anti-inflammatory effect by abrogating the production of pro-inflammatory cytokines even in the presence of LPS, and expanding the production of tolerogenic IL-10 and TGFβ. This peptide might represent, therefore, a novel agent as functional compound for the prevention of immune and inflammatory-mediated intestinal disorders.

P014

Disruption of epithelial barrier function by coeliac peripheral blood mononuclear cells

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Background: Immune cells are present in the small intestine mucosa in normal and inflammatory conditions. Once activated, these cells cause direct effect in the barrier function of epithelial cells in inflammatory bowel diseases (IBD). It is known that the epithelial barrier function is altered in coeliac disease (CD), common disease affecting the small intestine. In CD patients, the immune cells in the small bowel mucosa are activated after contact with antigen-presenting cells exposing gliadin-derived peptides, which leads to an inflammatory cascade causing villous atrophy and disruption of the epithelial barrier. Nonetheless, the mechanisms underlying the disrupted barrier function in CD is not clearly understood. This study aimed to verify the effect of immune cells derived from coeliac patients on the barrier function of intestinal epithelial cells
Methods: Peripheral blood mononuclear cells (PBMCs) were isolated from the blood sample of heathy donors (n = 3), CD patients on gluten-free diet (CD GFD; n = 2) and active CD patient (n = 2). CacoBBe cells were co-cultered with PBMCs and CD14+ cells (monocytes). To verify the role of active gliadin stimulation, the intestinal cells were treated with or without IL15/Tglia. In addition, to exclude direct toxic effect of gliadin on the epithelium, control CacoBBe cells were treated with IL-15/Tglia alone. The integrity of the barrier in the monolayer cells was monitored by measuring transepithelial resistance (TER). The localisation of proteins with role in epithelial barrier function (CD71, occludin, claudin-2 and ZO-1) was investigated using confocal microscopy after immunostaining
Results: A more pronounced decrease in TER was observed in intestinal epithelial cells after co-culture with coeliac PBMCs and CD14+ cells (active CD or CD GFD patients) comparing with healthy donors. However, no difference in TER was observed comparing active CD and CD GFD. As found in completely untreated cells, in cells treated with IL-15/Tglia alone, the TER did not decrease. Exposure of intestinal epithelial cells to coeliac PBMCs resulted in a decreased expression of occludin, while no effect was observed in claudin-2 localisation and expression. In addition, it was observed an abnormal structure in ZO-1 after co-cultered epithelial cells with coeliac PBMCs (CD GFD and active CD). Confocal microscopy revealed an altered localisation of CD71 after treatment with coeliac PBMCs and CD14+ cells, with evidence of a diffuse intracellular localisation when compared with untreated cells.
Conclusions: Coeliac PBMCs have an effect on epithelial barrier function of intestinal epithelial cells. This is associated with an altered expression pattern of key proteins for tight junction assembly.

P015

PNAd+ and MAdCAM+ high endothelial venules correlate with disease activity in ulcerative colitis

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Background: Tertiary lymphoid organs (TLOs) comprising peripheral node addressin positive (PNAd+) and/or MAdCAM+ high endothelial venules (HEVs) have been found to play an important role in local immunological dysregulation in chronic immune-mediated disorders and malignancies. Their presence have a predictive value for disease course and response to therapy. Identification of these HEVs in the early phase of ulcerative colitis (UC) might help stratify patients to enable personalised medicine. We aimed to investigate the presence of these HEVs at UC diagnosis and their development during follow-up. Furthermore, we studied their association with disease activity and response to therapy.

Methods: Retrospectively collected colonic biopsy specimens from 110 UC patients at first presentation and during follow-up were analysed by immunohistochemistry after determining the Geboes score. Immunostaining was performed using antibodies: MECA-79 (anti-PNAd), MECA-367 (anti-MAdCAM), ERG (endothelial cells), CD3 (T cells) and CD20 (B-cells). The expression of extrafollicular PNAd+ on all vessels (ERG) was correlated to disease activity, disease course and response to therapy.
Results: In total, 110 newly diagnosed UC patients were analysed. Percentages of PNAd expressing ERG+ vessels at baseline ranged from 0.0% to 29.8% (median 5.4; IQR 1.9–10.3). Higher numbers of extrafollicular PNAd+HEVs were associated with higher numbers of colonic lymphoid follicles (r = +0.7 p = 0.001). No extrafollicular PNAd+ HEVs were detected in biopsies of patients in remission during follow-up (n = 57 median 0.0: IQR 0.0–0.0). In active disease (n = 53), PNAd expressing HEVs were not significant different from baseline numbers (median 4.2: IQR 1.6–7.6, p = 0.178). Patients nonresponding to 5ASA induction therapy after initial diagnosis had significant higher baseline percentages of PNAd expressing ERG+ vessels (p = 0.046) in colonic biopsies compared with responding patients. Median percentage of MAdCAM expressing ERG+ vessels at baseline was 5.5% (IQR 2.6–10.1). During follow-up in both active disease and remission, significant elevation was demonstrated for MAdCAM expression on ERG+ vessels (resp. 7.5%(IQR 3.3–12.5), p = 0.028 and 8.8%(IQR 4.9–13.8), p = 0.022).
Conclusions: Formation of extrafollicular PNAd+HEVs was present in active disease while absent in remission. High numbers of PNAd+HEVs were associated with no response to 5ASA induction therapy and with more colonic follicles, suggesting TLO formation. MAdCAM expression increased during disease course independent of disease activity.

P016

Constitutive activity of the cation channel TRPM8 regulates monocyte to macrophage transition in humans to control intestinal inflammation

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Background: Abnormal intestinal monocyte to macrophage transition plays a critical role in inflammatory bowel disease (IBD). TRPM8 (Transient Receptor Potential Melastatin 8) is a ligand-gated cation channel activated by factors including cold and cooling compounds leading to cation influx. TRPM8 RNA is increased in both the colonic mucosa of Crohn's disease patients and mice with experimentally induced colitis in which activation of TRPM8 with synthetic agonists ameliorates disease. Mice with TRPM8-deficient macrophages develop worse colitis, implying that TRPM8 in macrophages is protective against intestinal inflammation. Our aim was to test the hypothesis that TRPM8 activity controls inflammation in the human intestine by modulating monocyte to macrophage transition.
Methods: Blood monocytes from healthy volunteers were differentiated into macrophages using M-CSF, in the presence or absence of TRPM8 antagonist (AMTB) or agonist (icilin). Intestinal CD14+ monocytes were extracted from colonic biopsies obtained from control patients. Flow cytometry was used to measure TRPM8 protein, membrane potential using DISBAC2(3) dye, phagocytosis of fluorescent microspheres, cell viability, and TNF-α production. RNA seq was used to determine differential gene expression.
Results: TRPM8 protein was detected in blood monocytes, *in vitro* derived macrophages and CD64+ monocyte/macrophages in the intestinal mucosa. Inhibition, but not activation of TRPM8 activity in blood monocytes resulted in membrane depolarisation after 3 h, which was associated with increased cell survival (p = 0.0001) and enhanced production of LPS-induced TNF-α (p = 0.0001, Figure 1) after 24 h. Inhibition of TRPM8 also enhanced TNF-α production by CD14+ intestinal monocytes. Macrophages generated from blood monocytes in the presence of AMTB had reduced phagocytic capacity (p = 0.03) and differential expression of 977 genes, indicating substantial effects on cell differentiation. Genes related to cell migration, including the gut homing integrin gene ITGB7, were decreased, whereas genes related to cytokine production were increased.

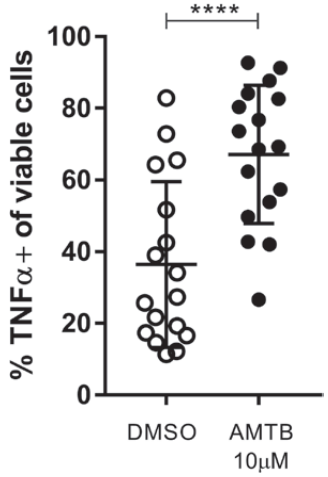

Figure 1. Increased LPS-induced TNF-α production in CD14+ monocytes after culture with AMTB.

Conclusions: TRPM8 is expressed in human blood and intestinal monocyte populations where it has constitutive activity that modulates the transition into macrophages and limits inflammation. Understanding alterations in this pathway in IBD may allow identification of novel therapeutic targets.

P017

Transcriptional reprogramming of the HIF pathway is associated with inflammation and mucosal hypoxia in ulcerative colitis patients

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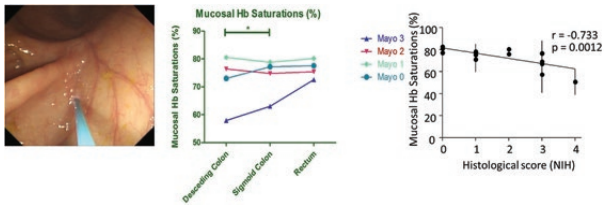
Background: Hypoxia is a feature of inflammation. Recent research into the protective role of prolyl-hydroxylase inhibitors in animal models of ulcerative colitis has suggested hypoxia and the HIF pathway may be involved in UC. In hypoxic conditions, HIF is stabilised and initiates the transcription of genes critical to the adaptation to hypoxia. In this study, we investigate the role of tissue hypoxia and the transcriptional activity of the HIF pathway in ulcerative colitis.

Methods: Healthy control (n = 7) and ulcerative colitis patients (n = 41)were prospectively recruited. Tissue oximetry was used during endoscopy procedures to assess the extent of mucosal hypoxia in ulcerative colitis patients. Transcriptional activity of HIF pathway components was investigated in biopsies taken from these same patients and *in vitro* using Caco-2 cells.
Results: 48 patients were included in the study.

	Control (n = 7)	ulcerative colitis (n = 41)	
Age (median; IQR)	45.43 (40.45–69.44)	39.86 (31.4–56.56)	p = 0.314
Gender (male; n (%))	5 (71.4)	26 (63.4)	
Haemoglobin (g/l) (median; IQR)	14.6 (14.2–14.9)	14.1 (13.2–15.3)	p = 0.417
Albumin (g/l) (median; IQR)	40 (37–45)	38 (34–40)	p = 0.042*
C-reactive protein (median; IQR)	2 (1–3)	6 (1–19)	p = 0.071
Faecal calprotectin (μg/g) (median; IQR)	15 (15–15)	448 (118–1921)	p = 0.032*

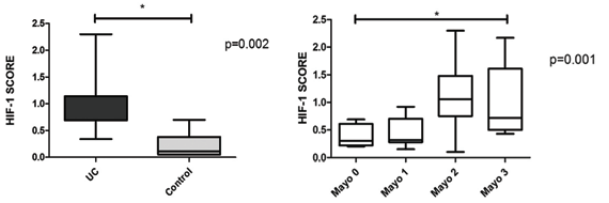
Patient demographics and biochemical data.

Mucosal tissue hypoxia was found to correlate with the extent of inflammation in ulcerative colitis patients. Mucosal saturations recorded in the sigmoid in Mayo 3 disease (63% (49.4–67.5); median; IQR) were significantly lower compared with Mayo 0-2 (eg, Mayo 2:74.8% (71.7–78.4): median; IQR) (p = 0.001).



(A) Endoscopic oxygen sensor during measurement. (B) Mucosal oxygen saturation in UC patients. (C) Pearson correlation of NIH histological score with oxygen saturation.

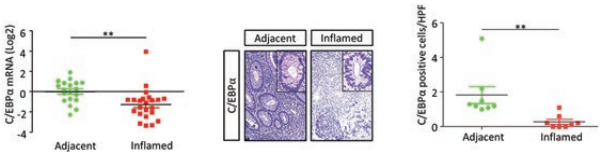
A transcriptional reprogramming of the HIF pathway to promote an HIF-1α response was found to occur in inflamed ulcerative colitis patient tissue and this response correlated with the extent of mucosal inflammation.



Gene	HIF-1α	HIF-2α	PHD1	PHD2	PHD3	FIH	VHL
Up or downregulated in UC	–	–	↓	↓	–	↓	–

(A) HIF-1 scores in UC and control groups. (B) HIF-1 scores in Mayo 0–3. (C) Gene expression of HIF pathway components in UC rectal biopsies

Part of this transcriptional regulation of the HIF pathway was found to be due to down-regulation of both PHD1 and C/EBPα which was found to be an inflammation sensitive transcriptional regulator of PHD1.



Expression of C/EBPα mRNA in inflamed and adjacent non-inflamed biopsies from UC patients. (b) Representative images of C/EBPα IHC staining of UC patient biopsy sections. (c) Analysis of C/EBPα-positive cells in biopsies

Conclusions: Mucosal hypoxia is a feature of active inflammation in UC and correlated with disease severity. Part of the inflammatory response includes a transcriptional reprogramming of the HIF pathway to promote a protective HIF-1α response which is due, in part, to down-regulation of the inflammation sensitive PHD1 regulator, C/EBPα.

P018

Macrophage targeting contributes to the inhibitory effects of dihydroartemisinin on DSS-induced colitis

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Background: Macrophages are a major component of the inflammatory milieu, which can be categorised into 'classically activated' M1 and 'alternatively activated' M2 subtypes based on their polarisation status. Accumulating evidences show that macrophage are key plays in inflammatory bowel diseases (IBD), especially M1 subtype. The present study investigated the role of macrophage targeting in the anti-inflammatory properties of dihydroartemisinin.
Methods: The acute colitis model was induced using DSS as described previously. Macrophages in colon tissue were detected by immunohistochemistry. Typical M1 and M2 markers were determined both *in vivo* and *in vitro*. *In vitro*,macrophage generation were performed using bone marrow cells, and macrophages were detected following dihydroartemisinin treatment.
Results: Dihydroartemisinin significantly resolved the inflammatory response of the colonic epithelium. There was a marked reduction of the colonic infiltration by CD68+ macrophages in mice treated with dihydroartemisinin. Interestingly, both M1 and M2 subtypes were significantly decreased. Concomitantly, CCL2, CSF1, main chemoattractants that support the recruitment and survival of macrophage, were markedly decreased by dihydroartemisinin treatment. And both typical M1 (IL-1β) and M2 (MR, Arg-1) markers were significantly decreased in dihydroartemisinin treated mice. *In vitro*, consistently, dihydroartemisinin directly reduced the polarisation of M1/M2 macrophage even in the presence of Th1/Th2 cytokines. Moreover, dihydroartemisinin could directly interfere with the generation of macrophage *in vitro*. These effects of dihydroartemisinin on macrophage were mediated largely via limiting NF-KB signalling.
Conclusions: Dihydroartemisinin inhibited colitis partly by reducing the infiltration and suppressing the function of macrophage.

P019 has been withdrawn.

P020

Regulation of intestinal epithelial homeostasis by the IBD risk gene CCNY

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Background: CCNY, encoding Cyclin Y, has previously been identified as a putative risk gene in Crohn's disease and ulcerative colitis; however, the function of CCNY in the gut is unknown. We have shown that Cyclin Y is a critical activator of the Wnt/β-catenin signalling pathway, which controls stemness and proliferation in intestinal epithelia. We thus investigated whether CCNY regulates epithelial homeostasis and wound repair in the gut.
Methods: To address the role of CCNY in intestinal epithelia, we used a RNA interference based loss-of-function approach in model cell lines. In addition, we generated transgenic mice with deletion of Ccny specifically in intestinal epithelial cells. These animals were subjected to the dextran sulphate sodium model of intestinal injury and repair, which mimics human inflammatory bowel diseases. We studied Wnt pathway activity in these models using reporter assays and pathway-specific antibodies, as well as functional in vitro assays. In addition, we determined colitis progression and epithelial homeostasis in mice using an established disease activity index and histopathological analyses.
Results: In contrast to non-intestinal epithelia, loss-of-function of CCNY did not reduce Wnt signalling activity in model intestinal cell lines. Accordingly, CCNY depletion did not impair epithelial proliferation or stemness in vitro. Moreover, markers of Wnt activity and cell proliferation were unchanged in Ccny mutant mice, and we observed no changes in disease activity during acute intestinal inflammation.
Conclusions: Our results thus far suggest that IBD risk gene CCNY is dispensable for intestinal epithelial homeostasis. The apparent uncoupling of Cyclin Y from Wnt signalling in the gut is the subject of ongoing investigation in our lab. In addition, we continue to investigate the possible contribution of CCNY to epithelial regeneration following colitis.

P021

An electrochemiluminescence (ECL) immunoassay for the detection of antidrug antibodies against anti-mucosal addressin cell adhesion molecule (MAdCAM) monoclonal antibody SHP647

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Background: Immunogenicity assessment is a regulatory requirement for biotherapeutic product (BTP) approval since antibodies that develop in response to a BTP may directly impact product safety and efficacy. A well-designed anti-drug antibody (ADA) immunoassay is critical for monitoring the immunogenicity profile of a BTP during its development. SHP647 is a fully human IgG_{2K} monoclonal antibody that targets human MAdCAM to reduce lymphocyte homing to the gut and gastrointestinal inflammation, and is in development for the treatment of Crohn's disease (CD) and ulcerative colitis (UC). A sensitive and specific ECL immunoassay for the detection of ADAs against SHP647 was developed and validated to support its use in clinical trials of SHP647.
Methods: SHP647 was either biotinylated as the capture agent, or labelled with ruthenium as the detection reagent. In the assay, human serum samples, positive controls and negative controls were diluted with assay buffer prior to co-incubation with both the capture and detection reagents overnight to form an antibody-drug complex. After incubation, each mixture was added to Streptavidin coated MSD plate to allow complexes to bind to the plate. In the presence of tripropylamine-containing read buffer, ruthenium produces a chemiluminescent signal that was triggered when voltage was applied. The resulting chemiluminescence was measured in relative units on a SECTOR Imager 6000™ instrument. Data are presented as endpoint log titers (log2) (the reciprocal of the serial dilution at which the sample response would be equal to the cut point of the assay).
Results: The assay precision (inter-run ≤4.0% and intra-run ≤3.4%) in normal human serum was demonstrated. Relative assay sensitivity was 3.25 ng/ml. The matrix specificity (recovery) ranged from 96.9% and 109.4% in 10 individual lots of normal, CD, or UC human serum. The assay achieved the detection of 300 ng/ml of ADA in the presence of 300 µg/ml of the drug. Interference was observed in the presence of 100 ng/ml soluble MAdCAM. The assay screening cut point factors and confirmatory assay cut points in normal, CD and UC populations were established.
Conclusions: The ECL immunoassay with sensitivity and high tolerance to both soluble MAdCAM and SHP647 for the detection of anti-SHP647 antibodies was successfully developed and validated in compliance with the regulatory requirements. The assay was used to support the Phase 2 OPERA II trial (NCT01298492) where the highest level of soluble MAdCAM in samples at Week 12 did not exceed 54 ng/ml and no samples had SHP647 level higher than 74.5 µg/ml. Therefore, the assay is considered suitable to support the OPERA II trial. However, the assay might not be able detect low levels of ADA when serum drug levels are high.

P022

Galectin-3, galectin-9, and galectin-3 binding protein in patients with inflammatory bowel diseases

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Background: Galectins are a family of lectins that bind β-galactosides. They effect variety of cellular and intracellular processes including inflammation, fibrosis, organogenesis, immunological response, and malignancy. Thus, galectins may be a therapeutic target for inflammatory diseases. Their role in inflammatory bowel diseases (IBD) has not been fully evaluated, yet. The study aimed to assess galectin-3,

galectin-9, and galectin-3-binding protein (M2BP) levels in patients with ulcerative colitis (UC) and Crohn's disease (CD), and to correlate it with inflammatory markers and the disease activity.
Methods: Consecutive patients, including 48 with UC, 77 with CD, and 30 healthy controls were included. The white blood cell count, haematocrit, platelet count, fibrinogen, C-reactive protein, galectin-3, galectin-9, M2BP levels in serum were measured and correlated with the disease activity.
Results: There were no significant differences in the median galectin-3 and galectin-9 levels between the UC group, CD group and the control group (Table 1). M2BP was significantly higher in the CD group vs. controls. The median M2BP level in the patients with active UC was significantly higher 72.74 (60.86–101.72) ng/ml than in the group with inactive disease 61.22 (39.31–72.60) ng/ml, $p = 0.006$. In the active CD group median M2BP level was higher than in the control group (79.854 (52.05–110.12) ng/ml, $p = 0.04$) In the UC group M2BP level correlated with CRP ($r = 0.304$, $p = 0.02$) and disease activity ($r = 0.298$, $p = 0.03$); galectin-3 correlated with galectin-9 ($r = 0.54$, $p < 0.001$). In the CD group, galectin-9 correlated with galectin-3 ($r = 0.549$, $p < 0.001$), and M2BP ($r = 0.4$, $p < 0.001$).
Conclusions: This is the first study to show that M2BP is increased in active IBD and in the UC its level is associated both with inflammatory markers and disease activity as well. In contrast, galectins 3 and 9 levels do not differ from healthy controls.

P023

A resting state fMRI study in patients with active Crohn's disease

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Background: Resting state functional magnetic resonance imaging (rsfMRI) measures spontaneous fluctuation in blood oxygen-level dependent (BOLD) signals in the brain at rest, generating neuroanatomically distinct functionally linked Resting State Networks (RSNs). Present RSN literature in CD is sparse, solely reporting in inactive disease and only focussed on specific RSNs. Here we use independent component analysis (ICA) to study changes across multiple RSNs in active CD.
Methods: 29 active CD patients and 27 age-, BMI- and gender-matched healthy controls (HC) were recruited. Active disease was defined as CRP > 5 mg/dl, or faecal calprotectin (FCP) >250 µg/g or through ileocolonoscopy or MRE. A hospital anxiety and depression (HAD) score was used as a patient-reported outcome. RsfMRI datasets were acquired on a 3T Philips Achieva scanner, with data corrected for physiological noise and motion. ICA analysis was carried out using MELODIC (FSL software). A multi-session temporal concatenation was used to generate 30 independent component (IC) maps of RSNs. A dual regression analysis with variance normalisation was performed to identify differences in RSN between HCs and CD patients. Anatomical T1-weighted images were collected to determine structural (grey matter volume (GMV)/cortical thickness) differences in CD (CAT, SPM software).
Results: CD participants had an age of (33 ± 14) years, Harvey–Bradshaw Index was (4 ± 1), CRP (9 ± 7) mg/dl and FCP (617 ± 554) µg/g. CD patients had significantly higher depression scores (CD: 3.0 ± 0.6, HC: 1.5 ± 0.5, $p < 0.05$). RSNs comprising the visual network, default mode network (DMN), salience network, dorsal attention network (DAN), frontal–parietal network (FPN), temporal and cerebellum networks were identified. Enhancement of activity and increased connectivity in DMN (posterior cingulate cortex (PCC)), the cerebellar network and thalamus, visual attention network, and FPN (postcentral cortex) was observed in CD. Atrophy (reduced GMV and cortical thickness (CT) in post-central gyrus and additional cortical thinning in right rostral middle-frontal cortex was seen in CD.

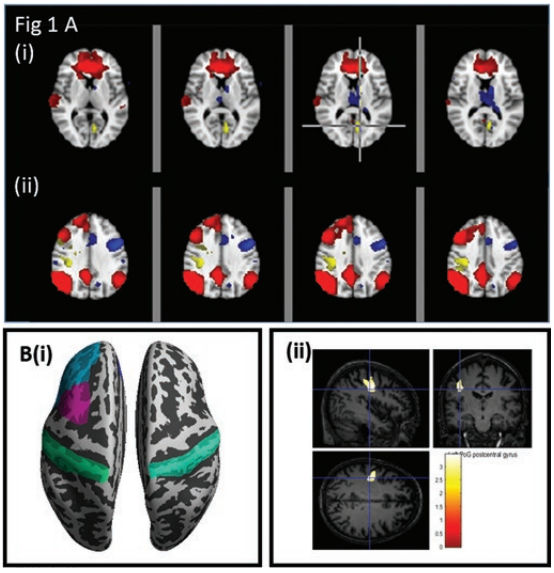

Figure 1. (A) RSNs (red = positive and blue = negative networks) areas of increased connectivity in CD>HC yellow in (i) DMN (posterior cingulate) and (ii) FPN (postcentral cortex). (B) Areas of atrophy in CD for (i) CT and (ii) GMV.

Conclusions: These data show abnormal increased connectivity in RSNs in CD patients in the DMN (PCC) and in FPN network (postcentral cortex which also showed associated atrophy). These changes may reflect neuroplasticity in response to chronic systemic inflammation and may relate to altered affective and cognitive self-referential processing.

P024

Plasma acetic acid, propanoic acid, and isobutyric acid are associated with treatment response in pouchitis patients treated with antibiotics

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Background: Restorative proctocolectomy is considered an option for patients with medically refractory ulcerative colitis. Short chain fatty acids (SCFA) are organic fatty acids with 1–6 carbons which arise from bacterial metabolism from carbohydrates entering the colon. In pouchitis, they have been found in significantly lower concentrations in faecal samples from patients with pouchitis when compared with healthy controls. The aim of the study was to measure SCFA in plasma in patients with pouchitis who were treated with antibiotics and compare levels of SCFA in those who responded to antibiotics vs. those who failed to respond to antibiotics.
Methods: Pouchitis was defined using the pouch disease activity index (PDAI) and pouchitis was considered when the score was 7. Response to antibiotics was defined as either a 2-point reduction in PDAI or a score of <7. Patients were classified as off antibiotics if they had stopped all antibiotics for a period of at least 2 weeks prior to sample collection. Blood was centrifuged at 1,600 g for 15 min. The plasma supernatant was then transferred into a 5 ml Eppendorf tube and snap frozen to be then stored at −80°C. Plasma SCFA were measured using an Agilent 7000C Triple Quadrupole GC/MS-MS System. Simca was used for multi-variate analysis and T-tests were used for univariate analysis.
Results: There were 23 patients. Thirteen samples were on antibiotics and 10 samples were off antibiotics. The median age of the patients was 43 (21–64). Seven patients were on ciprofloxacin and metronidazole, four were on ciprofloxacin and two were on Augmentin. There were 9 patients that responded to treatment and 14 that did not respond to treatment. On multi-variate analysis, there were no significant differences between patients who responded to treatment and those that did not. There were also no significant differences between patients on and off antibiotics. On univariate sub-analysis of patients where samples were taken off antibiotics there were significant decreases in isobutyric acid 671 507.8 µM vs. 727066.1 µM ($p < 0.03$) and significant increases in acetic acid 6250801 µM vs. 376499 µM in responders vs. non responders ($p < 0.04$).
Conclusions: Our study highlighted that there were significant differences in plasma SCFAs that could differentiate between patients with pouchitis who were able to maintain clinical response vs. non-responders when antibiotic therapy was withdrawn. This study may therefore suggest that SCFA may play a role in the maintenance of remission from pouchitis.

P025

Comparison of abdominal lymph nodes between healthy volunteers and patients with Crohn's disease

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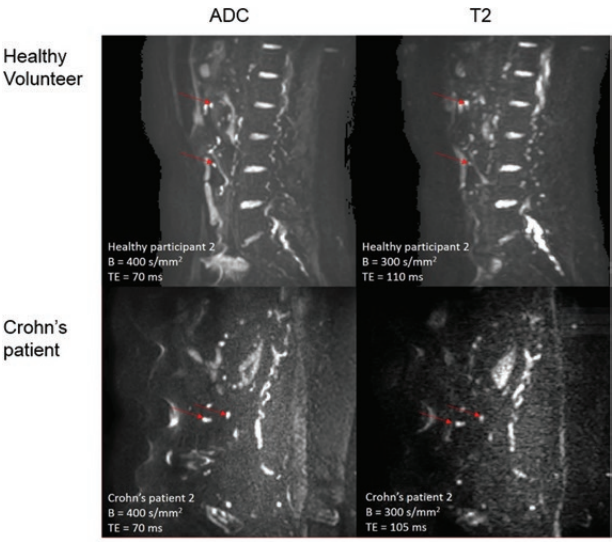
Background: Crohn's disease (CD) causes changes in the lymphatic system which have been studied using MRI. Dfusion Weighted Imaging with Background Suppression (DWIBS) provides a powerful method to isolate the nodes which are otherwise hard to identify on 3T images. DWIBS has been used to show a difference in Apparent Diffusion Coefficient (ADC) between benign and malignant enlarged nodes but work in inflammatory diseases is absent, and T2 measures may provide additional information on inflammatory activity. We hypothesised that lymph node ADC, T2, size and number may be useful disease activity measures.
Aim: to undertake a pilot study to investigate ADC, T2, number and size of abdominal lymph nodes in healthy volunteers and CD patients.
Methods: Healthy participants (HP) and CD patients were scanned on a Phillips 3T Ingenia (Best, the Netherlands). CD patients had active disease (CRP of >5 mg/dl or faecal calprotectin (FCP) of >250 µg/g or ileocolonoscopy or MR enterography). Slices were orientated sagittally, respiratory triggering was used to reduce through plane motion. The DWIBS sequence was used to measure ADC and T2. The length of the major and minor axes of the lymph nodes were recorded.
Results: HP (4 males, 3 females, mean age 32 ± 13 years) and patients with CD (3 males, 3 females, mean age 29 ± 11 years) were recruited. In CD, CRP was 7.9 ± 2.9 mg/dl and FCP was 755 ± 225 µg/g. Figure 1 shows lymph nodes identified on DWIBS images.

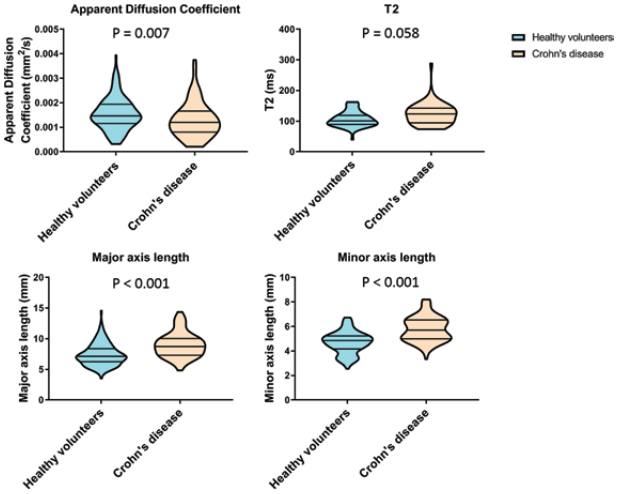


Top: Healthy volunteer. Bottom: CD patient. Two lymph nodes shown for each by the red arrows on an ADC image on the left and the same two nodes on a T2 image on the right.

P Values	Number of nodes	Apparent Diffusion coefficient ($x10^{-3}$ mm^2/s)	T2 (ms)	Major axis (mm)	Minor axis (mm)
Healthy volunteers	22±4	1.5 ±0.05	100±3.2	7.1±0.1	4.8±0.1
Crohn's disease	30±4	1.2±0.07 (p=0.007)	124±4.7 (p=0.058)	8.7±0.2 (p<0.001)	5.7±0.1 (p=<0.001)

Figure 2. shows the number, ADC, T2 and length of the major and minor axes calculated with the results summarised Figure 3.

ADC, T2 and length of the major and minor axis calculated for each group as a whole along with the standard error of the mean. The p values for comparisons between the healthy volunteers and CD patients with significant changes highlighted.



Violin plot showing the distribution of the measurements from the healthy volunteers and CD patients.

Fewer nodes were identified in CD than in the HP, but this was highly dependent on the quality of respiratory triggering which was worse in CD patients.

Conclusions: The size of the lymph nodes increased and ADC decreased in CD probably, indicating an increase in cellularity of inflamed lymph nodes. A non-significant increase in T2 was noted in CD possibly reflecting the inflammatory response in the lymph node. Lymph node size, ADC and T2 could provide a novel inflammatory marker in CD. These data need replicating in larger cohorts with changes after CD therapy assessed.

P026

Establishment of an *in vitro* system to evaluate the therapeutic effect of the investigational drug on ulcerative colitis using human colonic organoids

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Background: The goal of ulcerative colitis (UC) therapy has recently been to target mucosal healing. However, few drugs to directly target mucosal healing have been developed. Although the effects of investigational drugs can be estimated using *in vivo* mouse colitis model, it is unclear whether the target of the drugs is inflammation or mucosal damage. The establishment of an *in vitro* system to evaluate mucosal regeneration is necessary for targeting mucosal healing. We have established an *in vitro* chronic inflammation model by using mice colonic organoids.[1]

We aimed to establish an *in vitro* human model for chronic colitis using human primary colon organoids and to evaluate therapeutic effect of an investigational drug.

Methods: This study was approved by the Ethics Committee. Human colonic organoids were generated from non-inflamed colon. The mixture of inflammatory reagents was added into the medium to mimic UC. Gene Set Enrichment Analysis (GSEA) was performed for the comparison between organoids and biopsies from active UC patients. To assess the effect of investigational drug (KAG-308) on intestinal epithelial cells under chronic inflammation, the drug was added into the medium for 1 week. The effect of the drug was evaluated by microarray analysis, colony formation assay and proliferation assay. The molecular target of the drug was identified by microarray analysis. Colitis was induced in mice by 1.5% dextran sulphate sodium (DSS) in drinking water for 6 days and subsequently providing 0.5% DSS for 4 days.

Results: Microarray analysis of the inflamed organoids showed significant induction of inflammatory signalling-related genes. GSEA showed the similarities of up-regulated genes in between inflamed human organoids and biopsies from active UC patients, suggesting that the inflamed organoids might acquire UC like phenotype. Treatment with an investigational drug showed reciprocal dynamics of gene expression to inflammatory stimulation, suggesting this drug has antagonistic functions against chronic inflammation. Moreover, the genes which have reciprocal dynamics of its expression between inflammatory stimulation and drug treatment were identified as molecular target of this drug. Treatment with this drug also promoted stem cell population and cell proliferation of the organoids even under the inflammatory situation. Finally, this drug-induced mucosal healing in subacute DSS colitis model mice.

Conclusions: The establishment of *in vitro* chronic colitis model using human colonic organoid could reveal the effects and targets of an investigational drug in intestinal epithelial cells. Further maturation of this system might be more efficient to predict the effect on UC for the development of new drugs.

Reference

1. Hibiya S, Tsuchiya K, Hayashi R, *et al.* Long-term inflammation transforms intestinal epithelial cells of colonic organoids. J Crohns Colitis 2017;5:621–30. doi:10.1093/ecco-jcc/jjw186

P027

Machine learning approaches to identify prognosis indicators from microbiome data

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Background: Inflammatory bowel disease (IBD) has been shown to associate with alterations in intestinal microbiome. However, the precise nature of these microbial changes remains unclear. With the vast number of microbes present within the gut, novel and powerful computational techniques are required to distinguish between important microbial changes and noise. Machine learning (ML) allows for a data-driven approach to identify these discrete dynamic changes within the microbiome, while systems biology (SB) gives mechanisms to the findings of the ML algorithms. By combining ML and SB approaches, we aim to characterise key microbial factors in ulcerative colitis (UC) pathogenesis.

Methods: Interpreting the functional and mechanistic importance of microbiome features requires higher resolution than 16S rRNA sequencing. However, the lack of Whole Genome Shotgun (WGS) data at a scale required for ML-based classification is a bottleneck. To overcome this and to develop the ML pipeline, we generated a large artificial patient cohort using the SMOTE algorithm to oversample a small UC WGS cohort. The artificial dataset was created by preserving the complexity and distribution functions observed

in real WGS datasets. This generated enough samples to be able to train a deep learning model. We utilised the power of Artificial Neural Networks (ANNs) to obtain discrete underlying data structures from the microbiome data, thus eliminating noise from the feature space. Dynamic changes within the patient's microbiome are predicted by employing a heterogeneous ensemble (Random Forest, Gradient Boosting, etc.) to match the complexity of underlying relations of the microbiome.

Results: Using our ANN to encode the data, we identified potential candidate prognosis indicators from this artificial dataset. The ML pipeline was able to recover top-performing features from the synthetic dataset, thus determining the underlying structure of the dataset. As a next step, we have collected and interrogated publicly available microbiome data (NIH Integrative Human Microbiome Project) to enable the ML model to be applicable to actual UC cohorts.

Conclusions: We have developed an integrated ML-based microbiome pipeline to identify prognostic indicators for UC from artificial data. Furthermore, using SB approaches, we were able to interpret the predicted key microbial features and communities by inferring connections between microbial and host proteins relevant in UC. This pipeline will enable us to analyse and assess real UC patient microbiome data, and identify prognostic indicators for disease subtypes and personalised treatments.

P028

Telomere shortening and genetic anticipation in IBD

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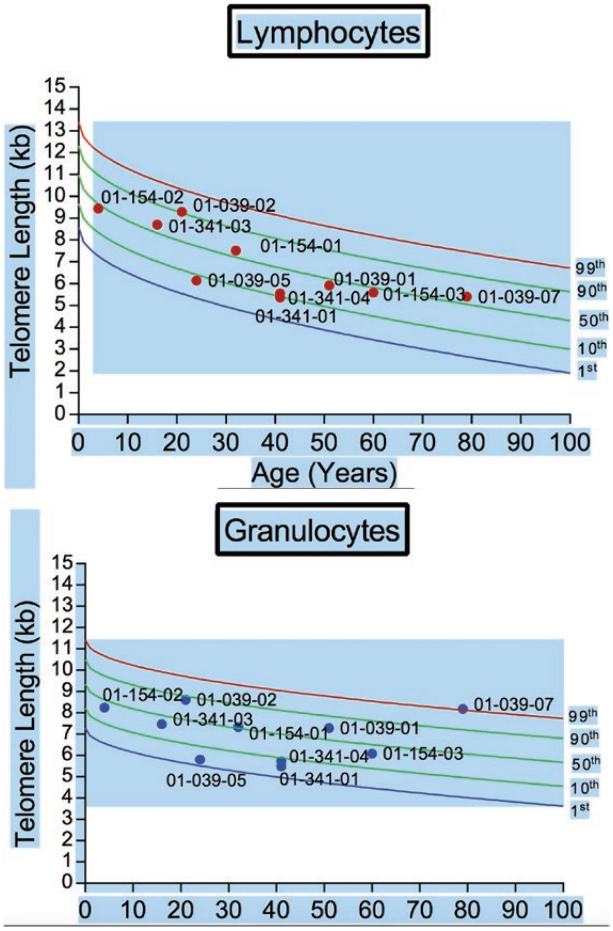
Background: Genetic anticipation, a decrease in age of onset and increase in severity of symptoms in later generations, has been suspected in inflammatory bowel disease (IBD) families. But inability to find a biological explanation and the potential for ascertainment bias pushed away this possibility. Most recently, telomere shortening has been described as a mechanism to explain genetic anticipation in dyskeratosis congenital and Li-Fraumeni syndrome. We aimed to study telomere length in IBD families and hypothesised that genetic defects causing this disease would affect telomere maintenance resulting in shortened telomeres.

Methods: We investigated three IBD families with three successive generation of affected individuals by either Crohn's disease or ulcerative colitis. We analysed telomere length in DNA from peripheral blood leucocytes and granulocytes by flow cytometry and fluorescence in situ hybridisation (flow FISH).

Results: One Crohn's disease family and two mixed (ulcerative colitis and indeterminate colitis) families with three successive generations were included in the study. Then parent-child pairs were analysed. The average difference in the age of diagnosis between the two successive generations of IBD was 17 years. All affected members were Ashkenazi jewish. In the CD family, two siblings, the mother and the grandmother were also NODs mutation carrier; all CD patients had inflammatory ileocolonic disease. In one the other two families, the child and the grandfather had left sided colitis and the mother indeterminate colitis while in the other most of the affected members (son, mother, and uncle) had pancolitis except for the first generation who had indeterminate IBD.

In our study, the anticipation in the age of IBD onset observed in successive generations was not associated with telomere shortening. However, we recognise that these families were mixed and genetic anticipation is predominantly suspected in CD patients. However, the age of onset was significantly younger in successive generation respecting the definition of this phenomenon.



Conclusions: Telomere shortening is not associated with earlier age IBD onset in successive generations, suggesting that it might not be the mechanism of genetic anticipation in this polygenetic disease.

P029

Serum bile acids profiling in IBD patients treated with anti-TNFs

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Background: Inflammatory bowel diseases (IBD), ulcerative colitis (UC) and Crohn's disease (CD), represents chronic conditions with a deficient intestinal absorption. This study represents the first attempt to screenshot bile acids (BAs) in a large cohort of IBD patients to evaluate changes under anti-TNFα chronic treatment.
Methods: Forty CD and 40 UC patients were prospectively enrolled and a fasting serum sample obtained. BAs were quantified by high-pressure liquid chromatography-electrospray-tandem mass spectrometry (HPLC-ES-MS/MS). Up to 15 different BAs, medical parameters (disease location, time to diagnosis, treatments, disease severity, CRP, and hepatic biochemistry) where admitted to a principal component multi-variate statistical analysis (PCA) to assess whether it is possible to discriminate IBD from healthy conditions and treatment regimens.
Results: Fifty per cent of each group was in treatment with biologics drugs (CD-BIO or UC-BIO; golimumab, adalimumab or infliximab, vedolizumab) and 50% never received biological drug. Our model allowed a quite clear separation of patients into two main clusters, CD biologic-free patients (CD NO BIO) for negative values of PC1 and CD BIO for positive values along the same axe.. CD-BIO have an increase in total BAs (4.11 ± 1.23 µM) compared with CD NO BIO (1.98 ± 0.42 µM), reaching concentrations similar to healthy subjects (3.94 ± 2.12 µM). The most discriminating parameter contributing to the clustering is the concentration of secondary BAs which significantly increase after biological treatment (1.54 ± 0.83 µM) compared with CD NO BIO (0.44 ± 0.17 µM) and reach levels similar to healthy subjects (1.39 ± 0.86 µM). The mean ratio between primary and secondary BAs decreases in CD BIO (2.25 ± 1.45) compared with untreated ones (4.00 ± 1.87) similarly to healthy individuals (1.93 ± 0.95). UC did not show any significant differences. Time to diagnosis and disease progression did not affect BAs composition. Disease extension was assessed and BAs composition was mostly affected in L1 CD patients. However, L2 and L3 showed an increase in BA after biological treatment.
Conclusions: These findings indicate that, in CD patients, anti-TNFs restore the efficiency of the BAs absorption. Of note, these results suggest that the passive absorption in the colon of the most lipophilic BAs (ie, secondary Bas) have been restored and therefore secondary BAs might serve as biomarker of the healing process. In this context, a systematic characterisation of the profile of all endogenous BAs, including secondary metabolites could be of great help in the evaluation of the illness gravity, strongly related both to the extent of the inflammation and the variation in the gut microbiota composition.

P030

Myeloid calcineurin in the control of immune checkpoint inhibition in intestinal tumour development

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Background: IBD is a risk factor for colorectal cancer (CRC) development and studies in colitis-associated CRC have delineated pathways through which inflammation promotes tumour development in the intestine. Intriguingly, similar pathways are operative in sporadic CRC and promote tumorigenesis in the absence of overt clinical inflammation. Here, we have investigated the cross-talk between myeloid tumour-infiltrating cells, intestinal epithelial cells and cytotoxic T cells in CRC development, with particular emphasis on the role of calcineurin, a phosphatase with critical roles in immunity and inflammation.
Methods: Intestinal tumour development was analysed in ApcMin/+ mice with or without myeloid-specific deletion of calcineurin or the calcineurin-dependent transcription factors nuclear factor of activated T cells (NFAT).
Results: Studies of ApcMin/+ mice revealed barrier dysfunction at sites of intestinal adenomas, which was associated with tumour infiltration by the commensal microbiota and microbiota-dependent activation of calcineurin and NFAT in myeloid tumour-infiltrating cells. Myeloid-specific deletion of calcineurin protected mice from tumour development as a consequence of reduced NFAT-dependent transcription of IL-6 and reduced IL-6-dependent activation of STAT3 in epithelial tumour cells. Intriguingly, however, protective effects of impaired STAT3 activation were not epithelial-cell-intrinsic. Instead, we could demonstrate that STAT3 promotes the transcription and epithelial expression of B7-H3 and B7-H4, two co-inhibitory proteins of the B7 family, which inhibit cytotoxic T-cell responses against the tumour. Accordingly, both antibody-mediated inhibition as well as epithelial deletion of B7-H3 and B7-H4 led to increased infiltration of tumours by activated CD8+ T cells and T-cell-mediated protection from tumour development.
Conclusions: Our studies reveal a novel pathway of calcineurin-dependent cross-talk between epithelial, myeloid, and lymphoid cells, which promotes tumour development through inhibition of cytotoxic T-cell responses and highlights novel, promising targets for checkpoint inhibition in CRC.

P031

Impact of nutritional antigens in inflammatory bowel disease patients

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Background: Inflammatory bowel disease (IBD) represents a dysregulation of the mucosal immune system. The combination of genetic predisposition and environmental factors, as microbiota and food antigens, seems to result in disease development. The pathogenesis of Crohn´s disease (CD) and Ulcerative colitis (UC) but also coeliac disease is linked to the loss of intestinal tolerance and barrier function. The healthy mucosal immune system has previously been shown to be inert against food antigens. The present study served to analyse food-antigen specific T cells in the peripheral blood of CD and UC patients.

Methods: Peripheral blood mononuclear cells of CD and UC patients, either active or in remission, were stimulated with different food antigens. Gluten, ovalbumin and soybean served as food antigens. Healthy controls and coeliac disease patients were included as controls. Gluten-activated $CD4^+$ T cells in the peripheral blood of CD and UC were analysed by a magnetic enrichment of $CD154^+$ cells and a novel subsequent cytometric antigen-reactive T-cell analysis ('ARTE' technology) followed by characterisation of the effector response.
Results: Among all tested food antigens, the highest frequency of antigen-specific T cells ($CD4^+CD154^+$) was found for gluten. Ovalbumin-specific T cells were nearly not detectable in the peripheral blood, while the reaction to soybean was slightly higher. The highest frequency of gluten antigen-specific T cells was revealed in the peripheral blood of active CD when compared with UC, coeliac disease on a gluten-free diet and healthy controls. Interestingly, CD in remission showed still higher frequencies of gluten-specific T cells than healthy controls. These gluten-specific T cells were characterised by up-regulation of the pro-inflammatory cytokines IFN-γ IL-17A and TNF-α . IFN-γ was exclusively elevated in CD patients with active disease. Gluten-specific T cells expressing IL-17A were increased in all IBD patients, again with the highest frequency in active CD patients. Furthermore, T cells of CD patients independent of disease activity revealed a high expression of the pro-inflammatory cytokine TNF- α.
Conclusions: We are able to analyse and quantify food antigen specific T cells in the peripheral blood of IBD patients. The detected differences in the effector response of these cells leads to a diagnostic characterisation within the patients groups in IBD. Furthermore, we identified gluten as immune stimulatory antigen also in CD patients. Additionally, these results demonstrate the modulation of the immune compartment, even in the periphery, by intestinal barrier disruption.

P032

Hepatocyte growth factor and MET in ulcerative colitis, novel drug targets impairing neutrophil recruitment?

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Background: Neutrophils are crucial in the maintenance of intestinal homeostasis and inflammation. However, during chronic inflammatory conditions, like inflammatory bowel disease (IBD), the intestinal immune system responds inaccurately resulting in excessive neutrophil infiltration and tissue damage. MET is a tyrosine kinase required for neutrophil chemoattraction and cytotoxicity in response to its ligand hepatocyte growth factor (HGF). A neutrophil specific deletion of MET improved the severity of chronic DSS-colitis, together with reduced immune cell infiltration. We aimed to study HGF levels in blood and tissue of patients with ulcerative colitis (UC) and healthy controls (HC).
Methods: We collected serum in HC and actively inflamed UC patients, prior to the start of anti-TNF therapy, and at endoscopic reassessment (8–14 weeks after treatment initiation). Endoscopic remission was defined as a Mayo endoscopic sub-score ≤1. HGF was measured using the MesoScale Discovery electrochemiluminescence technology (MSD, Rockville, USA). Additionally, RNA sequencing (Illumina HiSeq4000) was performed on inflamed colonic biopsies in a subset of 24 UC patients and 11 HC.
Results: Serum HGF was significantly up-regulated in 110 active UC patients compared with 30 HC ($p = 0.001$, fold change FC 1.5). Similarly, colonic HGF and MET expression were significantly up-regulated compared with healthy individuals ($p = 3.2E10–6$, FC 5.8; $p = 0.0007$, FC 1.8, respectively). Serum HGF correlated significantly with tissue MET expression ($r = 0.47$, $p = 0.03$), but not with tissue HGF expression ($r = 0.23$, $p = 0.30$). Patients with a Mayo endoscopic sub-score of 3 had significantly higher serum HGF levels when compared with patients with a sub-score of 2 prior to therapy initiation ($p = 0.007$, FC 1.2). Additionally, serum HGF levels correlated significantly with C-reactive protein ($r = 0.44$, $p = 9.5E10–12$), and absolute neutrophils counts ($r = 0.62$, $p = 2.2E10–16$). However, baseline HGF was not predictive for anti-TNF-induced endoscopic remission later on ($p = 0.39$). After anti-TNF administration, HGF levels overall decreased ($p = 1.2E10–7$) and reached values of HC in case of endoscopic remission ($p = 0.35$, $n = 54$), but not in case of non-remission ($p = 0.04$, $n = 56$). At the time of endoscopic assessment, patients with endoscopic remission had significantly lower HGF levels than those without ($p = 0.0003$, FC 0.72).
Conclusions: Colonic and serum HGF levels are significantly up-regulated in active UC patients, with restoration towards physiological levels in patients with anti-TNF-induced endoscopic remission. As murine findings earlier suggested that absence of MET in neutrophils reduces intestinal inflammation, targeting MET could be considered as a novel therapeutic approach in UC therapy.

P033

Periostin regulates ER-stress mediated intestinal subepithelial myofibroblasts function to promote fibrosis in Crohn's disease

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Background: Periostin is a secreted matricellular protein and a major component of the extracellular matrix (ECM) that contributes to intestinal fibrosis in the patients with fibrostenotic Crohn's disease. Currently, intestinal fibrosis has no efficient treatment. Previous studies showed that endoplasmic reticulum (ER) stress in intestinal epithelial cells plays a role in the pathogenesis of Crohn's disease. ER stress is also involved in the development of other fibrotic diseases. Subepithelial myofibroblasts (SEMF) are key drivers of intestinal fibrosis. However, the role of periostin in SEMF during the ER stress-mediated intestinal fibrosis in Crohn's disease remains unknown.
Methods: SEMF will be isolated from the patients with each Crohn's disease phenotype and placed into 3D organoid culture. Periostin expression in freshly isolated and cultured cells was determined by western blot and qRT-PCR. Its interaction with integrin αvβ3 was confirmed by proximity ligation hybridisation assay. Knockdown of periostin in cells was accomplished with siRNA. TGF-β1 was

measured by ELISA. Proliferation was measured by WST-1 assay. Migration by wounding assay.

Results: Periostin expression increased 9.3 ± 0.4 fold in vimentin staining-positive SEMF isolated from affected ileum of fibrostenotic Crohn's disease (Montreal B2) compared with normal ileum in the same patient. Periostin protein was not detected in patients with other phenotypes (Montreal B1 or B3). In the presence of 10 ng/ml IL-6 significantly increased periostin protein expression and its interaction with integrin αvβ3 in SEMF compared with controls. ER stress induced by tunicamycin elicited cell proliferation and enhanced migration was inhibited by 51 ± 3.1% and 53 ± 2.6% when periostin was knocked down in SEMF compared with scrambled controls. In addition, αvβ3-dependent activation of latent TGF-β1 was inhibited by 40 ± 2.1% and 25 ± 2.3% with knockdown of periostin in both control cells and cells with subjected to ER Stress.

Conclusions: Periostin promotes SEMF proliferation and migration. Periostin interacts with integrin αvβ3 and regulates latent TGF-β activation during ER stress-induced fibrosis.

P034

A dietary fibre intervention shapes the microbiome towards an anti-inflammatory tone

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Background: The intestinal microbiome in IBD shows characteristic changes already early in the course of disease. These include enrichment of *Proteobacteria* and reduction of short chain fatty acid (SCFA) producing *Lachnospiraceae*. Prebiotics are one way to modulate a dysbiotic microbiome but insight into the interactions between diet, microbiome and host remains limited. This study aims to decipher novel links between a dietary fibre intervention with partially hydrolysed guar gum (PHGG) and structural and metabolic changes of the microbiome, investigating the potential of dietary fibre in IBD prevention and supportive treatment.

Methods: A clinical trial including 19 healthy volunteers (8 males, 11 females) was performed. Stool, serum and urine samples were collected weekly for 9 weeks allowing every study participant to serve as their own control. The study included 3 periods: a 3-week baseline, a 3-week intervention, and a 3-week washout phase. During the intervention phase, participants received daily dosing of 5 g PHGG for 3 days followed by 10 g PHGG for 4 days in the first week, proceeding with 2 weeks of 15 g PHGG per day. A medical and nutritional history was taken for every participant at baseline, questionnaires on abdominal symptoms were completed weekly and stool habits were recorded daily using the Bristol Stool Chart. Microbiome structure was assessed by 16S metagenomics using both V1-V3 and V3-V4 regions and Tax4Fun was used to estimate functional profiles from taxa abundance. Faecal metabolomics were studied by nuclear magnetic resonance spectroscopy (NMR). Metagenomic and metabolomic data were linked using sparse regression matrices and analysis of co-occurrence/-exclusion.

Results: PHGG increased stool frequency and reduced stool consistency. This laxative effect was more pronounced in males than females and persisted during the washout phase. PHGG decreased α diversity during intervention, but this effect did not persist. B-diversity was not different between study periods but taxa changing significantly under PHGG treatment were detected: PHGG was associated with reduction in certain *Erysipelotrichaceae* and *Pasteurellaceae* and increase in certain *Lachnospiraceae*. Principal component analysis of NMR spectra showed significant gender-specific differences and numerous significantly changed metabolites before, during and after intervention were detected.

Conclusions: This study shows that a dietary intervention with PHGG induces beneficial changes of intestinal microbial composition and function along with changes in microbiota-derived metabolites. PHGG supplementation could be one way to attenuate IBD associated changes of the microbiome. We plan to investigate these effects by additional experiments in models of intestinal inflammation.

P035

Pharmacological inhibition of the canonical WNT signalling pathway represents a potential novel therapy for fibrosis in Crohn's disease

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Background: Intestinal fibrosis and subsequent stricturing does not respond to current therapies and is the main indication for surgery in Crohn's disease (CD). Complete understanding of the underlying molecular mechanisms of fibrosis is required to uncover novel therapies. Transforming Growth Factor (TGF-β) signalling promotes intestinal fibrosis in CD and cross-talk between TGF-β and the Wingless (WNT) signalling pathway contributes to fibrosis in other organs. However, the role of the WNT pathway in CD fibrosis is not well characterised. In this study, we evaluate markers of WNT signalling in stricturing CD patients and assess the ability of ICG-001, a potent WNT inhibitor that disrupts β-catenin transcriptional complexes, to inhibit TGF-β/ WNT signalling and limit fibrosis *in vitro*.

Methods: TGF-β/WNT cross-talk was analysed in intestinal fibroblasts (CCD-18Co cells) stimulated with TGF-β (10 ng/

ml) for 48 h in the presence or absence of ICG-001 (10 μM). β-Catenin and collagen I protein levels were assessed using immunofluorescence. Molecules within the WNT pathway modulated by TGF-β were identified using a targeted qRT-PCR array containing 92 WNT genes (TaqMan Array Human WNT Pathway). The mRNA levels of TGF-β / WNT markers were analysed by qPCR in the mucosa-overlying strictured intestine in CD patients.

Results: TGF-β increased nuclear β-catenin levels (1.94 fold, $p < 0.001$) and collagen I expression (1.28 fold, $p = 0.008$) in intestinal fibroblasts. Conversely, ICG-001 (10 μM) reduced β-catenin levels ($p = 0.039$), and collagen I expression ($p = 0.006$) in fibroblasts stimulated with TGF-β1, and inhibited fibroblast remodelling ($p = 0.0306$) and pro-collagen-Iα1 secretion/production ($p = 0.0024$) in a 3D organotypic model of the intestinal mucosa. TGF-β/WNT activation was associated with increased DKK1 mRNA expression in intestinal fibroblasts (7.66-fold, $p = 0.002$). DKK1 mRNA levels were higher in the mucosa overlying strictured intestine in CD patients (2.183-fold, $p = 0.037$). Experiments to determine the direct effects of DKK1 on collagen I production in intestinal fibroblasts are now required.

Conclusions: Increased WNT signalling in fibrotic strictures contributes to the development of TGF-β-induced fibrosis in CD patients. Treatment with ICG-001 can limit WNT signalling *in vitro* and represents a potential novel therapy for stricturing Crohn's disease.

P036

Expression of CD69 on peripheral lymphocytes predicts treatment response in Acute Severe ulcerative colitis

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Background: Disease severity in acute severe ulcerative colitis (ASUC) is currently assessed using clinical and endoscopic indices, and treatment response is determined following a trial of drug therapy. Immune profiling potentially offers new methods of classifying disease activity to determine the likelihood of a response to therapy. CD69 is a marker of lymphocyte activation and recent work implicates it in the regulation of intestinal inflammation, with CD69 expression on mucosal associated invariant T (MAIT) cells correlating with IBD disease activity. We aimed to identify biomarkers of steroid and infliximab (IFX) response by immune profiling of peripheral blood and intestinal mucosa.

Methods: Peripheral blood and mucosal biopsies were collected from 44 patients with ASUC on admission and 10 healthy controls. Clinical response to intravenous steroids and IFX salvage therapy was correlated with peripheral lymphocyte CD69 expression, and membrane TNF (mTNF) expression on monocytes measured by flow cytometry, and mucosal cytokine gene expression by RT-PCR.

Results: ASUC patients had a peripheral deficiency of MAIT, natural killer (NK), NKT and Th1 cell proportions compared with healthy controls. CD69 expression on these lymphocytes correlated with disease activity; with CD69 expression on MAIT and NK cell correlating more consistently across clinical, biochemical and endoscopic indices compared with CRP or albumin alone. CD69 expression on MAIT, NK, NKT, Th1, and Th2 cells was significantly higher in steroid non-responders and was predictive of steroid non-response [MAIT (AUROC 0.76, $p = 0.01$, cut-off 27.55%), NK (AUROC 0.81, $p < 0.01$, cut-off 16.75%), NKT (AUROC 0.71, $p = 0.04$, cut-off 33.1%), Th1 (AUROC 0.75, $p < 0.01$, cut-off 1.23%) and Th2 (AUROC 0.80, $p < 0.01$, cut-off 5.99%)]. Elevated Th2 CD69 expression also predicted IFX non-response (AUROC 0.74, $p = 0.03$, cut-off 6.75%) and was an independent immunological predictor of treatment response on multi-variate logistic regression. IFX non-responders had a nonsignificant trend towards higher mTNF expression on monocytes and subsets. Monocyte subset proportions and concomitant mTNF expression did not correlate with steroid response status. Mucosal TGF β expression in IFX non-responders was significantly higher compared with responders ($p = 0.03$). Mucosal TNF expression was not associated with treatment response or disease activity.

Conclusions: In ASUC, CD69 expression on key peripheral lymphocyte subsets is a novel biomarker of disease severity and has the potential to identify those at risk of treatment failure. Future work is required to discern the function of CD69 in ASUC, to assess why elevated expression is associated with treatment failure, and whether CD69 represents a potential therapeutic target in the future.

P037

USP16-mediated deubiquitination of calcineurin A controls peripheral T cells maintenance and attenuates intestinal inflammation

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Background: T cells play important roles in the pathogenesis of inflammatory bowel diseases (IBD). And ubiquitination and deubiquitination are important epigenetic modifications in immune responses. The process of how USP16 (ubiquitin carboxyl-terminal

hydrolase 16) regulates the intestinal inflammation has never been explored.

Methods: USP16 expression in isolated PBMCs and intestinal tissues of IBD patients and healthy controls were examined by quantitative real-time PCR (qRT-PCR) and immunohistochemistry respectively. T-cell-specific USP16 knockout mouse was generated with the Cre/LoxP technology. Colitis was induced in Rag1–/– mice by transfer of CD4+CD25-CD45RBhi T cells from C57/Bl6 or transgenic mice. T cells were isolated from mice, and the T-cell characteristics were analysed by flow cytometry and qRT-PCR. We used western blot and calcium flux to seek for the substrate of USP16, and immunoprecipitation and immunofluorescence were used to confirm the interaction. Plasmid transfection to the HEK293T cells and mass spectrometry were used to find the ubiquitinated point on the substrate.

Results: IBD patients and inflamed intestinal tissues have higher levels of USP16 than controls. T-cell-specific USP16-knockout mice exhibited less severe colitis and less CD4+ T cells infiltration than the C57/Bl6 mice. USP16-deficient T cells had homeostasis dysregulation, impaired proliferation, defected differentiation, and normal migration ability. The calcium-triggered deubiquitination of calcineurin A (CNA), encoded by Ppp3cb or Ppp3cc, in a manner consistent with these defects. We found that the CNA is constitutively ubiquitinated on lysine 327 and that the resulting polyubiquitin chain is rapidly removed by USP16 in response to intracellular calcium stimulation. The K29-linked ubiquitination of CNA impaired NFAT recruitment and the transcription of NFAT-targeted genes.

Conclusions: Our work elucidates the physiological function of calcineurin ubiquitination and its deubiquitinase USP16 in peripheral T cells. Notably, our results provide a critical mechanism for the regulation of calcineurin activity and a novel immunosuppressive drug target for the treatment of IBD.

P038

Expression analysis in colitis-associated carcinoma: a role for osteopontin?

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Background: There is an increased risk for ulcerative colitis (UC) and Crohn's colitis (CD) patients to develop colitis-associated carcinoma (CAC). This disorder is usually included in the diagnosis and treatment for the sporadic colorectal carcinoma (CRC), although its progression being molecularly different. Inflammation plays an important role in the CAC tumorigenesis; however, most of what is known about CAC is deduced from animal studies since reports using human samples are scarce. Furthermore, the aim of this study was to aggregate knowledge about the inflammatory and immune pathways that participate in the CAC progression.

Methods: Surgical colon samples were collected from 60 patients belonging to 6 experimental groups: Control, ulcerative colitis (UC), Crohn's disease-colitis (CD), UC- or CD-related CAC and CRC. RNA was extracted from paraffin-embedded samples and gene expression analysis was performed using the nCounter technique. A set of 624 genes related to immunology and epithelial barrier function was analysed. Data analysis was performed in the nSolver and Ingenuity Pathway Analysis (IPA) software.

Results: In the canonical pathway analysis, the CAC conditions showed considerably less activation of inflammatory and adaptive immunity pathways when compared with IBD, but activation of a number of signalling pathways related to NfkappaB signalling, which is known to play a role in the tumorigenesis of CAC. The most differentially expressed gene in both CD-CAC vs. CD and UC-CAC vs. UC was SPP1, with an increase of 18- and 8-fold, respectively. This gene was also represented in the upstream regulator analysis as an upstream regulator predicted to be activated in CAC vs. IBD. SPP1 codifies the osteopontin protein, a cytokine that participates in a variety of biological processes, including tumorigenesis. Genes related to osteopontin activation such as STAT3, SMAD3 and AKT show a trend of activation whereas genes involved in the negative regulation of osteopontin such as, TNF-signalling related genes, IFR1 and STAT1 present a trend of inhibition, supporting the hypothesis that its activation is important to CAC pathogenesis.

Conclusions: Several different signalling pathways are involved in the progression of CAC. Osteopontin, whose involvement in CAC progression has not been elucidated, might play an important role in its tumorigenesis and should be further investigated.

P039

Tracking intestinal epithelial cells with fluorescent dyes

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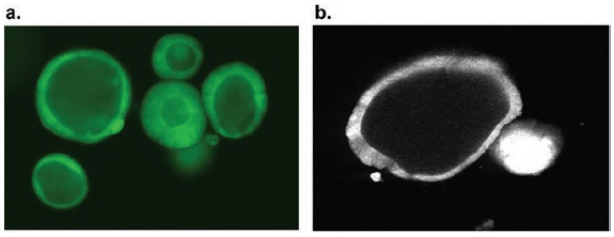
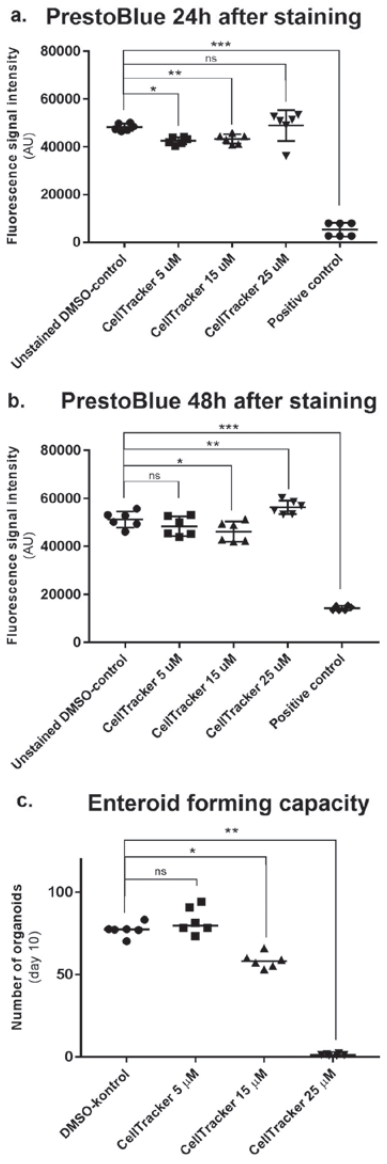
Background: Enteroids have been shown to be able to engraft onto injured intestinal mucosa in murine experimental colitis models. This observation may provide an innovative approach to accomplish mucosal healing in patients with inflammatory bowel disease. Nevertheless, there are several issues to be resolved before this approach can be attempted in humans. One such issue is how to label and track transplanted cells. Hence, we investigated the applicability of a panel of non-gene modifying fluorescent dyes and nanoparticles, and whether labelled enteroids could be visualised using the clinically approved imaging modality, confocal laser endomicroscopy.

Methods: Intestinal biopsies were harvested from healthy human colonic mucosa, and enteroids were established using standard protocols. Enteroids were then attempted stained with fluorescein, a carbocyanine dye (CellBrite™), an inert membrane permeable dye, 5-chloromethylfluorescein diacetate (CMFDA; CellTracker™), quantum dots (QTracker™) and PLGA nanoparticles. Only 5–25 µM of CMFDA was found suitable, and staining homogeneity, durability, cell viability and enteroid forming capacity following single cell seeding were evaluated, together with visualisation of stained enteroids *in vitro* over time using endoscope-based confocal laser endomicroscopy.

Results: CMFDA efficiently and homogeneously stained all enteroids



Abstract P039 – Figure 1
CMFDA stained enteroids. The viability and enteroid growth appeared to be unaffected by CMFDA staining



Abstract P039 – Figure 2
Viability and enteroid forming capacity. (a, b) Whereas single cell seeding revealed a significant reduction in enteroid forming capacity with increasing dye concentration (c). No transfer of dye to unstained enteroids in co-cultures was observed. The CMFDA-derived fluorescent intensity of stained cells decreased in a linear fashion, with a $t_{1/2}$ of approximately 24 h, and approached the background signal intensity after approximately 7 days. Furthermore, stained enteroids were easily identified *in vitro* using confocal laser endomicroscopy for a duration of at least 3 days (Figure 1b) .

Conclusions: It is plausible to track human intestinal enteroids using common fluorescent dyes (eg, CMFDA) and confocal laser endomicroscopy. This type of approach might clearly be limited to short-term tracking, which, however, may be sufficient to allow for confirmation of engraftment following transplantation.

P040

The cytokine milieu in patients with inflammatory bowel disease impacts the phenotype of mesenchymal stromal cells

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Background: Mesenchymal stromal cells (MSCs) have the capacity to promote healing of refractory perianal fistulas in Crohn's disease (CD) and pre-treatment with cytokines may enhance therapeutic efficacy. Furthermore, locally applied MSCs are under clinical development for treatment of refractory proctitis in ulcerative colitis (UC). Despite these clinical advances, the mechanism of action of MSC therapy is largely unknown. We hypothesise that the proinflammatory environment in the patient promotes the immunomodulatory properties of MSCs. Therefore, we analysed cytokine levels in inflamed tissues obtained from CD and UC patients. Next, we assessed the expression of immunomodulatory molecules by MSCs upon exposure to these cytokines.

Methods: U-plex cytokine assay and ELISA were used to measure the levels of 11 cytokines, including interferon-γ, interleukin (IL)-17 and IL-1β, in perianal fistula scraping of patients with CD (n = 20), colonic tissue samples (inflamed and non-inflamed) from patients with UC (n = 18) and adjacent healthy tissue from patients with colorectal carcinoma (n = 18). To determine the response of bone-marrow-derived MSCs to different proinflammatory environments, MSCs were exposed to defined (sets of these) cytokines and the expression of immunomodulatory molecules was determined by flow cytometric and qPCR analyses.

Results: Scrapings of perianal fistulas obtained from CD patients contained high levels of cytokines, including IL-1β and IL-17 (IL-1β 0.102 pg/µg vs. 0.012 pg/µg in normal colon tissue, p = 0.003, and IL-17 0.206 pg/µg vs. 0.009 pg/µg, p < 0.001). In contrast, inflamed colon of UC patients only showed the presence of a selected set of cytokines of which some, like IL-1β, were already present in non-inflamed colons. Next, we evaluated the response of MSCs to exposure of the individual cytokines and 4 different cytokine mixtures which resemble the complex proinflammatory milieus in inflammatory bowel disease. Interestingly, each cytokine mixture induced a unique expression pattern of intra –and extracellularly expressed immunomodulatory molecules in MSCs, including cyclo-oxygenase 2 and indoleamine 2,3-dioxygenase. Assays are ongoing to investigate the consequence of cytokine priming on the immunomodulatory function of MSCs.

Conclusions: The patient's proinflammatory milieu is strongly dependent on the underlying disease. We found *in vitro* evidence that

infusion of MSCs into inflamed UC tissue or CD fistulas induces up-regulation of immunomodulatory molecules in MSCs that are unique for the patient's cytokine milieu and that play a role in the immunomodulatory properties of the cells. Differences in cytokine expression between patients may explain the different clinical efficacies that are observed following MSC therapy.

P041

Differences in NOTCH signalling between stricturing and penetrating behaviour in Crohn's disease

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Background: Fibrosis and fistula development constitute the main complications associated to Crohn's disease. Notch signalling has been implicated in lung, kidney, liver, and cardiac fibrosis and in various disease conditions such as scleroderma. We aim to analyse here the pattern of NOTCH ligands, receptors, and effectors expression in surgical resections from stenotic and fistulizing CD patients and to determine the potential role of these ligands in favouring fistula and fibrosis.

Methods: CD patients (n = 41) were categorised according to Montreal classification (age at diagnosis, location, and behaviour). mRNA was isolated from resections of patients presenting a stricturing (B2, n = 26) or a penetrating (B3, n = 15) behaviour or from unaffected mucosa of patients with colorectal cancer (control, n = 15). The expression of Notch ligands, receptors, and effectors (HES1 and MATH1) was determined by RT-PCR or WB. Correlations between data were analysed using Pearson's correlation coefficient (*$p < 0.05$).

Results: A higher mRNA expression of NOTCH3 and NOTCH4 receptors was detected in CD patients compared with controls; in addition, the expression of these markers was higher in the fistulizing than in the stenotic behaviour (Table 1). The fistulizing group presented a generalised overexpression of NOTCH ligands (JAG2, DLL3, and DLL4) compared with controls and among them, only DLL3 expression was up-regulated in the stenotic group (Table 1). Similar levels of HES1 and MATH1 mRNA expression were detected between different groups while protein levels of HES1 were higher in the fistulising group than in control or stenotic groups (3.4 ± 0.1 A.U*#, 2.8 ± 0.2 A.U and 2.0 ± 0.1 A.U, respectively). The expression of DLL3 significantly correlated with FSP1 (r = 0.77, p = 0.04*), DESMIN (r = 0.80, p = 0.03*), and SNAIL1 (r = 0.59, $p < 0.04$*), only in intestinal tissue from the fistulizing CD group.

Conclusions: Activation of the Notch signalling pathway is detected in Crohn's disease patients presenting a penetrating (B3) behaviour compared with those with a structuring (B2) phenotype and it may be involved in fistula development over fibrosis.

P042

APL expression is down-regulated in an animal model of chronic colitis

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Background: Apelin (APL), originally isolated from alimentary tract, has been defined as the endogenous ligand for APJ, which is a known G protein-coupled receptor. It has been reported that APL is up-regulated in the colonic tissues of murine model of dextran sodium sulphate (DSS)-induced acute colitis, and it is suggested to be associated with the pathogenesis of inflammatory bowel diseases (IBD), such as Crohn's disease and ulcerative colitis, in humans. However, the mechanism and function of APL in the context of IBD are still not well understood. Here, we analysed APL expression in the murine model of chronic colitis.

Methods: Each cell type in the colonic tissue, including epithelial cells and lamina propria lymphocytes, were first isolated from wild-type C57BL6 mice (WT) to assess APL expression. Next, naïve T cells isolated from WT were adoptively transferred into Rag-deficient mice ($Rag^{-/-}$) to induce chronic colitis, followed by isolation of splenic and colonic $CD4^+$ T cells from these T-cell-reconstituted $Rag^{-/-}$ to compare with those of WT. In addition, WT naïve T cells were differentiated into either Th1, Th2, or Th17 *in vitro* to analyse APL expression. Finally, the $Rag^{-/-}$ receiving naïve T cells were administered synthetic APL peptide to assess the severity of colitis.

Results: Semi-quantitative PCR (qPCR) revealed that $CD4^+$ T cells express relatively higher level of APL compared with other cell types including the epithelia in colonic tissue from WT. However, APL expression in the colonic tissues from the $Rag^{-/-}$ induced chronic colitis was unexpectedly down-regulated compared with those without colitis, which is not consistent with the previous report using acute DSS colitis model. Subsequently, qPCR revealed significantly decreased APL expression in the splenic and colonic T cells from $Rag^{-/-}$-induced colitis compared with that of WT. APL expressions in all of the differentiated T cells *in vitro*, such as Th1, Th2, and Th17, were also significantly down-regulated compared with that of non-differentiated control. Given these results, synthetic APL peptide was injected into the $Rag^{-/-}$ that underwent T-cell reconstitution to antagonise the APL down-regulation. This resulted in reduced severity of colitis compared with that of vehicle-injected control.

ΔCT	NOTCH1	NOTCH2	NOTCH3	NOTCH4	JAG2	DLL1	DLL3	DLL4	HES1
Non-IBD	14.2 ± 0.4	9.9 ± 0.2	17.4 ± 0.2	13.4 ± 0.3	16.02 ± 0.2	23.2 ± 0.3	20.4 ± 0.7	18.9 ± 0.2	9.5 ± 0.3
B2	14.5 ± 0.2	9.9 ± 0.2	16.0 ± 0.3*	11.5 ± 0.3*	15.0 ± 0.3	23.1 ± 0.5	15.7 ± 0.7**	19.5 ± 0.4	9.8 ± 0.3
B3	13.6 ± 0.2	9.2 ± 0.4	14.8 ± 0.3**#	9.6 ± 0.9**#	14.1 ± 0.2**	23.0 ± 0.4	16.4 ± 0.9*	17.6 ± 0.3*#	9.2 ± 0.3

Relative mRNA expression of NOTCH ligands and receptors vs. the housekeeping gene β-ACTIN in intestinal mucosa. Significant differences vs. the respective Non-IBD patients are shown by *$p < 0.05$ or **$p < 0.05$ and vs. B2 CD patients by #$p < 0.05$.

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Conclusions: These results suggest that T cells can be one of the major sources of APL in colonic tissues, and APL down-regulation in effecter T cells may lead to the development of chronic colitis. In addition, APL may be a novel therapeutic target for IBD.

P043

Secretome modulation of Caco-2 cell line induced by a multi-strain probiotic

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Background: Probiotics are defined as live, non-pathogenic bacteria that confer health benefits beyond their nutritional value. Particularly VSL#3, a probiotic mix containing 4 strains of Lactobacilli (*L. paracasei*, *L. plantarum*, *L. acidophilus* and *L. delbrueckii* subsp. *bulgaricus**), 3 strains of Bifidobacteria (*B. longum***, *B. infantis****, *B. breve*) and *Streptococcus thermophilus*, has demonstrated efficacy in the management of diseases characterised by increased intestinal permeability such as irritable bowel syndrome and ulcerative colitis. *Recently reclassified as *L. helveticus*. **Recently reclassified as *B. longum* subsp. *lactis*. ***Recently reclassified as *B. infantis* subsp. *lactis*. The aim of the present study was to study secreted bioactive factors to evaluate the mechanisms of action of VSL#3 to enhance intestinal epithelia.

Methods: Two different lots of VSL#3 (Nutrilinea Srl, Gallarate (VA), Italy, lot #802097 and lot #802100) were used. Caco-2 cell line were treated with a conditioning media (CM) prepared using 1 g of probiotic formula grown in D-MEM cell culture medium (free of serum and antibiotics) at 37°C for 48 h without shaking and in anaerobic conditions. Caco-2 were treated with diluted CM at 1:10 and 1:25 for 24 and 48 h. Media culture for each conditions has been collected and analysed by a deeper proteomics approach. Differential protein expression in was evaluated by shotgun proteomics analysis based on nLC-HDMSE and carried out on Synapt G2-Si mass spectrometer. Protein identification and protein expression analysis were perfomed by Protein Linx Global Server (PLGS v. 3.0.3, Waters Corp).

Results: The analysis of supernatants from Caco-2, treated with CM, showed the presence of bacteria strain-specific proteins. Human proteins synthesised from CaCo-2 were also identified, such as caspase 1, IL8, HSP70, HSP70b, HSP90, HSP105. The production were time- and dose- dependent. In CM diluted 1:10, probiotic derived proteins have been shown to be more expressed at 24 h. Human caspase 1, IL8, HSP 70, HSP 70b, HSP 90, HSP 105 were also found up-regulated in CaCo-2 treated for 24 h with CM diluted 1:10.

Conclusions: This is the first time where a probiotic secretome was explored. The study on probiotic secretome is useful to understand if the probiotic was well reconstituted. Analysis of secretome from CaCo-2 treated with CM helped us to understand the mechanism by probiotics can enhance intestinal barrier: by strengthen the autophagy process, an arm of innate immunity, by overexpression of caspase 1, IL8 and HSP 70, and by HSPs dependent modulation of inflammation.

P044

A novel porcine model of Crohn's disease anastomotic stricture

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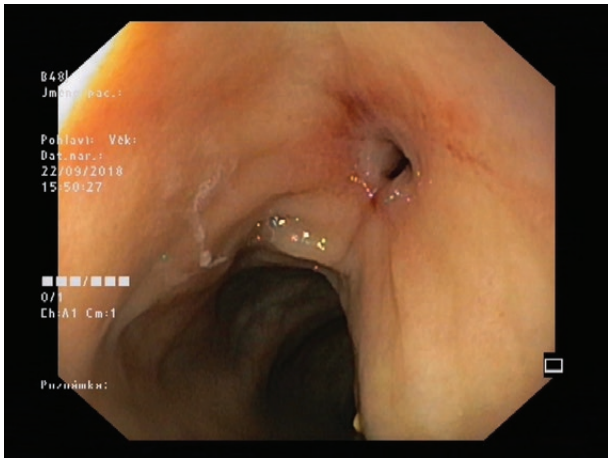
Background: Ileocolonic resection is the most common surgical procedure performed in patients with Crohn's disease (CD). Up to 70% of patients experience recurrence of the disease within 1 year at the site of anastomosis. Frequently, these patients have to be re-operated due to reoccurrence of fibrostenotic stricture which can hardly be managed medically. In order to develop and test advanced endoscopic methods of treatment of these strictures a suitable model of anastomotic stricture in large animal would be of benefit.

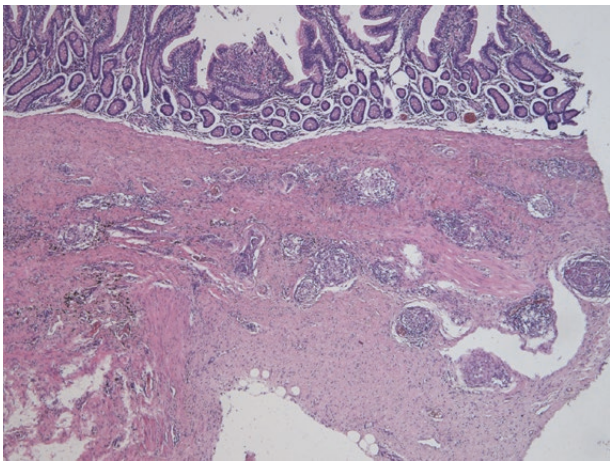
Methods: A side-to-side ileo-colic anastomosis 20 cm from anus was created in a modified Y-roux manner in 13 pigs with the bowel continuity preserved. Two weeks after surgery we started endoscopic submucosal injection of a 5% Phenol and 0.2% Trinitrobenzensulfonic acid solution. This solution was injected every 2 weeks in each quadrant at the site of anastomosis until the development of stricture, but at least 4 times. The site of anastomosis was assessed and measured endoscopically in 2 weeks after the last application and then resected and sent for histology. This project was approved by the respective ethics committee.

Results: Thirteen female pigs (47.1 ± 8.2 kg) were included with no postoperative complications. After a mean of 4.6 ± 0.7 injections of 10.6 ± 3.2 ml of the solution the anastomotic stricture was created in 12 pigs. Mean diameter of the stricture was 11.4 ± 2.2 mm. The strictures were macroscopically inflamed and ulcerated, not passable for the endoscope.



Anastomotic stricture in a porcine model

The histopathologic evaluation revealed the presence of an intense chronic inflammation with lymphoplasmacytic infiltrate and numerous eosinophils. Multiple histiocytic granulomas with multi-nuclear foreign-body giant cells occasionally with an abscess in the centre were present as well as epithelioid microgranulomas similar to those in CD.



Epithelioid microgranulomas

In one pig we were unable to induce stricture even after 6 applications.

Conclusions: We developed a novel reproducible porcine model of anastomotic stricture with histologically verified changes mimicking Crohn's disease which is suitable for further applications.

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P045

Local inflammation modulates vitamin D receptor protein levels in fibroblasts

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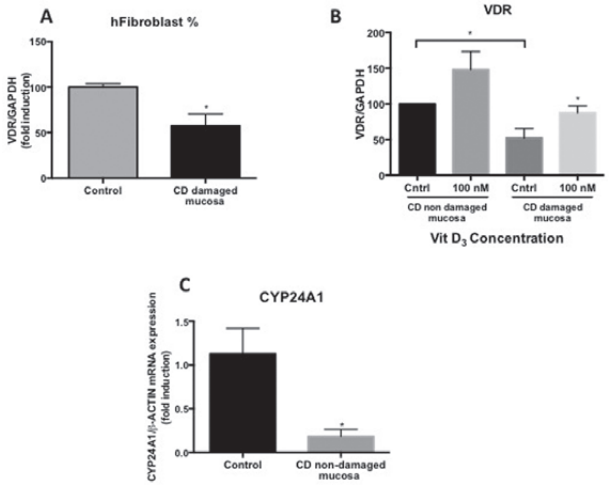
Background: Vitamin D deficiency and a defective signalling has been reported in Crohn's disease (CD) patients. Vitamin D signals through the vitamin D receptor (VDR) which is a member of the nuclear receptor family of transcription factors that play an immunoregulatory role in the gut. We have previously demonstrated that a single-nucleotide polymorphism (SNP) in the VDR gene can modify the expression of this protein in peripheral blood mononuclear cells of CD patients. We aim to analyse the modulation of the VDR protein in human intestinal fibroblasts.

Methods: We used intestinal fibroblasts isolated from intestinal tissue of the non-damaged mucosa and the damaged mucosa of CD patients. Control cells were obtained from the non-damaged intestine of patients with colorectal cancer. Fibroblasts were treated with 1,25 Vitamin D_3 (100 nM) for 24 h. VDR protein levels were determined by western blot and VDR, CYP24A1, COL1A1 and αSMA gene expression by qPCR. Statistical significance was measured by t-test.

Results: VDR protein levels were significantly lower in fibroblasts obtained from the damaged intestine of CD patients than that obtained from controls (Figure 1A). In fibroblasts from CD patients, we detected lower VDR protein levels in those obtained from damaged mucosa than in those from the non-damaged. Treatment of these cells with vitamin D_3 significantly increased VDR protein expression in all cases, but VDR protein levels were much lower in fibroblasts from damaged intestine (Figure 1B). The mRNA expression of VDR and its target, CPY24A1, was significantly lower in fibroblasts from the damaged tissue than in fibroblasts from the non-damaged. In contrast, the mRNA expression of collagen 1a1 and αSMA was higher in fibroblast from damaged intestine. When compared fibroblasts obtained from the non-damaged intestine of CD with control fibroblasts, the mRNA expression of CYP24A1 was significantly lower in cells from CD patients, suggesting that factors other than local inflammation may be involved (Figure 1C).



Conclusions: Local inflammation, and probably genetic factors, are involved in the decrease in VDR protein levels detected in fibroblasts from CD patients.

P046

Iron mobilisation into the intestinal epithelium prevents hypoxia-associated autophagy and reduces inflammation through the inhibition of NF-κB

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Background: Environmental hypoxia influences the development of inflammatory bowel diseases. Adaptive responses to hypoxia are mediated through hypoxia-inducible factors, which are tightly regulated by oxygen- and iron-dependent hydroxylases. Regulation of uptake, storage and export of iron is mediated by signals reflecting oxygen and intracellular iron levels in enterocytes. Conversely, iron modulates responses to hypoxia. We sought to elucidate the effects of iron levels on hypoxia-associated responses in the intestinal epithelium.
Methods: Human subjects were exposed to hypoxia, and colonic biopsies and serum samples were collected. The human intestinal epithelial cells HT-29, Caco-2 and T84 were subjected to hypoxia in the presence of iron or the iron chelator deferoxamine. Changes in inflammatory gene expression and signalling were assessed by qPCR and western blot. Chromatin immunoprecipitation was performed using antibodies against NF-κB and primers for promoter binding regions of TNF and IL-1β
Results: Human subjects presented reduced levels of ferritin and iron in the intestinal epithelium following hypoxia. Hypoxia reduced iron deprivation-associated TNF and IL-1β expression in HT-29 cells through the induction of autophagy. Contrarily, hypoxia triggered TNF and IL-1β expression, and NF-κB activation in Caco-2 and T84 cells. In Caco-2 cells, iron blocked early and late-stage autophagy while reducing hypoxia-associated TNF and IL-1β expression, and the binding of NF-κB to the promoter of TNF and IL-1β.
Conclusions: Hypoxia-induced autophagy reduces inflammation in HT-29 cells. In Caco-2 cells, iron uptake is essential to prevent hypoxia-induced inflammatory processes. Iron mobilisation plays a crucial role in the maintenance of homeostasis in the hypoxic intestinal epithelium.

P047

Neuroendocrine cells densities alterations in colonic mucosa of patients with inflammatory bowel disease

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Background: Several published studies on human and animal models showed increased densities of NEC in colonic mucosa of inflammatory bowel disease (IBD) colitis compared with non-IBD controls.
The aim of our study is to determine de NEC densities in colonic mucosa of patients with IBD in our Department.
Methods: Colonic biopsies from 11 patients with IBD and 11 patients screened for colorectal cancer were evaluated histopathological with haematoxylin–eosin staining and immunochemical with chromogranin A (CgA) and synaptophysin antibodies (Syn). We assessed the number of NEC by manual counting at optic microscope on 10 oriented crypts and 20 transverse sectional crypts.
Results: In IBD group NEC had a patchy and superficial distribution, organised in groups or nodules of 3 to 6 hyperplastic cells/crypt with a mean density of 3.16 CgA positive and 2.54 Syn postive NEC/crypt in IBD group compared with 1.7 CgA positive and 1.28 Syn positive NEC/crypt in non-IBD controls; $p = 0.0001$, $p = 0.002$. When compared with IBD duration, NEC densities decreased with IBD evolution so that in patients with IBD duration between 1 and 5 years mean NEC densities were 3,4 NEC/crypt (CgA) and 2.8 NEC/crypt (Syn) compared with 2.76 NEC/crypt and 1,72 NEC/crypt, respectively in patients with disease evolution longer than 5 years; $p = 0.19$, $p = 0.14$.
There are no significant differences between NEC distributions in active vs. inactive disease with a mean density of 2,3NEC/crypt (CgA) and 3 NEC/crypt (Syn) in active IBD colitis and 3 NEC/crypt (CgA) and 3.5 NEC/crypt (Syn) in inactive colitis; $p = 0.1$ and 0.2, respectively.
Conclusions: Our study showed an increased density of CgA and Syn positive NEC in patients with IBD. We observed a decreased in NEC densities with IBD evolution possibly related to IBD treatment

P048

Exploring mucosal function as a clinical endpoint in ulcerative colitis

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Background: The standard for assessing disease activity, clinical remission and response to therapy in ulcerative colitis (UC) includes evaluation of symptoms (eg, stool frequency and rectal bleeding) and endoscopic mucosal status. The ultimate goal is reversal of inflammation and normalisation of the gut including mucosal function (ie, barrier integrity). During active disease, the composition of the tight junction (TJ) complex is altered compromising barrier integrity. We hypothesise that mucosal integrity does not correlate with mucosal healing as assessed by endoscopy and histology. In this exploratory study, we studied mucosal barrier integrity (ie, TJ proteins) and correlated it to endoscopic and histological findings in quiescent UC.
Methods: We obtained sigmoid biopsies during endoscopy from 33 UC patients (mean age 39, 23–75 years., 18 females) in clinical and endoscopic remission and 17 gut-healthy controls (mean age 46, 20–68 years., 9 females). The median remission and disease duration prior to inclusion were 8 months (1–61) and 96 months (3–420). Histology was assessed using Geboes score. Mucosal barrier integrity was assessed by examining levels of protein and mRNA for TJ proteins claudin-2, claudin-4, occludin, and tricellulin. All levels

were examined by western blot (WB) with densitometric analysis and quantitative polymerase chain reaction (qPCR). All evaluations were blinded and performed by central reading.
Results: The majority of UC patients, 24 (73%), had a Mayo endoscopic sub-score of 0 and the remaining, 9 (27%), scored 1. Histologically, 22 (67%), had signs of mild-to-moderate chronic inflammation, while only 11 (33%) had no signs of inflammation assessed by Geboes score. All controls were with normal endoscopic and histological findings. On protein level, only claudin-4 was reduced (55%, $p = 0.012$) in UC remission patients compared with controls. mRNA levels were significantly up-regulated for both claudin-2 (5-fold, $p = 0.034$) and claudin-4 (2-fold, $p = 0.031$), while occludin was down-regulated (3-fold, $p < 0.0001$). Tricellulin was unaltered. Furthermore, the correlation between barrier integrity and histology appears weak.
Conclusions: Compared with healthy controls, some UC patients in clinical and endoscopic remission demonstrate an altered expression of TJ proteins. No apparent correlation was found between these changes and histology. It is unresolved whether these abnormalities carry an increased risk for early and/or increased severity at relapse. We propose to further evaluate mucosal functional remission as a potential target-to-treat endpoint.

P049

Dietary walnus to prevent indomethacin-induced intestinal damages

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Background: Non-steroidal anti-inflammatory drugs (NSAIDs), the most highly prescribed drugs in the world for the treatment of pain, inflammation, and fever, caused gastric mucosal damages including ulcer directly or indirectly, by which development of GI safer NSAIDs is unmet medical needs. This study was aimed to document the preventive effects of walnut phenolic extract (WPE) against NSAIDs-induced gastric damages along with molecular mechanisms for future clinical implications.
Methods: RGM-1 gastric mucosal cells were administered with NSAIDs and compared the expressions of inflammatory mediators after indomethacin alone or combination of indomethacin and WPE. The expressions of inflammatory mediators, including COX-1 and COX-2, prostaglandin E2, 15-hydroxyprostaglandin dehydrogenase (15-PGDH), and anti-oxidant capacity, were analysed by western blot analysis, RT-PCR, and ELISA,, respectively. HO-1, Nrf-2, keap1 of Phase 2 enzymes were investigated. *In vivo* animal models were followed with *in vitro* investigations.
Results: NSAID increased the expression of COX-2 and decreased COX-1 and 15-PGDH, but WPE significantly attenuated NSAID-induced COX-2 expression. Interestingly, WPE-induced expression of 15-PGDH. By using deletion constructs of the 15-PGDH promoter, we have found that c-Jun is the most essential determinant for WPE-induced up-regulation of 15-PGDH expression. We confirmed that knockdown of c-Jun abolished the ability of WPE to up-regulate 15-PGDH expression. In addition, WPE significantly increased HO-1 expression. WPE increased nuclear translocation of Nrf2 by Keap-1 degradation and silencing Nrf2 markedly reduced the WPE-induced HO-1 expression. We have found that WPE-induced HO-1 up-regulation was attenuated in cells harbouring the mutant Keap1 in which the cysteine 151 residue was replaced by serine. These *in vitro* findings were exactly validated in indomethacin-induced gastric rat models.
Conclusions: Daily walnut intake can be promising nutritional supplement providing potent anti-inflammatory, anti-oxidative, and mucosa protective effects against NSAID-induced GI damages.

P050

Serum adropin levels in patients with Crohn's disease

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Background: Crohn's disease is a chronic inflammatory condition that primarily affects the gastrointestinal tract, with high possibility of systemic complications. Adropin is a novel discovered protein highly expressed in various organ systems that has an important role in energy homeostasis, metabolic control and intercellular communication. Adropin could be involved in the pathogenesis of number of diseases, according to the fact that different studies connected low adropin levels with metabolic syndrome, insulin resistance, coronary disease and heart failure. The main aim of this study was to compare serum adropin levels in patients with Crohn's disease and matched control subjects. Furthermore, additional goal was to investigate relationship between adropin and other standard biochemical parameters, and anthropometric measurements as well.
Methods: In this study, 40 patients with Crohn's disease were enrolled (23 males and 17 females), as well as 40 age- and gender-matched control subjects. Serum adropin levels was measured by ELISA kit (Phoenix Pharmaceuticals), while other biochemical parameters were determined with standard laboratory procedures. Detailed anamnestic data and anthropometric measurements were taken from each participant.
Results: Crohn's disease group had significantly lower serum adropin levels when compared with controls (2.13 ± 0.47 vs. 3.02 ± 0.55 ng/ml; $p = 0.001$). Regarding other biochemical parameters, there was no statistical significance in concentrations of glucose, total cholesterol, HDL, LDL and triglycerides between study and control group, while CRP levels were significantly higher in Crohn's disease group (20.12 ± 18.36 vs. 1.78 ± 1.56 mg/l; $p = 0.001$). Adropin showed significant positive correlation with both LDL ($r = 0.373$, $p = 0.014$) and HDL ($r = 0.341$, $p = 0.023$) concentrations, while significant negative correlation was found between adropin and CRP ($r = -0.368$, $p = 0.019$).
Conclusions: Our study demonstrated lower serum adropin levels in patients with Crohn's disease in comparison to controls. It is possible that adropin has a role in the complex pathophysiology of Crohn's disease. However, more investigations are necessary for further clarification of that connection.

P051

DNA methylation signatures associated with pathogenesis Crohn's disease-related genes

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Background: Epigenetic mechanism in Crohn's disease (CD) pathogenia is important for gene expression regulation, as complex interactions between genes and the environment occur. DNA methylation is an epigenetic mechanism that negative regulates DNA expression. However, little is known about the associations of DNA methylation and CD pathogenesis. The study of the level of methylation in CD-related genes may help to identify key elements in the pathology of CD, and to select new therapeutical targets. Therefore, we aimed to assess the DNA methylation changes on specific genes, previously related to the CD pathogenesis, and their possible associations with the pathology.
Methods: We included 31 subjects: 11 active CD (aCD) at the onset of disease and prior to any specific medication; 12 inactive CD (iCD) with clinical, analytical and morphologic remission; 8 healthy controls (CTR). DNA was obtained from peripheral blood and analysed by Sequenom. Gene-selection was based on the previous information regarding their role in CD. Candidate genes were: Catalase (CAT), α-defensin 5 (HNP-5), FasR, FasL, TNF, TNFRSF1A, TNFRSF1B, PPA2, ABCB1, NOD2, PPARγ, PKCζ. In addition, a prospective cohort of new patients and controls was recruited for the validation of results: 24 aCD; 24 iCD; 24 CTR. We used the elastic net algorithm for the statistical analysis and the R software (version 3.1.0).
Results: We studied a total of 280 CpGs from the selected genes. Only 16 CpGs showed differential methylation profiles between the three experimental groups (aCD, iCD and CTR). From these 16 CpGs, we selected for validation those with the higher differences between aCD, iCD and CTR: HNP-5 CpG_11 and CpG_13; CAT CpG_31.32; TNF CpG_4 and CpG_12; ABCB1 CpG_6.7.8. Results validated the genes HNP-5 and TNF with $p < 0.001$. HNP-5 showed increase in methylation, whereas TNF showed decrease in methylation. In both cases the level of methylation was maintained and did not change by the activity of CD (aCD vs. iCD). Subanalysis comparison between aCD and iCD showed significant differential methylation profile in the following CpGs: TNF CpG_10; FAS CpG_7.8.9; ABCB1 CpG_6.7.8, CAT CpG 6.8.9.31.32, TNFRS1BF CpG_10.11.12.
Conclusions: The identification of DNA methylation signatures associated with pathogenesis CD-related genes could help to improve the diagnosis and management of CD patients. The permanent increased methylation of HNP-5 gene and the permanent decreased methylation of TNF gene confer a signature for CD patients' identification. The differential profile of methylation between aCD and iCD could be used as an activity signature. New treatments focussed on modifying those methylation signatures could be explored for CD management.

P052

Heat shock protein GP96 is essential for maintaining intestinal epithelial architecture by supporting its self-renewal capacity

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Background: The intestinal epithelium is characterised by a remarkable self-renewal capacity and a high turnover of intestinal epithelial cells (IEC), which emerge from intestinal stem cells (ISC). Defects in proliferation and differentiation of ISC into mature IEC result in impaired barrier function, which is linked with systemic diseases, such as fatty liver disease and diabetes. Glycoprotein (GP)96 is a master chaperone for cell surface receptors including toll-like receptors (TLRs), integrins and the Wnt co-receptors LRP5/6. Wnt signalling is essential for the maintenance of the ISC niche, thus we here investigated how deletion of GP96 specifically in IEC affects intestinal homeostasis.
Methods: To study the role of GP96 in the intestinal epithelium, we used GP96-VillinCre-ERT2 mice which harbour a loxP flanked GP96 gene and Tamoxifen-inducible Cre expression specifically in IEC. To deplete GP96 from IEC, those mice were injected with Tamoxifen at five consecutive days (1 mg/day) and terminated on Day 5, 6, and 7 after the first dose to observe the changes in epithelial integrity over time. As a control, littermates with a loxP flanked GP96 gene without the VillinCre-ERT2 construct were injected with Tamoxifen.
Results: IEC-specific GP96 depletion resulted in rapid weight loss within 6 days after the first Tamoxifen injection. At Day 6, the intestine of GP96-VillinCre-ERT2 mice revealed visible signs of inflammation, characterised by a general shortening of the colon and the small intestine, as well as thickening of the colon wall observed by mouse endoscopy. Colon wall thickening was in sharp contrast to the transparent and fragile appearing small intestine and caecum wall. This was in line with a significant, successive reduction of IEC numbers upon depletion of GP96, as observed when harvesting IEC, and by histological analysis of small intestinal tissue sections. Additionally, the entire intestine was filled with bile-containing intestinal fluid, while solid food or faecal pellets were completely absent. Of interest, apoptosis was not affected upon GP96 depletion in IEC; however, proliferating cells as determined by Ki67 staining, at the crypt base were markedly reduced, indicating that loss of GP96 affects ISC proliferation/function.
Conclusions: Our results underline the importance of GP96 in maintaining homeostasis of the intestinal epithelial architecture. Elucidating molecular mechanisms that are decisive for the fate of the ISC niche will promote the understanding of the pathogenesis of inflammatory diseases associated with barrier defects. Given the pronounced phenotype upon deletion of GP96 in IEC, it might serve as a promising novel therapeutic target in diseases involving intestinal barrier defects.

P053

Adipose-derived stem cells ameliorate colitis by suppression of inflammasome formation and regulation of M1-macrophage population through prostaglandin E2

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Background: Inflammatory bowel disease (IBD) is an idiopathic disease caused by a dysregulated immune response to intestinal microbes in an individual with a genetic predisposition. Therefore, alleviation of inflammation is very important to treat IBD. Mesenchymal stem cells (MSCs) have been highlighted as new candidates for treating autoimmune disease based on their immunomodulatory properties.
Methods: In this study, we investigated the anti-inflammatory mechanism and therapeutic effects of adipose tissue-derived MSCs (ASCs) using THP-1 macrophages and dextran sodium sulphate (DSS)-induced mice with chronic colitis.
Results: LPS-treated THP-1 cells expressed mRNA of CD11b, an M1 macrophage marker, at Day 2. However, THP-1 co-cultured with ASCs expressed mRNA of CD206, CD68, CCL18, legumain, and IL-10, markers of M2 macrophages. In THP-1 cells co-cultured with ASCs, precursor (pro)-IL-1β, Cox-2, and NLRP3 increased dramatically compared with LPS-treated THP-1 cells. Secretion of IL-1β and IL-18 was significantly inhibited by ASCs, but PGE2 production was highly increased in co-culture conditions of THP-1 and ASCs. IL-18 secretion was inhibited by PGE2 treatment, and PGE2 inhibited inflammasome complex (ASC/Cas-1/NLRP3) formation in THP-1 cells. In the DSS-induced chronic colitis model, ASCs ameliorated colitis by decreasing the total number of macrophages and the M1 macrophage population.
Conclusions: Our results suggest that ASCs can suppress the inflammatory response by controlling the macrophage population, and ASCs may be therapeutically useful for the treatment of IBD.

P054

CD103+SIRPα+ DC are specifically decreased in the inflamed colon from patients with ulcerative colitis but not with Crohn's disease

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Background: Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammation of the human gastrointestinal (GI) tract. Intestinal dendritic cells (DC) are essential to maintain the balance between immunity against pathogens and tolerance towards nutrients and commensals. However, there is not much information about DC composition in the human GI tract both in health and IBD.
Methods: Human GI biopsies were obtained from healthy controls and IBD patients (including UC and CD; both active and quiescent). Tissue was disaggregated and lamina propria mononuclear cells (LPMC) characterised by flow cytometry.
Results: Human intestinal DC were identified within singlet viable leucocytes as CD14-CD64-HLA-DR+CD11c+. Type 1 DC were defined as CD103+SIRPα- while type 2 DC were identified as SIRPα+ and further divided into subsets based on the expression of CD103. The proportion of total DC displayed a gradient throughout the healthy human gut as it was higher in the colon (either distal or proximal) compared with the ileum. DC proportion was further decreased in the duodenum. Type 1 (minority) and type 2 (majority) conventional DC did not change their proportion throughout the healthy gut. However, CD103+SIRPα+ DC were the main subset in the duodenum as opposed to CD103-SIRPα+ DC which were predominant in the colon and the ileum. Compared with their CD103-SIRPα+ type 2 counterparts, CD103+SIRPα+ had higher levels of HLA-DR, CD40, CD86, CCR7, CD137L, ICOSL and PD-L1. CD103+SIRPα+ were also more phagocytic and had lower expression of blood-related markers like CLA and CCR2, suggesting that they are derived from CD103-SIRPα+ DC following mucosal conditioning. Indeed, CD103+SIRPα+ numbers were increased following LPMC culture, although this process was reverted in the presence of pro-inflammatory LPS. CD103+SIRPα+ DC displayed an enhanced production of IL-10, both in resting conditions and in the presence of LPS. In IBD, type 2 DC constitutively displayed lower expression of SIRPα irrespectively of IBD-type (CD or UC) or condition (active or quiescent). Nevertheless, the inflamed colon from UC patients, but not from CD, specifically displayed lower numbers of tolerogenic CD103+SIRPα+ DC. These results were in agreement with the colonic cytokine milieu, which was much more pro-inflammatory in UC patients compared with CD.
Conclusions: Tolerogenic PD-L1 expression and IL-10 production was associated with CD103+SIRPα+ DC, confirming therefore their tolerogenic phenotype. Human colonic DC from IBD patients constitutively display lower levels of SIRPα. The specific reduction of CD103+SIRPα+ DC in the inflamed mucosa from UC, but not CD, suggests the presence of different pathogenic mechanisms occurring in IBD.

P055

Transcriptional profiling of ulcerative colitis in remission

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Background: This study addresses whether existing transcriptional profiles can improve and support the current definition of UC in remission apart from the today existing endoscopic, histological and laboratory scoring systems.
Methods: Mucosal biopsies from treatment-naïve UC patients (n = 14), healthy controls (n = 16), and UC patients in remission (n = 14) underwent RNA-Seq using the Next Seq550 instrument from Illumina. The algorithm package STAR-2.5.2b was used for downstream analysis. Principal component analysis (PCA), Limma, and p-value adjustment methods were used to obtain a dataset of significantly differentially expressed genes (DEGs). Gene annotations were performed by using the PANTHER classification system (http://pantherdb.org/), and KEGG (www.genome.jp/kegg/). For functional enrichment the clusterProfiler package and REACTOME database (https://reactome.org/) was used. Fractions of specific cell populations in samples were estimated by applying the R/Bioconductor CellMix manual (http://web.cbio.uct.ac.za/~renaud/CRAN/web/CellMix/). TNF-α levels in biopsies were estimated by qPCR and values <7000 copies/µg protein are considered as non-inflamed tissues.
Results: Analyses revealed 927 significantly DEGs in remission when compared with UC and normal samples. PCA showed a clear distinction between remission-, normal and UC samples along the first principal component 1 (PC1) with 45.7%, and second principal component (PC2) with 9.3% of the total variance. Cell fractions of

monocytes, T cells, neutrophils, B cells/ lymphoid cells and myeloid cells decreased during remission, while the fraction of epithelial cells increased when compared with UC. This is in concordance with the observed inverse regulation of the common up-regulated inflammatory UC genes during remission. A circumvent situation is also observed for down-regulated UC genes with genes involved in TGFβ signalling, transport and drug metabolism. Aside from DEGs involved in innate—and adaptive immune responses, genes like neuropeptide YY (PYY) and neurotrophic receptor tyrosine kinases (NTRK1 and NTRK2) showed increased expression during remission.

Conclusions: : Apart from reduced major key inflammatory activities seen for UC, we propose that a gut–brain communication network is involved during remission beside the partial restoration of immunological functions and recovery of local homeostasis in the epithelial mucus layer and lamina propria. In addition, a certain role for the composition of bacterial gut flora may be implied. These results can be useful for the development of treatment strategies for remission and might be useful molecular targets for further investigations aiming to predict relapse of UC patients in the future.

P056

Transcriptional profiling of intestinal epithelial organoids derived from paediatric Crohn's disease patients

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Background: Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD) with onset occurring from childhood to late age. Despite a comparable genetic susceptibility, disease phenotype and natural history vary between paediatric and adult-onset CD. Recent studies have highlighted the importance of the intestinal epithelial barrier in the pathogenesis of IBD [1] [2] [3].

We hypothesise that the intestinal epithelium of patients with CD is characterised by age-dependent differences in the gene expression signature.

Methods: Biopsy samples from the ileum and colon of paediatric and adult patients with CD were collected. Isolated crypt units were used to generate epithelial organoid cultures (EpOCs). After *ex vivo* expansion, EpOCs were induced to differentiate into the main lineages (d-EpOCs), and total RNA was extracted for expression profiling by microarray.

Results: Paediatric and adult EpOCs followed similar differentiation programmes when induced to generate d-EpOCs, while maintaining a colon vs. ileum-specific pattern of marker expression. Nonetheless, a panel of genes was significantly altered in colonic EpOCs generated from paediatric vs. adult CD patients. Several of these genes were associated with the induction of a pro-inflammatory response (ie, CXCL gene family, REG1A, RETNLB).

Conclusions: Our results suggest that paediatric patients with CD harbour specific lasting alterations in the epithelial compartment. This could contribute to differently shaping the phenotype of the disease in these patients.

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P057

Gut microbiome diversity in acute severe colitis is distinct from mild-to-moderate ulcerative colitis

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Background: Although the gut microbiome of patients with ulcerative colitis (UC) has been characterised, there has been no study of gut microbial diversity in patients with acute severe colitis (ASC). The present study compared the gut microbiome of patients with UC, ASC, and healthy controls (HC).

Methods: Patients with mild-to-moderate UC (n = 23), ASC (n = 21), and healthy controls (n = 24) were recruited prospectively. A metagenomics approach was used to explore gut microbial diversity and genetic repertoires. Ulcerative colitis was diagnosed using ECCO guidelines and ASC was diagnosed using Truelove and Witts' criteria.

Results: Genus level diversity (Simpson diversity measure) was significantly lower in ASC than in mild–moderately active UC (p < 0.05), or HC (p < 0.001).

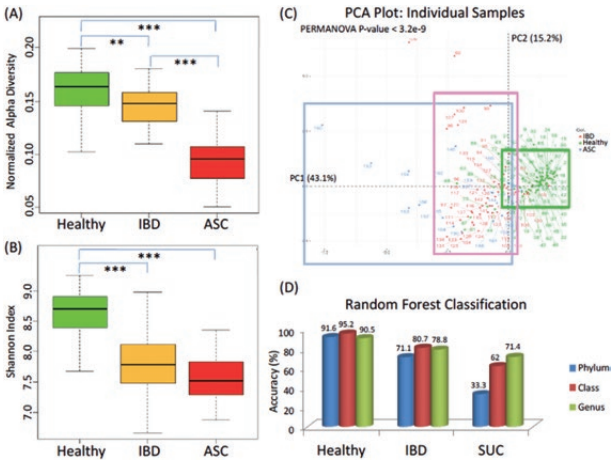

Figure 1

The gut microbiome in ASC was highly unstable, as characterised by high intra-cohort variation (analysed using J-divergence measure) which was significantly greater than in UC or HC. On principal coordinate analysis, the microbiome of HC and UC were similar, with the ASC cohort being distinct from both.

On quantitative evaluation of these differences (random forest classifiers), both ASC vs. HC and UC comparisons revealed excellent classification accuracy, with >90% patients being correctly classified.

Statistical comparison of the ranked abundances identified four distinct clusters of genera (G1A, G1B, G2A, G2B), with specific trends in their abundance patterns across the three groups: the G1A/G1B clusters had the least, whereas G2A/G2B had the highest abundance in the ASC cohort. Interestingly, several known health-associated bacteria (Faecalibacterium, Prevotella, and Roseburia) exhibited different oligotypes, with distinct oligotypes segregating into health and disease states (ASC).

Conclusions: Gut microbial diversity is lower in ASC than in mild–moderate UC or healthy controls. Gut microbiome composition is increasingly unstable in ASC, with a distinct abundance of specific genera varying between healthy controls and ASC. Mild–moderate UC lies within the spectrum.

P058

Do circulating exosomes interfere with vedolizumab efficacy in IBD patients?

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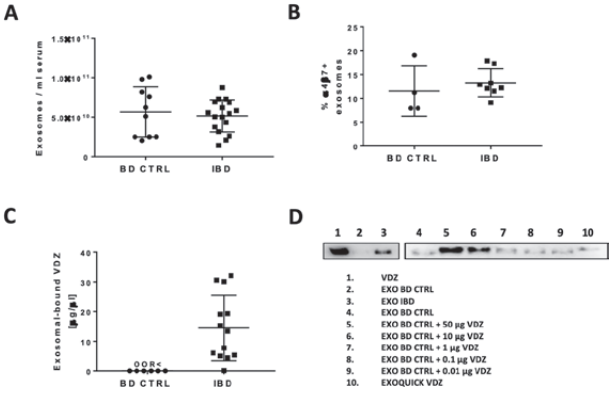
Background: Crohn's disease (CD) and ulcerative colitis (UC),collectively referred to as the inflammatory bowel diseases (IBDs), are chronic relapsing-remitting inflammatory disorders of the gastrointestinal tract. The attenuation of lymphocyte translocation into the inflamed gut tissue results in a reduction in local inflammation and thus decreases IBD severity. Such mechanism emerged as a new target in IBD therapy. Vedolizumab (VDZ) is a selective monoclonal antibody targeting α4β7 integrin, which is expressed specifically by a subset of gastrointestinal-homing T-lymphocytes. Although VDZ showed promising results in various clinical studies, in common with all existing biological IBD therapies, a significant number of patients either fail to initially respond or lose response with time. Validated markers and mechanistic insights to predict the populations that will derive sustained benefit from VDZ therapies are currently lacking. We hypothesised that circulating exosomes express on their surface high levels of α4β7 integrin, which could bind VDZ and interfere with its activity and therapeutic efficacy.

Methods: Exosomes were isolated from serum of blood donors (BD CTRL) and VDZ-treated patients (IBD) by polymer-based precipitation (Exoquick), analysed for concentration (Exocet) and validated for exosomal markers expression. The surface expression of α4β7 integrin was evaluated by flow cytometry on exosomes-bound beads. The levels of exosome-bound VDZ were investigated by Promonitor-VDZ ELISA kit and western blot analysis. Finally, exosomes isolated from blood donor's serum were incubated with increasing concentration of VDZ and then exosomal-bound VDZ levels were analysed by immunoblotting analysis.

Results: The number of circulating exosomes was not different between blood donor and IBD patients (A). Flow cytometry analysis revealed that serum exosomes, either from the IBD patients and from the BD donors, express high levels of the VDZ target, α4β7 integrin (B). A significant VDZ levels were measured in exosomes purified from VDZ-treated patient's serum exosomes (C). Of note, we found that exosomes purified from blood donor's serum were able to bind VDZ in dose-dependent manner (D).



Conclusions: Our preliminary data suggest that circulating serum exosomes bind VDZ, as they express on the surface the target integrin. Accordingly, exosomes might contribute to drug sequestration, possibly affecting the therapeutic efficacy of VDZ in IBD patients. Further studies are needed to define the possible correlation between VDZ exosomal sequestration and patient's response.

P059

The metformin inhibits MDSC and M2 macrophage via AMPK-induced inhibition of HMG-CoA reductase in tumour microenvironment of colitic cancer

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Background: MDSC (myeloid-derived suppressor cell) and M2 macrophage in tumour microenvironment contribute to tumour progression by inducing immune tolerance to tumour antigens and cancer cells. It has been reported that metformin has anti-inflammatory and anti-tumour effects. However, there is no report on the effect of metformin on inflammatory cells of tumour microenvironment and its mechanism.
Methods: THP-1 cells were used, and treated with metformin 0.25, 0.5, 1, 2.5, and 5 mM for 48 h. We performed a flow cytometry analysis, utilising surface markers such as CD33, arginase, CD206, CD163, and CD68, to estimate MDSC and M2 macrophage fraction of THP-1 cells. To investigate AMPK-mTOR and cholesterol pathway, we performed western blot analysis for p-AMPK and p-S6, and treated AICAR (AMPK activator), Compound C (AMPK inhibitor), rapamycin (mTOR inhibitor), simvastatin (HMG-CoA reductase inhibitor), and mevalonate (mediator of cholesterol metabolism).
Results: The treatment of metformin on THP-1 cells decreased the fraction of MDSC (CD33, arginase), and M2 macrophage (CD206, CD163). In the western blot analysis, metformin treatment activated p-AMPK and inhibited p-S6. The fraction of MDSC and M2 macrophage was decreased by AICAR and increased by Compound C treatment. The inhibitory effect of metformin on MDSC and M2 macrophage was reversed by Compound C and mevalonate treatment. In addition, rapamycin or simvastatin treatment to THP-1 cells also decreased the fraction of MDSC and M2 macrophage, which was reversed by mevalonate treatment. In APCmin-DSS cancer model, metformin decreased the number and volume of tumour and the number of MDSC and M2 macrophage in tumour microenvironment.
Conclusions: The inhibitory effect of metformin on MDSC and M2 macrophage in colitic cancer microenvironment is mediated by AMPK-activation-induced inhibition of HMG-CoA reductase.

P060

The protective effect of necrosis inhibition on acute murine colitis induced by dextran sulphate sodium

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Background: Inflammatory bowel diseases (IBD) were characterised by uncontrolled chronic inflammation, which lead to cell death and organ damage. Although necrosis is thought to be a main cell death mechanism of IBD, few attempts have been made to reduce necrosis in IBD. The aim of this study investigated the effect of necrosis inhibition using a novel necrosis inhibitor (NI, NecroX-7) in acute murine colitis model and *in vitro* study.
Methods: In order to confirm the necrosis inhibition effect of NI, intestinal epithelial cell line (IEC-18, rat) was used to analyse Cleaved PARP-1 fragment with western blot assay. And acute dextran-sodium sulphate (DSS)-induced colitis was generated in C57BL/6 mice. NI (30 mg/kg) was administered once a day via oral gavage for 8 days from the day before DSS administration. The severity of colitis was assessed by weight, colon length, and histological score, and HMGB1 immunochemistry was performed on harvested colon tissues to evaluate necrotic cell death qualitatively. The inflammatory cytokines mRNA expressions were measured by quantitative RT-PCR.
Results: The expression of cleaved PARP-1 (55 kDa, necrosis marker) was reduced in the NI group, compared with the control group, whereas the cleaved PARP-1 fragment (89 kDa, apoptosis marker) was not different between two groups. *In vivo* study, NI treatment significantly reduced colitis represented by colon length (DSS + NI group 68.0 ± 4.7 mm vs. DSS group 62.6 ± 3.8 mm, $p = 0.048$) and histological score (DSS + NI group 11.4 ± 1.6 vs. DSS group 7.9 ± 1.3, $p = 0.043$). The immunohistochemical staining of HMGB-1 revealed that NI also reduced HMBG-1 expression significantly. In addition, the expression of inflammatory cytokines such as IL-1β, IL-12, MCP-1, TNF-α was reduced in NI group, especially IL-1β was significantly different between two groups ($p = 0.011$).
Conclusions: A necrosis inhibition effectively reduced DSS-induced colitis and inflammatory cytokines. Necrosis inhibition might be a new approach to treat inflammatory bowel disease.

P061

Succinate promotes EMT in intestinal epithelial cells through SUCNR1: Relevance in fistula development

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Background: Intestinal fistula is a common complication in CD patients whose aetiology is unknown. It is associated with an exacerbated inflammation and epithelial-to-mesenquimal transition (EMT), a process which allows a switch from epithelial towards a fibrotic phenotype. Under inflammatory conditions, succinate is accumulated and activates its receptor, SUCNR1, which has recently been related to intestinal fibrosis. We aim to analyse the role of succinate and SUCNR1 in EMT.
Methods: HT-29 cells were treated with succinate (0, 0.1, 0.5, 1.5 mM) or TGF-β (5 ng/ml) during 48 h and transfected with SUCNR1 siRNA. Expression of EMT markers was analysed by qPCR and western blot. Intestinal fibrosis was induced *in vivo* using the heterotopic transplant model in WT and Sucnr1–/– mice and expression of EMT markers was analysed by qPCR and by confocal microscopy. Intestinal resections were obtained from CD and

non-IBD patients. The expression of SUCNR1, Snail1, Snail2 and E-Cadherin was analysed by qPCR and succinate levels were quantified with a Succinate Assay Kit. Results are expressed as fold induction (mean ± SEM, $n \geq 5$). Statistical analysis was performed with one-way ANOVA followed by Newman–Keuls test. Correlations were analysed with the Spearman coefficient.

Results: Succinate induces, in HT-29 cells a significant increase in Vimentin, Snail1, and Snail2 expression and a significant reduction in E-Cadherin expression compared with vehicle-treated cells and these changes were significantly prevented in cells transfected with SUCNR1 siRNA, (1.87 ± 0.09 vs. 1.12 ± 0.12, 1.85 ± 0.18 vs. 0.90 ± 0.09 and 2.57 ± 0.43 vs. 1.07 ± 0.26 vs.,, respectively). WT-grafts at Day 7 showed a significant increase in Vimentin expression (3.50 ± 0.48), Snail1 (4.87 ± 0.79) and Snail2 (2.45 ± 0.25) and a significant reduction in E-Cadherin expression (0.52 ± 0.07) vs. WT-grafts at day 0. KO-grafts at Day 7 showed a significant reduction in Vimentin expression (1.84 ± 0.14), Snail1 (1.91 ± 0.28) and Snail2 (1.07 ± 0.26) and an increase in E-Cadherin (0.94 ± 0.05) compared with WT-grafts at Day 7. Finally, in intestinal resections from B3-CD patients: (a) levels of succinate were higher than in that from B2-CD patients or non-IBD patients (244.90 ± 26.03 μM, 142.00 ± 21.66 μM and 99.73 ± 11.12 μM,, respectively); (b) SUCNR1 mRNA expression was significantly increased when compared with B2-CD or non-IBD controls. SUCNR1 mRNA expression correlates positively with Snail1 (r = 0.560) and Snail2 (r = 0.588) and negatively with E-cadherin (r = –0.714).

Conclusions: Succinate activates EMT in intestinal epithelial cells through SUCNR1. Both succinate levels and SUCNR1 expression are increased in intestine from B3-CD patients and correlates with EMT markers, which points to a new possible target for fistula treatment.

P062

Differences in immune cell population subsets in inflammatory bowel disease patients under anti-TNF treatment

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Background: In autoimmune diseases targets attacked by the immune system differ one from another and the immune system deregulation seems to be the main cause of these pathologies. The aim of this study was to determine the existence of a differential pattern in the immune system cells (in terms of cell percent, ability of cytokines production and transcription factor activation) in inflammatory bowel disease (IBD) patients under infliximab (IFX) therapy.

Methods: A pilot case–control study was performed. Inclusion criteria were IBD patients in clinical remission under IFX treatment. After informed consent, blood samples were obtained in IBD patients just before IFX infusions and in a healthy control. Patients were classified in different groups: Crohn's disease (CD) without rheumatologic manifestations (Group 1), ulcerative colitis (UC) without rheumatologic manifestations (Group 2) and IBD patients with associated rheumatoid arthritis (RA) (Group 3). Blood samples were used to determine the immune cell status of patients and negative control. To investigate the immune system cell distribution, peripheral mononuclear blood cells were isolated from fresh blood to characterise: monocyte, dendritic cells (DC), Th1, Th17, Treg, and B cell. Cells were then incubated with specific fluorescent antibodies' cocktails, then identified with flow cytometry. T cells ability to produce TNF-α, IL-17 and INF-γ was tested by performing intra cellular staining, while T-bet, Fox-P3, and Ror-γ t expression was tested trough intra nuclear staining. Data were collected with flow cytometry.

Results: Fifteen IBD patients (60% female, mean age 42) were consecutively included, 7 CD,5 UC and 3 IBD with RA. The surface staining demonstrated differences between the group's cell subtype. CD and IBD-RA patients showed a decrease of CD25Hi CD127- Treg subset in comparison with negative control. Decrease of transitional B cell subset CD38Hi CD24Hi CD19+ was observed in CD patients, while UC patients maintain normal values. The cytokine production in T cell, showed a significative increase of TNF-α, especially in IL-17 with a five-fold increase, while no significant difference in IFN-γ production, in CD and UC patients. Regarding the transcription factor expression T-bet and Ror-γ t increased significantly in CD and UC vs. negative control. T-bet was more specifically expressed in UC, whereas Ror-γ t more in CD.

Conclusions: The immune system cell subset is highly modified by the disease type (CD, UC, IBD+RA). IFX treatment does not seem to unmask the immune system cell´s capability to produce proinflammatory cytokines. Transcription factors expression showed that patients are affected by a Th1 disease, due to the increase of T-bet.

P063

Representative and comprehensive analysis of colonic and ileac biopsies from IBD patients by gene expression profiling using the straightforward, fast, and affordable novel application Whole Transcriptome AmpliSeq on the Ion Torrent NGS platform

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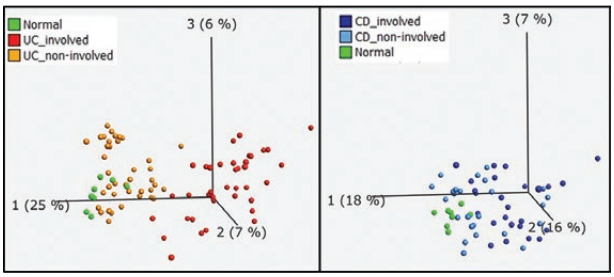
Background: Whole transcriptome (WT) AmpliSeq analysis of 20 803 genes offers significant advantages compared both to hybridisation-based genechip analysis (specificity and sensitivity), and to RNA-Seq (costs and reproducibility), while data show good correlation to both platforms. We applied WT AmpliSeq for gene expression profiling (GEP) of colonic and ileac biopsies from patients with active ulcerative colitis (UC) and Crohn's disease (CD) to create a new representative dataset fostering disease understanding, and helping to prioritise new targets and biomarkers.

Methods: Mucosal biopsies from inflamed and non-inflamed areas of patients with CD and UC as well as control subjects were immediately immersed in RNAlater. RNA was extracted by RNeasy with DNase digestion (Qiagen), quantified by UV spectrophotometry, and quality controlled by Bioanalyzer (Agilent). 10 ng total RNA were subjected to ultrahigh-multiplexed RT-PCR using the AmpliSeq Transcriptome Human Gene Expression kit (Thermo Fisher). Sixteen to 18 barcoded samples were sequenced on a 540 chip by an Ion

GeneStudio S5 System (Thermo Fisher). The resulting Excel matrix of normalised reads [RPM = reads per million mapped reads] was analysed by GeneSpring (Agilent) and QOE (Qlucore).

Results: 172 biopsies were analysed from 36 CD, 26 UC, and 6 non-IBD patients. Biopsies from inflamed and non-inflamed areas were included for each IBD patient. Biopsies yielded total RNAs of varying quality (RIN 3.4–9.9). Due to small amplicon design, no differences could be noted between extremes. Unbiased PCA analysis revealed no gender bias and no effect of age. UC samples separated reasonably well into involved and non-involved biopsies while CD samples were much more mixed, reflecting possibly a more systemic instead of localised inflammation.



Gene signatures of active inflamed CD and UC (few exclusive genes), and a large common overlap in comparison to normal controls could be identified, in line with previous findings by genechips on a lack of major differences between CD and UC inflamed biopsy transcriptomes. Statistically significant differentially expressed genes between UC and CD with highest levels in inflamed UC could be identified, eg, the T-cell-specific CD3D (IHC confirmed), the plasma cell marker SDC1 (CD138), and the chemokine CXCL13, the B cell-attracting chemokine 1.

Conclusions: WT AmpliSeq can perform GEP of large numbers of mucosal biopsies enabling further research of IBD pathomechanisms and of new biomarker signatures for better patient stratification.

P064

The role of the vagal innervation in a DSS-induced colitis mouse model

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Background: Environmental factors have been identified that affect the course of Crohn's disease (CD) and ulcerative colitis (UC); one of the most relevant is cigarette smoke (CS) and its main active constituent, nicotine. CS has been shown to have a negative effect on the clinical progression of CD and to increase the risk of onset while showing a favourable effect on reducing the disease progression, severity, and occurrence of UC. Both smoking and nicotine are considered as immunosuppressive and alter a wide range of immunologic functions, including innate and adaptive responses. Nicotine can also influence the immune system through its actions on the central nervous system via the activation of the autonomic nervous system, which connects the brain directly to visceral target tissue, through sympathetic and parasympathetic innervations. The parasympathetic nervous system, primarily the vagus nerve, it is one of the endogenous mechanisms that help to regulate the innate immune response, and activation of this response attenuates systemic inflammation, such as in UC and CD. The existence of counterinflammatory vagal-dependent mechanisms has been assessed in colitis mouse models with conflicting results, and the molecular mechanism by which this therapeutic intervention can have an immune-regulatory effect in UC remains unclear.

Methods: In order to understand the possible role of the vagus nerve in the CS-dependent attenuation of colitis symptoms in a dextran sulphate sodium (DSS) mouse model, mice were exposed to CS corresponding to 3 concentrations of nicotine (24, 32, and 40 µg/l) for a total of 4 weeks. DSS was provided in drinking water followed by a seven-day recovery period before necropsy. Finally, animals exposed to the medium nicotine concentration (32 µg/l) and the sham control groups were subject to vagal denervation 2 weeks prior CS exposure.

Results: Using an omics approach (transcriptomics) together with classical endpoint analysis, we showed that the nicotine dose-dependent effect on the development of mouse UC is not influenced by the vagus nerve. Accordingly, several inflammatory pathway signalling, such as toll-like receptors, interferon γ, nuclear factor kappa B, and signal transducer and activator of transcription, were down-regulated in CS-exposed mice in a nicotine dose-dependent manner but independently of vagal integrity.

Conclusions: The current study allows investigation of possible new molecular mechanisms responsible for the attenuation of DSS-induced mouse colitis by CS constituents, such as nicotine. Moreover, these findings indicate that although vagal integrity is important, other counterinflammatory mechanisms come into play if vagal integrity is compromised.

P065

Olfactory receptor, OR51E2 is a marker for innate immune cells in ulcerative colitis

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Background: Olfactory receptors (ORs) are one of the largest gene family of human genome and the GPCRS. Ectopic expression of ORs have been detected in various tissue including testis, prostate, kidney and GI tracts. Previously, we identified meaningful expression of OR51E2 genes in UC patients using NGS sequencing. We aimed to determine the exact function and roles of OR51E2 in the pathogenesis of ulcerative colitis.

Methods: Immunohistochemical staining of OR51E2, CD 68, CD 163, CD 38, F 4/80 and syndecan-1 were evaluated in both human colon from ulcerative colitis and control and inflamed mice induced by 3% DSS colitis. Human monocyte cell line, THP-1 cells were differentiated to macrophage and polarised to M1 or M2 phenotypes using PMA. Expression of OR51E2 and macrophage marker were analysed by qPCR. To identify ligand for olfactory receptors, SCFAs (butylate, b-ionone, propionate) were treated in both NCM 460 cells and macrophages polarised from THP-1 cells with various concentration. OR51E2 were analysed by q PCR and immunocytochemistry. For *in vivo* study, SCFAs were administrated in WT mice and WT mice treated with 5 days of 3% DSS. Q PCR and IHC was done for OR51E2 and macrophage markers including F4/80 and CD 163.

Results: We found that UC patient had more OR51E2 protein expression in lamina propria compared with control group to control patients of normal colonic mucosa and the damaged mice mucosa induced by DSS. Immunohistochemical analysis revealed an increase in the proportion of CD 163 positive cells expressing of OR51E2 with about 70% of all OR51E2 positive lamina propria mono nuclear cells ($p < 0.05$). In case of mice colon, OR51E2 and CD 163 immunoreactivity were more colocalised in lamina propria compared with F4/80. The genetic expression of OR51E2 from M1 macrophage polarised from THP-1 cells was significantly down-regulated compared with the expression of M0 and M2 macrophage. Butylate treatment to M0 macrophages was significantly increase in M2 polarisation with an significant increase in OR51E expression but there was no butylate effect on the NCM 460 cells.
Conclusions: Taken together, our data suggest that ectopic OR51E2 can be a marker of innate immune cells and also be associated with M2 polarisation. SCFA as a ligand for OR51E2 can modulate colonic inflammation by affecting macrophage polarisation.

P066

Validation of assay for detection of free soluble mucosal addressin cell adhesion molecule-1 (MAdCAM-1) in human serum and cerebrospinal fluid

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Background: Mucosal addressin cell adhesion molecule-1 (MAdCAM-1) plays a key role in gut immune surveillance and homing of α4β7 integrin-expressing lymphocytes to the gut mucosa during inflammation. MAdCAM-1 is predominantly expressed on the endothelium of high endothelial venules in the gut and gut-associated lymphoid tissue, and is not constitutively expressed in the CNS. SHP647 is a fully human monoclonal anti-MAdCAM-1 antibody in development for the treatment of ulcerative colitis and Crohn's disease. To better understand the relationship between SHP647 target engagement (binding to MAdCAM-1) and downstream clinical effects, we developed an assay to measure free concentrations of MAdCAM-1 in both serum and cerebrospinal fluid (CSF).
Methods: The assay was a hybrid of immunocapture and nano liquid chromatography–tandem mass spectrometry (LC–MS/MS). Biotinylated SHP647 was used as a capture agent, followed by trypsin digestion and LC–MS/MS for separation and detection, respectively. The immunocapture conditions of the assay were optimised to provide good recovery of endogenous MAdCAM-1 levels using low concentrations of biotinylated SHP647 under a short incubation time. Assay performance was assessed in human serum and CSF from healthy donors and donors with inflammatory bowel disease.
Results: Inter-assay and intra-assay precision and relative accuracy were acceptable (relative standard deviation ≤25% and ±25%,, respectively) in human serum and CSF. Calibration standard responses for free soluble MAdCAM-1 were linear over the range of 0.5–512 pM in serum and 0.5–30 pM in CSF; using a weighted ($1/\text{concentration}^2$) linear least squares regression. To test whether the assay was selective to measure free soluble MAdCAM-1 in serum, an excess of SHP647 (500 times the endogenous concentration of MAdCAM-1) was added to blank serum samples allowing existing endogenous MAdCAM-1 to bind to the drug. Mean MAdCAM-1 detected fell from 325 pM to 1.95 pM, demonstrating that the assay is selective for free soluble MAdCAM-1 in serum without measuring soluble MAdCAM-1 bound to SHP647. Soluble MAdCAM-1 in serum and CSF samples was stable at 4°C up to 24 h and over 5 freeze/thaw cycles at –20°C and –70°C; CSF samples were stable up to 182 days at –20°C and –70°C, and serum samples were stable for 577 days at –70°C and 381 days at –20°C.
Conclusions: The immunocapture LC–MS/MS assays described are valid for the detection of free soluble MAdCAM-1 in human serum and CSF samples within the investigated concentration ranges. In serum, the assay was shown to be selective and sensitive for free soluble MAdCAM-1 not bound to SHP647. These data support the use of these immunocapture LC–MS/MS assays for the detection of free MAdCAM-1 in serum and CSF in clinical trials.

P067

Human colonic subepithelial myofibroblasts from IBD patients demonstrate a differential expression of Th-related cytokine receptors compared with healthy controls

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Background: Crohn's disease (CD) and ulcerative colitis (UC) are the two major forms of inflammatory bowel diseases (IBD) and are characterised by chronic and relapsing/remitting inflammation of the intestinal tract that may ultimately lead to fibrosis. Subepithelial myofibroblasts (SEMFs) play a key role in fibrogenesis, as they have been found to produce excessive collagen quantities or enzymes lysing the extracellular matrix (ECM). The aim of the study was to examine whether SEMFs isolated from patients with IBD present different expression patterns of Th-related cytokine receptors compared with healthy controls.
Methods: SEMFs were isolated from endoscopically obtained colonic biopsies from healthy controls and IBD patients (CD and UC: CD-SEMFs, UC-SEMFs), set to culture and total RNA was extracted. Cytokine receptors mRNA expression was assessed with reverse transcription quantitative (RT-q) PCR.
Results: Unstimulated SEMFs had a basal expression of most of the studied cytokine receptors. As to Th1-related receptors, both CD- and UC-SEMFs expressed reduced levels of IL1R1 (CD: median 0.43-fold, IQR 0.31–0.51, UC: median 0.15-fold, IQR 0.15–0.16) and TNFRSF1A (CD: median 0.39-fold, IQR 0.38–0.51, UC: median 0.27-fold, IQR 0.25–0.29), but presented different expression patterns for IL12RB2; CD-SEMFs expressed reduced levels, while UC-SEMFs increased (CD: median 0.59-fold, IQR 0.48–0.6, UC: median 1.46-fold, IQR 1.44–1.51). As to Th2-related receptors, only UC-SEMFs expressed reduced mRNA levels of IL4R (median 0.24-fold, IQR 0.22–0.25) and IL13RA2 (median 0.23-fold, IQR 0.16–0.26). Concerning the Th17-related receptors, only CD-SEMFs expressed reduced levels of IL17RA (median 0.58-fold, IQR 0.5–0.78), while both CD- and UC-SEMFs were found to express

reduced levels of IL23R (CD: median 0.4-fold, IQR 0.28–0.43, UC: median 0.58-fold, IQR 0.57–0.59). Finally, regarding the Treg-related receptors, CD-SEMFs expressed reduced levels of IL10RA (median 0.4-fold, IQR 0.32–0.55) and IL10RB (median 0.53-fold, IQR 0.39–0.65), while UC-SEMFs of TGFBRB2 (median 0.48-fold, IQR 0.34–0.63) and IL10RB (median 0.54-fold, IQR 0.5–0.59).
Conclusions: These data suggest that SEMFs might be a dynamic crosslink between the inflammatory and the fibrotic process, as they express most of the Th-related cytokine receptors. CD-SEMFs appear to have reduced expression levels of Th1- and Th17-related cytokine receptors, while in UC-SEMFs, Th2-related cytokine receptors were found down-regulated.

P068

Aberrant brain function in active-stage ulcerative colitis patients: a resting-state functional MRI study

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Background: Patients with ulcerative colitis (UC) usually display cognitive impairments, such as memory loss, attention deficit and declining executive function, especially during active disease. However, the potential neurological mechanisms of these symptoms remain unclear.
Methods: Forty-one patients with mildly to moderately active UC, as well as 42 matched healthy controls, were recruited for examination using psychological scales, cognitive function testing and resting-state functional magnetic resonance imaging (rs-fMRI). Seed points were identified via amplitude of low-frequency fluctuation (ALFF) analysis, and whole-brain functional connectivity (FC) was calculated based on the graph theoretical. Correlation analyses were performed among clinical indexes, neuropsychological assessments and neuroimaging data.
Results: Compared with the healthy controls, UC patients exhibited lower ALFF values in the bilateral hippocampal/parahippocampal (HIPP/ParaHIPP) region and higher ALFF values in the left posterior cingulate cortex (PCC.L) and left middle frontal gyrus. With HIPP/ParaHIPP as the seed point, activity in the FC in the bilateral middle frontal gyrus, anterior cingulate cortex, and left caudate nucleus increased; these brain regions are mainly related to working memory. Using the PCC.L as the seed point, activity in the FC in the middle cingulate cortex and the left angular gyrus increased; these brain regions are mainly related to the attention network and executive functions.
Conclusions: These results indicated that the limbic lobe might be the core of the brain-gut axis and play an important role in cognitive impairments, suggesting potential mechanisms for cognitive impairment in UC patients during active disease.

P069

New methylation biomarker panel of inflammatory Mucosa in Korean Crohn's disease

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Background: Inflammatory bowel disease (IBD) is known to be caused by a genetic predisposition involving multiple genes; however, there is growing evidence that abnormal interaction with environmental, particularly epigenetic, factors can have a significant contribution during the development of IBD. Although many studies, particularly genome-wide association studies (GWAS), have been performed to identify the genetic changes underlying the pathogenesis of Crohn's disease (CD), the role of epigenetic changes in the development of complications arising from CD is poorly understood.
Methods: We employed an unbiased approach to define DNA methylation alteration in CD patients using the HumanMethylation450K BeadChip platform. We validated the methylation levels of 19 genes that showed hypermethylation in CD patients compared with normal control. Technical validation was performed using quantitative MSP analysis. And, we performed functional implication of hypermethylated genes in CD analysed by gene-network
Results: Compared with normal controls, the majority of differential DNA methylation in CD patient samples was in the promoter, intergenic, and gene body regions. The DNA methylation profile in CD revealed 134 probes (23 hypermethylated and 111 hypomethylated probes) that were differentially methylated. Among hypermethylated genes in CD patients, we selected candidate genes (ZFP36L1, ANXA2, EP400, FHIT, TPPP, IL5RA, KBTBD11, MDFIC, MUM1, PUSL1, RUNX3, C19orf24, TRPM4, PPP1R15A, CDT1, SFRS1, EPHA4, CCDC42B, and HNRNPUL1) that were hypermethylated (>3-fold increase in methylation) in CD patient samples. We determined the methylation levels of these 19 genes between normal and CD samples from the methylation profile, and indeed found that most of 19 candidate genes were significantly hypermethylated in CD patients compared with normal controls. We validated the methylation levels of 19 genes that showed hypermethylation in CD patients compared with normal control. MSP analysis showed that the Fragile Histidine Triad (FHIT) genes were hypermethylated in a disease-specific manner. Gene network analysis of the hypermethylated candidates suggested putative molecular interactions relevant to IBD pathology.
Conclusions: Our DNA methylation profile identifies newly hypermethylated genes in CD, as well as the gene network associated with disease development, which may contribute to the pathogenesis and activity of IBD.

P070

The level of nuclear factor kappa B (NF-kB) translocation during infliximab therapy in children with IBD

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Background: NF-kB is a universal transcription factor located in the cell cytoplasm that translocates into the nucleus when it is activated. This leads to the synthesis of proinflammatory cytokines,

chemokines, growth factors and activation of cell effector functions. The aim of this study was to assess the level of NF-kB translocation in lymphocyte populations during treatment with infliximab (IFX) in children with IBD.

Methods: In total, 31 children aged 12–18 years were examined: 21 patients with IBD (12 UC, 9 CD) (Group 1) and 10 clinically healthy children (Group 2). Blood samples were taken from Group 1 patient before the infusion of IFX and next day after infusion. Intracellular NF-kB localisation was quantitatively analysed in lymphocyte populations by Amnis NF-kB kit by ImageStreamX MKII (Amnis). For populations of CD3 + CD4 + (Th), CD3 + CD8 + (Tc), CD3-CD19 + (B cell), CD3-CD16 / 56 + (NK), CD3 + CD4 + CD161 + (Th17), CD3 + CD4 + CD25highCD127low (Treg) was estimated the total number of cells and the percentage of cells with NF-kB translocation (the level of activation). The IDEAS image analysis software was applied. Similarity score algorithm was used for assess events of translocation.

Results: In Group 1 on IFX treatment with clinical and endoscopic relapse there is an increase in cells with NF-kB translocation in the main populations of lymphocytes compared with a Group 2, mostly in Th (37.7 ± 2.7% vs. 14.9 ± 1.0, $p < 0.01$) and Tc (39.4 ± 3.0% vs. 15.3 ± 1.5, $p < 0.01$). The total number of Th17 (% of CD4 +) in Group 1 before the IFX infusion averaged 34.6%, and Treg (% of CD4 +) – 11.6%, which exceeded the level of these populations in Group 2 (Th17 18.6%; Treg 7.8%). At the same time, NF-kB translocation level of in the Treg population did not differ from Group 2, and in the population of Th17 lymphocytes the level of NF-kB translocation was 1.7 times higher. It was observed a 1.4 times decrease in the activation level of Th17 and 2 times increase in the activation of Treg while the quantity of those lymphocyte populations were stable.

Conclusions: The level of translocation NF-kB, measured by the ImageStream platform, is a rapidly changing index that allows to evaluate the functional activity of the lymphocyte populations at the time of the laboratory investigation. The level of NF-kB translocation in the lymphocyte populations, which is an important marker of the autoimmune activity in IBD (Treg, Th17) reflects the body's response to the administration of IFX. An increase in Treg activity and a decrease in Th17 activity under the action of a TNFα blocker explains the molecular mechanism leading to a weakening of the inflammatory process.

P071

Supporting extrapolation of indications for ABP 501, the first adalimumab biosimilar: focus on Crohn's disease

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Background: ABP 501 (EU: AMGEVITA® [adalimumab]; US: AMJEVITA™ [adalimumab-atto]) is the first approved biosimilar to adalimumab (HUMIRA®). The primary mechanism of action (MOA) of adalimumab is mediated by binding to soluble tumour necrosis factor (TNF)-α, inhibiting its proinflammatory signalling. Secondary mechanisms mediated by binding to membrane bound (mb) TNF-α may play a role in inflammatory bowel disease (IBD) and include reverse signalling, mixed lymphocyte reactions (MLRs) and effector functions such as antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). To support extrapolation to IBD, specific *ex vivo* functional studies explored the similarity of ABP 501 to adalimumab reference product (RP) in these mechanisms.

Methods: Multiple lots of ABP 501 and RP sourced from the USA (US) and the European Union (EU) were compared. Binding of ABP 501 and RP to soluble TNF (sTNF) α and mbTNF α were tested. Blocking of TNF α-induced caspase activation, IL-8 secretion and lymphotoxin (LT)-α (TNF-β) bioactivity (ie, specificity) were also assessed. To confirm similarity in Fc-mediated functions, ADCC using engineered NK92 cells expressing the high-affinity variant of FcgRIIIa (158V) and CDC were tested. ADCC was also assessed in peripheral blood mononuclear cells (PBMCs) isolated from healthy volunteers and patients with Crohn's disease.

Results: Relative binding to sTNF α was similar [ABP 501, 108%; RP (EU), 111%; RP (US), 112%], demonstrating similarity in potency. Relative binding to mbTNF α was also similar [ABP 501, 103%; RP (EU), 106%; RP (US), 105%]. Relative activity in reverse signalling was similar [ABP 501, 99%; RP (EU), 99%; RP (US), 98%]. Relative activity was similar in NK92 ADCC [ABP 501, 85%; RP (EU), 87%; RP (US), 86%] and CDC [ABP 501, 100%; RP (EU), 94%; RP (US), 94%]. PBMCs isolated from healthy volunteers and patients with Crohn's disease showed similar, dose-dependent ADCC activity with all three agents.

Conclusions: ABP 501 adalimumab biosimilar has previously been shown to be highly similar to adalimumab RP in several analytical assessments, clinical pharmacokinetics, efficacy, safety and immunogenicity. We have demonstrated that similarity extends to biological activity across key MOAs, including those mediated through mbTNF-α that may be important for the efficacy of adalimumab in IBD. Coupled with previously reported effector function and reverse signalling assessments, *ex vivo* ADCC activity in PBMCs isolated from healthy volunteers and patients with Crohn's disease contribute to the totality of evidence supporting efficacy of ABP 501 in IBD.

P072

Quantitative phase imaging for the characterisation of Crohn's disease-derived intestinal strictures

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Background: Intestinal strictures are a frequent complication of Crohn's disease (CD). The differentiation of inflammatory from the fibrotic components of CD strictures is crucial for the right choice of therapy. However, currently available imaging modalities have limited capability to determine the degree of fibrosis. Digital holographic microscopy (DHM) enables stain-free quantitative phase contrast imaging and provides determination of the refractive index (RI), which is directly related to tissue density. Therefore,

this study evaluates quantitative phase imaging (QPI) with digital holographic microscopy (DHM) for the assessment of fibrosis within CD strictures.

Methods: In total, 26 surgical resection specimens were obtained from non-stenotic and stenotic tissue areas of 13 CD patients with symptomatic intestinal strictures. Clinical characteristics were extracted from medical records. Cryostat sections from stenotic and non-stenotic bowel segments for each patient were evaluated separately by conventional H&E staining and were simultaneously analysed by DHM. RI measurements were performed in the epithelium (e), the submucosa (sm) and the muscularis propria (mp).

Results: The included patients had a moderately increased disease activity (CD activity index [CDAI]: 202 ± 25.9, white blood cell count: 10.8 ± 1.0 × 10^9/l, C-reactive protein: 4.6 ± 1.5 mg/dl). Employing DHM, 360 digital holograms were generated in 26 surgical specimens and ultimately 3600 measurements within defined ROIs were performed. The average RI of stenotic compared with non-stenotic tissue samples was significantly higher in all layers of the intestinal wall (e: 1.355 vs. 1.354, $p = 0.013$; sm: 1.364 vs. 1.359, $p < 0.001$ and mp: 1.357 vs. 1.355, $p < 0.001$).

Conclusions: QPI using DHM reliably assesses density differences in the intestinal wall and is capable to distinguish non-stenotic from stenotic tissue. Thereby, QPI could help to quantitatively characterise CD strictures in the future.

P073

Evaluation of DPPH free radical scavenging activity by HPLC technique: a screening method for drugs and nutrients used in inflammatory bowel disease

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Background: Oxidative stress is considered as one of the etiopathogenetic factors involved in development of inflammatory bowel disease (IBD). In this context, recent studies have suggested that the drugs and biologically active compounds with additional antioxidant activity may be beneficial in the treatment of IBD. Scavenging of α,α-diphenyl-β-picrylhydrazyl (DPPH) free radical is the basis of a common antioxidant assay. Therefore, the focus of present study was to develop a high-throughput and selective HPLC method for evaluating the DPPH free radical scavenging activity of compounds and to evaluate the antioxidant capacity of eight drugs and nutrients commonly used in IBD treatment.

Methods: Chromatographic analysis was performed using Agilent 1100 HPLC with diode array detector. XBridge C18 column (3.5 µm particle size, 4.6 × 150 mm) by Waters was used as stationary phase. Isocratic elution was applied using a 80:20 (v/v) mixture of methanol and ultrapure water. DPPH assay was monitored with diode array detector at 517 nm at 25°C with total run time of 5 min. Scavenging strength of compounds was shown using TROLOX as standard antioxidant and it was expressed as TROLOX equivalent antioxidant capacity (TEAC). It was calculated through the obtained calibration curve which presented linearity between 0.01 mM and 0.14 mM range ($R^2 = 0.99$).

Results: The highest antioxidative activity was found for 0.1 mM mesalazine (up to 310 times stronger than others) followed by aminosalicilates, sulfasalazine and balsalazide. On the other hand, olsalazine has shown no antioxidant activity. Furthermore, antioxidative nature of 1 mM solutions of immunosuppressant drugs was observed: 6-mercaptopurine and 6-thioguanine showed twice as much antioxidative power compared with azathioprine. Folic acid showed poor antioxidant activity. Obtained results imply that majority of the antioxidative power of IBD drugs originates from free 5-ASA present in the structure, whilst that of immunosuppressants might originate from the purine ring and mercapto group.

Conclusions: The proposed method was found to be useful for high-throughput screening of antioxidant activity of currently used drugs and biologically active compounds as well as new drug candidates for IBD treatments. This work has been supported in part by the Croatian Science Foundation under the project number [UIP-2017-05-3949]. This work has been supported in part by the European Union from the European Social Fund.

P074

Autoimmunity against type IV collagen in ulcerative colitis

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Background: Immunological disorders play an important role in the pathogenesis of ulcerative colitis (UC). IV collagen is a type of collagen found primarily in the basal lamina It can be assumed that the immune disorders leading to the production of autoantibodies to collagen play a role in the pathogenesis of UC. The aim was to study the level of IgM and IgG to type IV collagen (COL) in UC.

Methods: We prospectively included 61 patients with UC and 30 healthy controls. Mean age in UC was 37 ± 1.5 years and in control group 30 ± 1.5. Severity of UC was assessed by Mayo score: remission, 5; mild, 25; moderate, 26; severe, 5. Level of serum IgM and IgG to COL4 was assessed by enzyme immunoassay.

Results: In active UC levels of IgM to COL4 was increased (0.32 [0.21; 0.55] mkg/ml; $p < 0.001$) and in remission (0.42 [0.19; 0.42] mkg/ml; $p< 0.05$) compared with healthy (0.13 [0.12; 0.15] mkg/ml). The difference between remission and exacerbation was not detected ($p >0.05$). In patients with severe UC IgM to COL4 was 0.45 [0.42; 0.87] mkg/ml, which was higher than in moderate UC 0.29 [0.17; 0.52] mkg/ml ($p > 0.05$) and mild 0.32 [0.22; 0.55] mkg/ml ($p > 0.05$). The level of IgG to COL4 in active UC (16,92 [11,11; 49.64] mkg/ml; $p < 0.01$) and in remission (81.95 [55.99; 220.43] mkg /ml; $p < 0.001$) were higher than in the control group 11,16 [9.39; 13,1] mkg/ml. In patients with severe UC IgM to COL4 was 18.1 [7.93; 29.35] mkg/ml, which was higher than in moderate UC 15,82 [10.34; 29.47] mkg/ml ($p > 0.05$) and mild 12.1 [8.6; 23,29] mkg/ml ($p > 0.05$).

There was increasing of ESR ($r = 0.38$; $p < 0.05$) and leukocytosis ($r = 0.42$; $p < 0.05$) with increase of IgM level to COL4.

Conclusions: In active UC the level of serum antibodies of class IgM and IgG to COL4 increased compared with healthy. The maximum increase was found in the group of patients with severe relapse

P075

Adaptive defensive response is critical to determine dextran sulphate sodium-induced colitis

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Background: Dextran sulphate sodium (DSS)-induced colitis in mice is one of the most frequent and useful animal model in the study of inflammatory bowel disease, of which pathogenesis are immune derangement and mucosal damages. Curiously, colitis usually developed after 4–5 days of DSS administration in spite of its toxicity. We hypothesised host defense system might delay the presentation of colitis after DSS administration.
Methods: We measured the serial expressions of either inflammatory mediators and signalling or host defense Phase 2 enzyme with signalling in wild-type mice administered with DSS, COX-2 KO, and Nrf2 KO mice.
Results: Dextran sulphate sodium (DSS)-induced colitis in mice is one of the most frequent and useful animal model in the study of inflammatory bowel disease, of which pathogenesis are immune derangement and mucosal damages. Curiously, colitis usually developed after 4–5 days of DSS administration in spite of its toxicity. We hypothesised host defense system might delay the presentation of colitis after DSS administration. In accordance with emergence of colitis, COX-2 expressions correlated with degree of colitis as much as NF-kB activation ($p < 0.01$). When traced the expressions of host defense proteins such as HO-1, NQO-1, γ-GCS, HO-1 expressions with Nrf2 induction were also significantly correlated with COX-2 expressions. When colitis was induced in COX KO mice with DSS administration, significantly lowered damages were noted, in which HO-1 expressions were also significantly decreased compared with WT littermates ($p < 0.001$). On the other hand, when colitis was induced in Nrf2 KO mice, significantly higher degree of colitis was noted, in which COX-2, HO-1, and γ-GCS were significantly increased compared with WT littermates ($p < 0.01$).
Conclusions: Host defense system can determine the degree of colitis, by which medications enhancing defense systems might be prerequisite in the treatment of IBD.

P076

Conserved inflammatory profile between mice and humans allow unsupervised patient stratification and temporal allocation of IBD-risk genes

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Background: Although ulcerative colitis (UC) patients show heterogeneous clinical manifestation, such as diverse response to biological therapies, they are classified as one group. Therefore, an unsupervised molecular re-classification of UC patients has been evoked to design tailored therapies. Moreover, independently on the re-classification, those UC patients who do not respond to biologicals are in urgent need for novel therapeutic targets. Genome-wide association studies (GWAS) have identified potential new target genes, however, their function and optimal therapeutic window remain to be elucidated.
Methods: Due to unsuccessful attempts to classify UC patients based on their colonic transcriptomic profile, we generated and utilised time-series transcriptome data from a mouse model of colitis, which was then cross-compared with human datasets. We also use the time-series transcriptome mouse data to allocate in time the expression of human IBD-risk genes.
Results: Restricting the analysis to the most differentially expressed genes shared between mouse and human, we were able to cluster UC patients into two subgroups, termed UC1 and UC2. We observed that UC1 transcriptional profile is richer in genes associated with neutrophil activity and cytokine signalling than UC2 transcriptional profile. In addition, only 10% of UC1 patients responded to biological therapies (Figure 1). Finally, we temporally allocate IBD risk genes throughout the different phases of intestinal inflammation—tissue damage and tissue repair—providing useful insights on the time of relevance of the IBD risk genes.

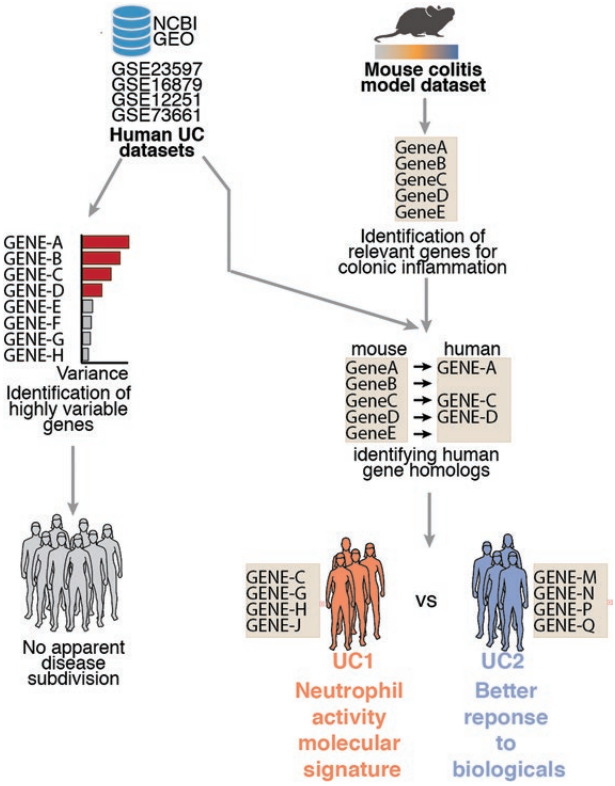

Figure 1. Schematic diagram of the pipeline used to stratify patients in UC1 and UC2.

Conclusions: By forward-translating UC disease information from mouse to human we first identified two molecularly distinct UC subgroups characterised by different immunological signatures and responsiveness to biological therapies and second, we associated IBD risk genes to specific phases during intestinal inflammation and recover. Thus, we proposed a new re-classification of UC patients that might be used in clinical practice accompanied with personalised therapies.

P077

SMAD7 shows a biphasic expression pattern during progression of ulcerative colitis-associated colorectal cancer

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Background: Ulcerative colitis (UC) is an idiopathic inflammation of the intestine with an increased risk of developing colitis-associated cancer (CAC). Currently, clinical trials are underway aiming to inhibit SMAD7 to ameliorate inflammation. While the direct effect of depleting SMAD7, an inhibitory molecule in the transforming growth factor-β1 (TGFβ1) pathway, may be therapeutic in UC, its indirect effect on CAC development is largely unknown. TGFβ1 is known to enhance late stages of sporadic colorectal cancers (CRC), where SMAD7 is also elevated. Therefore, we hypothesise that removing inhibition of this pathway by depleting SMAD7 may also be detrimental for CAC. We therefore evaluated the expression of SMAD7 in the colonic epithelium during the inflammation associated neoplastic process to determine a possible role of SMAD7 in CAC.

Methods: The expression of SMAD7 protein and mRNA in colonic epithelia was assessed by immunohistochemistry (IHC) and *in situ* hybridisation (ISH),, respectively, in a cohort of 53 archival colon samples (17 CAC, 12 dysplastic, 12 inflammed, 12 non-neoplastic/non-inflammed) from patients who have undergone colectomies for UC and CAC. The expression within the epithelial cells was evaluated by both digital quantification and validated by blind scoring by a pathologist. Significant differences were tested with one-way ANOVA and Mann–Whitney U test.

Results: Cytoplasmic expression of SMAD7 protein is significantly higher in the inflammed epithelium compared with non-inflamed epithelium ($p < 0.0001$). Interestingly, a significant decrease of the same was detected in dysplasia ($p = 0.01$), although this group is characterised by a higher variability. SMAD7 levels are elevated in cancer compared with dysplasia, suggesting a biphasic expression ($p = 0.009$), which could be in part due to the different genetic composition. SMAD7 mRNA expression was not significantly different across different stages of CAC ($p = 0.49$). We hypothesise that the lack of correlation between mRNA and protein levels could be attributed to yet unknown post-transcriptional or post-translational regulations.

Conclusions: In our cohort of UC affected colon tissues, SMAD7 demonstrated a biphasic expression pattern along the different stages of CAC with peaks during active inflammation and cancer. The increase in SMAD7 expression during neoplastic transformation, comparable to sporadic CRC, may be a protective response of the epithelium to inhibit the effect of TGFβ1. Although inhibiting SMAD7 as a therapy for UC may remit inflammation, we hypothesise it may exacerbate CAC due to further enhancement in TGFβ1 signalling. We envisage further mechanistic studies *in vitro*, in particular in organoids, could help in understanding the TGFβ superfamily pathway in CAC.

P078

Mucosal tissue short chain fatty acids contribute to prediction of pouchitis in restorative proctocolectomy

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Background: Restorative proctocolectomy is a surgical option in patients with ulcerative colitis who become refractory to medical therapy. Short chain fatty acids (SCFA) are organic fatty acids with 1–6 carbons which arise from bacterial metabolism from carbohydrates entering the colon. Various studies have implicated SCFA in both the development of IBD and flares of IBD. Furthermore, it has been shown that SCFA concentrations are significantly lower in faecal samples from patients with pouchitis when compared with healthy controls.

Our study aimed to assess longitudinal changes in SCFA that occur in a pouch to determine whether they can predict or are associated with the development of pouchitis. To date no study has analysed short chain fatty acids in mucosal biopsy tissue from these patients.

Methods: Patients who underwent restorative proctocolectomy at a single centre underwent pouchoscopy at the time of restoration of continuity and then every 6 months for a year. Biopsies from the pouch were retrieved from the pouch body. Pouchitis was defined using the pouch disease activity index. The development of pouchitis was assessed at months 6 and 12 months.

Biopsies samples were snap frozen at time of biopsy and stored in −80°C. Samples were thawed and weighed. SCFA were measured using an Agilent 7000C Triple Quadrupole GC/MS-MS System. Simca was used for multivariate analysis and T-tests were used for univariate analysis.

Results: There were 56 biopsy samples. There were 22 patients (17 males); 16 UC and 6 FAP patients with longitudinal follow-up. The median age of the cohort was 40 years (range 20–60 years). Of the UC patients four developed pouchitis within 1 year.

When comparing UC patients at the time of closure of ileostomy, there were there were significant decreases in caproic acid (4674 μM vs. 12 217 μM; $p < 0.01$), valeric acid (1580 μM vs. 3695 μM; $p = 0.01$), isovolaric acid (721 μM vs. 2940 μM; $p = 0.05$), isobutyric acid 35 072 μM vs. 76 074 μM; $p = 0.03$) and lactic acid (1580 μM vs. 3732 μM $p = 0.02$) between those who developed pouchitis within a year and those who did not develop pouchitis at 1 year. There were no significant differences detected between UC patients and FAP patients at each time point analysis.

Conclusions: The study has suggested that a decrease in SCFA found in the mucosal tissue at time of closure of ileostomy may predict onset of pouchitis within a year. This study is the first to demonstrate that SCFA can be analysed from biopsies. Future studies need to determine factors that may contribute to tissue SCFA levels which may help develop a potential therapeutic target to optimise and potentially reduce the incidence of pouchitis.

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P079

Increased faecal proteolytic activity in pouchitis patients mediates epithelial barrier disruption through activation of protease-activated receptor-2

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Background: Pouchitis in ulcerative colitis (UC) patients is thought to occur due to disruption of the epithelial barrier resulting in an abnormal immune response to a dysbiotic microbiota. We aimed to examine whether faecal proteolytic activity is increased during pouchitis and results in epithelial barrier dysfunction and explore the pathways involved.
Methods: Faecal protease activity was measured using a FITC-casein florescence assay. Caco-2 cells monolayers were exposed to faecal supernatants of participants. Trans-epithelial electrical resistance and FITC-Dextran were used to determine monolayers' maturity and permeability. Tight junction (TJ) proteins integrity and protease-activated receptors (PARs) activation were assessed by immunoblot and immunofluorescence. A truncated PAR2 protein in Caco-2 cells was achieved by stable transfection using CRISPR/Cas9 plasmid. PAR2 expression/activation was examined in human pouch biopsies using antibodies directed to the N-terminus of the protein.
Results: Twenty-five patients, including 10 pouchitis, 6 normal pouch (NP) and 9 healthy (HC) participants, were recruited. Pouchitis patients exhibited a 5.19- and 5.35-fold increase in proteolytic activity ($p \leq 0.05$) compared with NP and HC participants,, respectively. Faecal supernatants from pouchitis patients activated PAR2 on Caco-2 monolayers and disrupted TJ proteins, resulting in increased epithelial permeability. Truncation of PAR2 in Caco-2 monolayers, leading to its inactivation, abrogated increased faecal protease-mediated permeability. Human pouch biopsies displayed PAR2 activation in pouchitis but not in NP specimens.
Conclusions: Increased luminal proteolytic activity in pouchitis patients leads to disruption of tight junction proteins and increased epithelial cells permeability in a PAR2-dependent manner. This mechanism may initiate or propagate pouch inflammation.

P080

Thioguanine nucleotide cut-off levels to predict leucopoenia should be considered differently based on NUDT15 R139C genotypes in Chinese Crohn's disease

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Background: To date, excessive level of thioguanine nucleotide (6-TGN) poses an increased risk for leucopoenia, which has been identified in Caucasian patients. However, basing on 6-TGN levels alone would overlook NUDT15-deficient patients who are prone to thiopurine-induced leucopoenia in East Asian. In our study, we investigated the relationship between 6-TGN levels and leucopoenia in different NUDT15 R139C genotypes to obtain the cut-off level in each subgroup.
Methods: Patients with Crohn's diease (CD) in the sixth affiliated hospital, Sun Yat-sen university form July 2014 to December 2017 were retrospectively studied. The CD patients with stable dosage of thioprine were recuited. Clinical and epidemiological characteristics were reviewed from medical records. NUDT15 R139C was genotyped. 6-TGN/6-MMPR concentrations were measured with high-performance liquid chromatography (HPLC).
Results: A total of 434 CD patients with at least one 6TGN measurement were included in this study. Leucopoenia was observed in 78 individuals (18.0%) with median 6-TGN level of 332.3 pmol/8 × 10^8 RBC, which was marginally different from the median level of 291.9 pmol/8 × 10^8 RBC in the patients without leucopoenia ($p = 0.040$). Then we compared 6TGN levels of the whole patients after dividing them into three groups according to the genotype of NUDT15 R139C. For CC genotypes ($n = 361$), the median 6-TGN concentrations in patients who developed leucopoenia was significantly higher than that in patients who did not ($p < 0.0001$, 474.8 (174.2–1179.5) vs. 305.7 (62.2–1822.9) pmol/8 × 10^8 RBC). For CT carriers ($n = 69$), the 6-TGN levels were also higher in patients developing leucopoenia ($p = 0.027$, 292.8 (80.7–701.5) vs. 216.2 (62.9–631.0) pmol/8 × 10^8 RBC). ALL of the TT ($n = 4$) developed leukopoenia with the median 6-TGN concentration of 135.8 (90.0~291.3) pmol/8 × 10^8 RBC. The cut-off 6-TGN levels of 319.2 pmol/8 × 10^8 RBC in CT subgroup was 96.9% specific to leucopoenia, with a sensitivity of 43.2% and area under curve (AUC) of 0.66 ($p = 0.027$). Meanwhile, the cut-off 6-TGN levels in CC subgroup was 409.6 pmol/8 × 10^8 RBC with the 73.5% specificity and 59.5% sensitivity to leucopoenia ($p < 0.0001$, AUC = 0.71). 6-MMPR was not correlated with leucopoenia ($p > 0.05$).
Conclusions: In Chinese CD patients, it is strongly recommended to consider different 6TGN cut-off levels to predict thiopurine-induced leucopoenia based on NUDT15 R139C genotypes.

P081

Effect of bile acid on lymphocyte migration in the small intestine

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Background: The introduction of the western diet has been proposed as an explanation for the increase in inflammatory bowel disease (IBD) incidence. Among them, greater consumption of fat is known to increase risk of IBD. We have reported that dietary fat augmented intestinal immune system by increasing lymphocyte migration to the intestinal microvessels by using intravital microscope system in the animal models of IBD. High fat diet increases secondary bile acid, especially deoxycholate (DCA), which is reported to be involved in

the exacerbation of IBD along with direct effect of fat. Each bile acid distinctively affects gut immunity and its mechanism remains to be clarified. Recently, aberrant migration of lymphocytes to intestinal mucosa has been regarded one of critical pathogenesis of IBD. We aimed to investigate the effect of several kinds of bile acid on gut immunity in the view point of intestinal microcirculation.
Methods: (1) Effect of bile acid exposure on intestinal mucosa: Thoracic duct lymphocytes (TDL) were collected from the thoracic duct of donor rats. We intravenously injected CFSE-fluorescence labelled TDL into recipient rats, and migration in intestinal mucosa was observed by a confocal microscope to evaluate the TDL migration. In some recipient rats, bile acids were injected into ligated ileum at both ends to evaluate the direct effect on intestinal mucosa. Tauro Colic Acid Natrium (tauro-CANa, 4 mM) or DCA (4 mM), PBS were injected into the intestinal lumen. PBS was used as a control sample. Mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1) neutralising antibody was administered intravenously in some rats. Mucosal damages were measured histologically. (2) Effect of bile acid exposure on TDL: TDL were cultured at 4°C for 2 h with above-mentioned bile acids. Expression levels of L-selectin and α4 integrin in the obtained lymphocytes were examined by flowcytometry.
Results: (1) A small number of lymphocytes adhered to intestinal microvessels in control group. There was no change in TDL adhesion in the Tauro-CANa exposed group. TDL adhesion increased in the DCA exposed group. Increased lymphocyte adhesion by DCA was partially blocked by neutralising antibody of MAdCAM-1. Histologically, a part of intestinal mucosa was damaged by DCA, and inflammatory cell infiltration was observed in the mucosa. (2) Expressions of α4 integrin and L-selectin on TDL did not alter with or without addition of bile acids.
Conclusions: DCA caused injury of ileal mucosal epithelium and increased lymphocyte adhesion to the vascular endothelium in the ileal mucosa, suggesting that the gastrointestinal immunity could be altered by some bile acids via increase in expression of adhesion molecules on microvessels.

P082

Xenobiotic nuclear receptors: linking bile acid signalling to alterations in CYP3A4 metabolism in Crohn's disease

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Background: The Cytochrome P450 (CYP) 3A4 is the cornerstone of drug metabolism in humans. The impact of disease on CYP3A4 activity is still incompletely defined. Given the importance of CYP3A4 to the disposition of many clinically-important substrates, including new classes of orally-administered, small-molecule immunomodulators for inflammatory bowel disease and its high concentration in the intestine, understanding the effect of Crohn's disease (CD) on CYP3A4 activity is highly relevant. We aimed to assess the impact of CD on CYP3A4 activity using the endogenous *in vivo* probe 4β-hydroxycholesterol (4BOHC) and to propose a molecular mechanism for any detectable differences from non-CD controls.
Methods: Our study was conducted in two parts: in a cross-sectional study of individuals with (n = 74) and without (n = 71) CD, plasma 4BOHC concentrations as well as a plasma bile acid profile of 12 bile acids were determined using liquid chromatography-mass spectrometry. *In vitro* modelling, employing luciferase transactivation assays, was used to evaluate the effect of differential bile acid profiles (control, inactive and active CD) on the activation of CYP3A4 via nuclear receptors, pregnane X receptor (PXR) and farnesoid X receptor (FXR) in HepG2 cells.
Results: The plasma 4BOHC concentrations were higher in the control population vs. the CD population (CD= 18.68 ng/ml ± 13.02 ng/ml, non-CD= 46.38 ng/ml ± 40.70 ng/ml, $p \leq 0.0001$). The ratio of plasma bile acids was different between subjects with and without CD and further varied by disease activity. To explore the impact of CD-specific plasma bile acid profiles on PXR and FXR activation, two models were created. In HepG2 cells transfected with hPXR and CYP3A4-pGL3 plasmids (model 1), no difference was seen in the luciferase activity amongst the cells exposed to the cohort-specific bile acid profiles at 25 μM or 50 μM. At 75 μM, bile acid-activated CYP3A4-reporter activities were significantly decreased in the CD cohorts compared with the control cohort, though no difference was seen based on disease activity. To evaluate the effect of CD-specific bile acid signalling on FXR (another CYP3A4 regulator), HepG2 cells were transfected with hFXR and BSEP-pGL3 plasmids (model 2) and exposed to cohort-specific bile acid profiles. At 25 μM and 50 μM, reduced FXR-mediated activation of BSEP was seen with the active CD bile acid profile compared with the control profile. At 75 μM, bile acid-activated BSEP-reporter activity was significantly decreased in the disease state and further so in active disease.
Conclusions: Our data show that CYP3A4 activity is decreased in CD and that disease-dependent changes in nuclear receptor-signalling may contribute to CD-dependent variation.

P083

The transcriptomic signature of IL-23-treated lamina propria mononuclear cells is significantly enriched for genes in the Th17 pathway and is enriched in active UC

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Background: Subunits of interleukin-23 (IL-23) and its receptor have been identified as susceptibility genes in genome-wide association studies (GWAs) in ulcerative colitis (UC). Moreover, functional pre-clinical studies have shown that IL-23 is a key cytokine in the pathogenesis of UC. Here, we define an IL-23-induced transcriptomic signature in lamina propria mononuclear cells (LPMCs). We hypothesised that this signature would be enriched in active UC (aUC) compared with inactive UC (iUC) and healthy controls (HC), and enriched in anti-TNFα non-responders compared with anti-TNFα responders.
Methods: LPMCs were isolated from colonic biopsies obtained endoscopically from 5 aUC and cultured in the presence or absence of IL-23 for 4 h. Cells were lysed, RNA was extracted and RNA sequencing performed using the Illumina platform. Analysis of differentially expressed genes (DEGs) was performed between the untreated and IL-23 treated LPMCs using DESeq2, filtered with $p < 0.01$ and examined for enrichment in biological pathways using

Ingenuity Pathway Analysis (IPA). To assess association of the transcriptomic signature to clinical phenotypes, Gene Set Variation Analysis (GSVA) enrichment scores were calculated in open access data sets of microarray data of colonic biopsies from HC and UC including the ACT1 trial (GSE16879 HC = 6, UC = 24; GSE57091 HC = 11, iUC = 23, aUC = 74; GSE23597 anti-TNFα responders = 2, non-responders = 7).

Results: In total, 112 DEGs were identified, including IL22, IFNγ and IL17F which are downstream targets IL-23. Canonical pathway analysis of the DEGs demonstrated 'Th17 activation' pathway as the most significantly enhanced. GSVA enrichment scores using the 'LPMC untreated v IL23' signature showed a significantly higher score in UC compared with HC in data set GSE16879 ($p = 0.006$). Furthermore, there was significantly greater enrichment in aUC compared with iUC in data set GSE59071 ($p < 0.00001$). However, GSVA enrichment scores calculated on colonic biopsies of patients with UC before commencing anti-TNFα therapy did not show a significant difference between anti-TNFα responders and non-responders (dataset GSE16879 $p = 0.07$; dataset GSE23597 $p = 0.1$).

Conclusions: The herein described IL-23 signature induces an appropriate and expected downstream transcriptional profile. GSVA enrichment scores in open access datasets shows enrichment in aUC compared with both HC and iUC. However, enrichment scores were not significantly different when comparing anti-TNFα responders and non-responders though this may be due to lack of power due to a low sample numbers. Transcriptomic signatures have the potential to act as biomarkers to aid clinical decision making.

P084

Clinical response to Ustekinumab in Crohn's disease is linked to a dose-dependent reduction of T follicular helper cells

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Background: The pathogenesis of Crohn's disease (CD) is characterised by strongly dysregulated $CD4^+$ T-cell responses. The differentiation and function of pro-inflammatory Th1 and Th17 cells is supposed to be efficiently targeted by Ustekinumab (UST), a human monoclonal antibody directed against the shared p40-subunit of interleukin-12 (IL-12) and interleukin-23 (IL-23). However, IL-12 and IL-23 are also involved in the differentiation of other T-cell subsets such as T follicular helper (Tfh) cells, which are essential for the formation and maintenance of germinal centres and promote B cell function. We therefore investigated the impact of UST therapy on Tfh cell profiles in CD patients.

Methods: Peripheral blood mononuclear cells (PBMCs) were longitudinally isolated from CD patients before and during UST therapy ($n = 25$) and analysed by flow cytometry. CD patients treated with anti-TNF antibodies ($n = 21$) and healthy donors ($n = 22$) served as controls. The results were correlated with plasma UST concentrations and clinical response status.

Results: Overall, the peripheral Tfh cell frequencies were comparable in UST and anti-TNF treated patients and healthy donors. However, subgroup analyses revealed that patients with clinical response to UST displayed a significant reduction of Tfh cell frequencies following initiation of therapy. Moreover, Tfh cell frequencies in responders were lower than in non-responders to UST therapy, but not affected by the clinical response status in anti-TNF treated patients. These findings suggest that the Tfh phenotype observed in UST-treated patients is mediated by UST rather than differences in disease activity. In keeping with this notion, Tfh cell frequencies were significantly reduced in patients with UST plasma concentrations > 4 mg/l when compared with concentrations below 4 mg/l, suggesting a dose-dependent effect.

Conclusions: Our data indicate that UST affects peripheral Tfh cell frequencies in CD patients. This interaction appears to be associated with the clinical response status as well as UST plasma concentrations. These findings may therefore have clinically significant implications for Tfh-mediated immune functions such as vaccine responses.

P085

Crohn's disease patients under combined therapy with Azathioprine and Infliximab present persistent inflammation together with a counter regulatory response during clinical disease remission

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Background: Crohn's disease (CD) is characterised by a chronic dysregulation of the gut mucosal responses. This study aimed to evaluate peripheral blood mononuclear cells (PBMC) phenotype and its responsiveness to the activating stimulus of Crohn's disease patients treated with Infliximab (IFX) combined with Azathioprine (AZA).

Methods: We enrolled 20 healthy controls (HC) and 40 CD patients in clinical remission (25 using IFX and 15 using IFX plus AZA—Ethics Committee approval n°. 2.023.23). Immunophenotyping of PBMC was performed by flow cytometry. Leucocytes were stimulated with anti-CD3/CD28 by 5 days or with LPS by six h. Cytokines (IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-17A, IFN-γ, and TNF-α) were measured in the culture supernatants and plasma samples by Cytometric Bead Array. LPS was measured in plasma by Enzyme Immunoassay.

Results: Combined AZA+IFX therapy led to decreased NK (CD16+) and B cells compared with HC, in contrast to increased CD14+

monocytes, as well as CD14++CD16+ (intermediary) cells in both IFX and combined groups, indicating a tendency towards an inflammatory response. Besides that, LPS and IL-6 were augmented in all CD' plasma, suggesting that these patients still present bacteria translocation to circulation and systemic inflammation. Moreover, increased amounts of TNF and IL-17A were detected in the supernatant of stimulated cultures of AZA+IFX patients, compared with HC and IFX,, respectively, though the lower levels of IL-17 were found in IFX-treated patients. Most interestingly, there was a notable augment of Foxp3+ cells in CD despite the treatment, indicating a counter regulatory response to the residual inflammation (Tables 1 and 2).

Table 1. Mean of cells frequency.

	HC (%)	IFX (%)	IFX+AZA (%)	*p-value*
Leucocyte population				
$CD3^-CD16^+$	**13.04**[a]	8.62	**7.04**[b]	0.0160
$CD3^-CD19^+$	**8.93**[a]	7.04	**5.73**[b]	0.0107
$CD4^+CD25^+FoxP3^+$	22.49	41.36	40.89	0.0360
$CD14^+$	**84.49**[a]	87.48	**88.75**[b]	0.0500
$CD14^{++}CD16^+$	**3.44**[a]	**8.39**[b]	**7.01**[b]	0.0090

'a' and 'b' represent statistical differences between the indicated groups.

Table 2. LPS and cytokine dosage.

	HC (%)	IFX (%)	IFX+AZA (%)	*p*-value
Plasma				
LPS (EU/ml)	**0.1324**[a]	**0.2414**[b]	**0.2493**[b]	**<0.0001**
IL-6 (pg/ml)	**0.1633**[a]	1.6260	**1.4280**[b]	**0.0214**
Supernatant				
TNF (pg/ml)	**1729.0**[a]	1921.0	**3254.0**[b]	**0.0217**
IL-17A (pg/ml)	280.2	**185.1**[a]	**567.5**[b]	**0.0247**
Proliferation (%)	48.13	64.54	62.38	0.0984

'a' and 'b' represent statistical differences between the indicated groups.

Conclusions: Patients in disease clinical remission still present relevant markers of inflammation, in spite of the constrained NK/B lymphocytes and augmented regulatory population induced by AZA and IFX treatment, which have relevant impact in the ongoing CD immune response.

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P086

Eukaryotic microbial dysbiosis in treatment-naïve patients with newly diagnosed Crohn's disease

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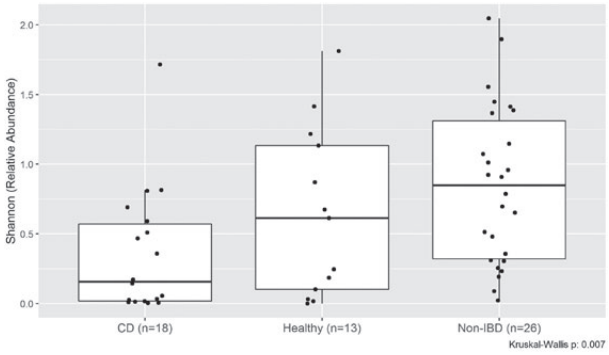
Background: Dysregulated mucosal immune response to gut microbiota is thought to play a role in the pathogenesis of Crohn's disease (CD). Alterations in eukaryotic microbiota in CD were also reported as potential triggers for perpetuating inflammatory processes. Data on eukaryotic dysbiosis in IBD are scares and its potential contribution to CD pathogenesis-presumable.

The aim of the study was to evaluate whether eukaryotic microbiota composition in patients with newly diagnosed treatment naïve CD differs from that of patients with gastrointestinal symptoms but without a diagnosis of CD, and from that of healthy controls.

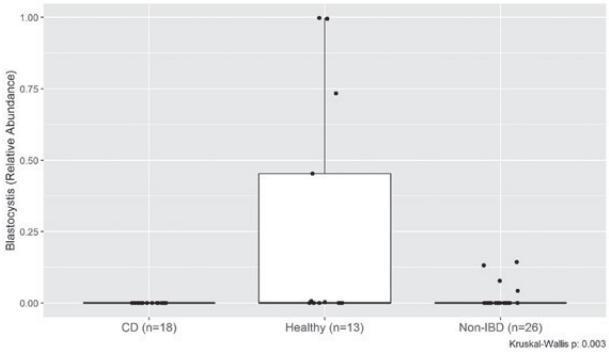
Methods: Patients with newly diagnosed CD were prospectively recruited. Two control groups were assessed: (1) gastrointestinal symptoms (GIS)—patients with suspected CD but with negative endoscopic and imaging investigation, (2) healthy controls (HC)- healthy volunteers with no GIS. Faecal samples were analysed for eukaryotic microbial composition using 18S amplicon sequencing.

Results: Overall, faecal samples from 57 patients were analysed: CD-18, GIS-26, and HC-13. Average age: CD- 34.6 ± 13.4 years, GIS- 36.7 ± 16.8 years, HC- 51.2 ± 14.2, years. Male/Female ratio: CD-0.16, GIS-0.86, HC- 0.54. Shannon diversity score was lower in CD compared with the GIS and HC groups (mean 0.35 ± 0.45 vs. 0.69 ± 0.6, and 0.84 ± 0.5; $p = 0.007$ (Figure 1).



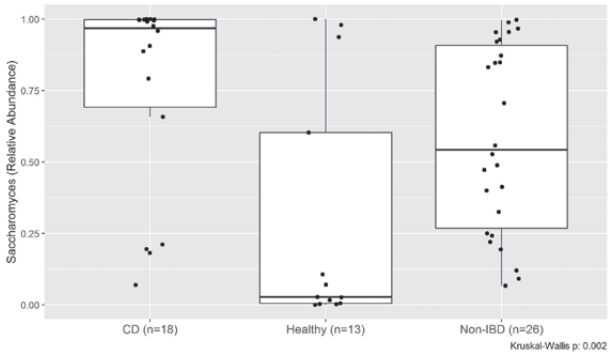
Shannon diversity scores

The unicellular eukaryote Blastocystis was found almost exclusively in the HC or GIS (Figure 2)



Blastocystis relative abundance by group.

mean relative abundance: HC-0.24 ± 0.4, GIS- 0.01 ± 0.03, CD-0, $p = 0.003$). The fungal genus Saccharomyces was significantly more prevalent in CD vs. GIS and HC (mean relative abundance: 0.76 ± 0.34 vs. 0.58 ± 0.32 and 0.29 ± 0.4, $p = 0.002$ (Figure 1)



Saccharomyces relative abundance by group.

Conclusions: Patients with treatment-naïve CD have reduced diversity of faecal eukaryotic microbiome and low relative abundance of Blastocystis. In contrast to previous data, Saccharomyces was significantly more prevalent in treatment-naïve CD patients than controls, suggesting its possible role in early stages of disease pathogenesis.

P087

Urinary formate and glycine are associated with treatment response in patients treated with antibiotics for pouchitis

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Background: Restorative proctocolectomy (RPC) is considered the preferred surgical choice for patient with ulcerative colitis (UC) who have failed medical therapy and in some patients with familial adenomatous polyposis (FAP). It has been shown through metabolic profiling of urine that CD patients have higher levels of formate and lower levels of hippurate and 4-cresol sulphate when compared with healthy controls. To date extensive metabolic profiling in RPC has yet to be studied. This study aimed to determine compounds found in urine that are associated with treatment response in patients that have been treated for pouchitis.

Methods: Patients with pouchitis were recruited from a single centre. Pouchitis was defined using the pouch disease activity index (PDAI) and pouchitis was considered when the score was ≥ 7. Response to antibiotics was defined as either a two points reduction in PDAI. Mid-stream morning urine samples were collected. Samples we stored at –80°C until analysis. 1H-NMR profile were recorded using the Bruker® Avance III 600MHz spectrometer, with a Samplejet 96 well autosampler. Standard 1-dimension NMR experiments with water suppression was performed at 300 K. All NMR spectra were automatically referenced to TSP at 0 ppm, phased and baseline-corrected on Topspin 3.2. Spectra were exported to Matlab for pre-processing. The full resolution 1H NMR spectra were imported into the SIMCA-P software package and multivariate data analyses were carried out. Once the NMR spectral regions related to the discrimination between two sample classes have been identified using supervised multivariate discriminant analysis, statistical total correlation spectroscopy (STOCSY) was applied. Metabolite assignment was performed by comparing chemical shifts, Jres coupling, and peaks multiplicity with information in databases (such as Human Metabolome DataBase, HMDB).

Results: There were 21 patients. The median age of the cohort was 50 years (range 28–79). A total of 11 patients were on antibiotics and 10 patients were off antibiotics. Nine were responders. On multivariate modelling there were significant differences found between responders and non-responders (CV-ANOVA $p = 0.05$). Significant spectral differences that corresponded to the multi-variate model correlated with Formate (8.84 PPM) Trigonelline (4.45PPM) and Glycine 3.57(PPM) all of which were higher in responders.

Conclusions: Trigonelline, formate and glycine may help differentiate patients with pouchitis who will respond to treatments vs. those that do not. It is currently unclear as to the mechanism as to why these metabolites are reduced in non-responders and further work is required to understand this and validate our findings.

P088

Transcriptome landscape of protein-coding genes and long noncoding RNAs in the colon and blood of DSS-induced mouse model of Acute ulcerative colitis

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Background: Ulcerative colitis (UC) is an inflammatory disorder initiating from the rectum and affecting the mucosal lining. Gene expression analysis is a powerful tool for understanding disease development and the underlying pathophysiology. Thus, we used one of the most well established mouse models of UC to investigate the expression changes of protein-coding genes and long noncoding RNAs (lncRNA) in colon and blood of diseased and healthy mice. We further aimed to investigate the most significant biological processes and pathways that these differentially expressed genes are part of.

Methods: A dextran sodium sulphate (DSS)-induced mouse model of UC was established by administering DSS to the drinking water at a final concentration of 1.5% (wt/vol) for 7 days. Total RNA (excluding small RNA) from colon tissue and blood samples of 3 DSS-treated and 3 healthy mice was extracted and sequenced by Illumina Hiseq 4000. We obtained an estimate of gene expression level by mapping and quantification to the annotated mouse genome, and then performed differential gene expression and pathway analyses between DSS-treated and control mice. Groups of tightly connected

genes were identified by Markov clustering of the STRING functional associations between these genes.

Results: Our preliminary analysis identified ~2000 protein-coding genes and ~300 lncRNAs in colon as well as ~500 protein-coding genes and ~50 lncRNAs in blood to be significantly (log FC > 1, p_{adj} < 0.1) differentially expressed between the two groups (mainly up-regulated in DSS-treated mice) (see Figure 1). We also found ~200 common genes up-regulated in DSS-treated mice in both colon and blood. Furthermore, network and functional enrichment analysis showed a strong enrichment of genes in immune system related processes and disease pathogenesis (Figure 2).

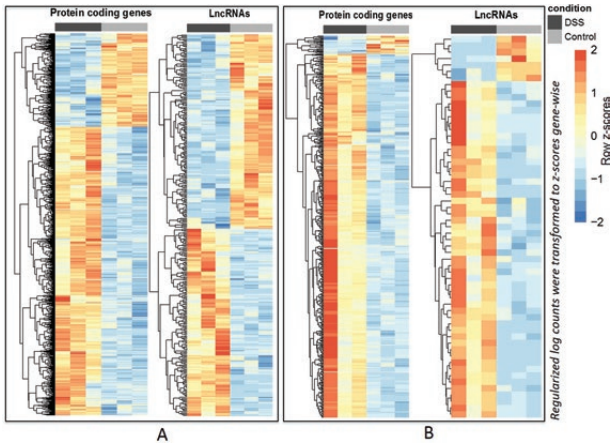

Figure 1. Heatmap of differentially expressed genes (log FC > 1, p_{adj} < 0.1), based on z-scores of normalised log counts of (A) colon and (B) blood.

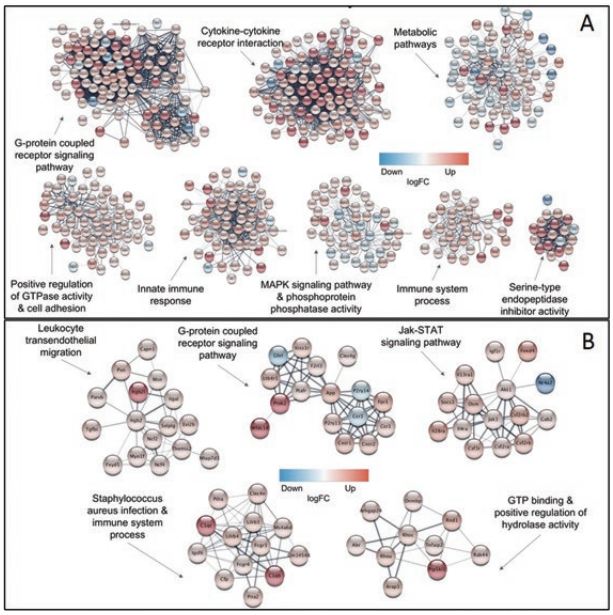

Figure 2. Functional enrichment and network analysis of the differentially expressed genes in (A) colon and (B) blood.

Conclusions: Our data show a significant differential transcriptional signature between the diseased and the healthy animals that can be used to stratify the two groups. Moreover, this study expands our molecular understanding of putative new targets that may be important in the pathophysiology of UC.

P089

Extensive characterisation of cellular sources of IL-22BP in inflammatory bowel diseases indicates that T cells do not express IL-22BP

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Background: IL-22 is an epithelium-targeting cytokine of major importance in the gut. Its secretion is dramatically increased during inflammatory bowel diseases (IBD) flares. Actions of IL-22 during gut inflammation have been largely addressed, placing IL-22 as a chief cytokine to orchestrate intestinal epithelial cell (IEC) barrier functions (AMPs and mucus expression induction) and regeneration and therefore to promote mucosal healing. However, excessive actions of IL-22 could also promote tumour cell proliferation, indicating that IL-22 actions need to be tightly controlled. IL-22 binding protein (IL-22BP) is a soluble, secreted and specific inhibitor preventing IL-22 binding to its membrane IL-22R expressed on epithelial cells. Using IL-22BP-deficient rats, we demonstrated an IL-22BP-dependent inhibition of IL-22-protective functions on IEC during DSS-colitis. In human, we previously showed that IL-22BP was up-regulated in IBD inflammatory lesions and identifed dendritic cells (DCs) and eosinophils as the sources of IL-22BP. A recent report suggests that CD4+ T cells represent another cellular source of IL-22BP during IBD both in human and mice. Given these controversies, we decided to extensively revisit the cellular sources of IL-22BP.

Methods: The expression of IL-22BP mRNA was assessed by Q-PCR in FACS-sorted cells isolated from human mesenteric lymph nodes (MLN) and intestinal mucosa from IBD patients.

Results: We observed that in the gut mucosa of IBD patients, only DCs and eosinophils expressed IL-22BP mRNA. DCs from MLN also strongly expressed IL-22BP mRNA. Lamina propria and MLN CD4+ and CD8+ T cells, either of the naïve or memory/effector phenotype, did not significantly express IL-22BP mRNA, even after *in vitro* stimulation. Confirming these data, we did not observe any IL-22BP protein expression in CD3+ cells in colon biopsies from IBD patients analysed by immunofluorescence. We therefore generated IL-22BPGFP reporter rats and confirmed our previous data that IL-22BP expression is restricted to mononuclear phagocytes in this species. Again, T cells did not express IL-22BP in gut mucosa or lymphoid organs. Finally, we demonstrated that T cells from Il22ra2–/– rats induced similar colitis and wasting disease upon transfer in Il2rg–/– rats when compared with T cells from Il22ra2+/+ rats.

Conclusions: Taken together, our data confirm that IL-22BP expression is restricted to myeloid cells (DCs and eosinophils) and do not support a role of T cells as a source of IL-22BP in IBD.

P090

Exposure to high fat diet early in life impacts colitis severity in adult mice

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Background: Epidemiological data report an association between obesity and inflammatory bowel disease (IBD). Likewise, animal models demonstrate that maternal high-fat diet (HFD) and maternal obesity increase susceptibility to IBD in the offsprings. However, underlying cellular and molecular mechanisms remain enigmatic. We aim to determine how exposure to HFD early in life impact the intestinal immunity and increase the susceptibility to develop IBD at adult age.
Methods: The impact of HFD on immune system response was assessed during suckling, weaning or adulthood period. Dextran sodium sulphate (DSS)-induced colitis was employed as experimental model of IBD. The differential response to DSS in mice fed HFD treated or not with cocktail of antibiotics until 2, 4, 6, or 12 weeks was compared with mice fed normal chow.
Results: Exposure to HFD early in life lead to an increase, during weaning, in intestinal permeability, expression of pro-inflammatory cytokines and hydrogen sulphide production by the microbiota. In this context, intestinal permeability, cytokine expression and hydrogen sulphide engaged in a mutual positive feedback that imprinted increased susceptibility to colitis in the adult. This pathological imprinting was prevented by the neutralisation of TNF-α and IFN-γ, or the production of hydrogen sulphide, or by normalisation of intestinal permeability or by antibiotics treatment during weaning.
Conclusions: As the human population is increasingly hygienic and exposed to HFD, normalisation of diet and complementation with key bacteria may become effective strategies to prevent, early in life, the development of IBD later in life.

P091

Increased paracellular permeability in colonic biopsies from patients with ulcerative colitis in remission compared with patients with irritable bowel syndrome

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Background: Ulcerative colitis (UC) and irritable bowel syndrome (IBS) are two chronic intestinal disorders where the pathophysiology is incompletely understood. Unlike IBS, UC goes with inflammation during active disease. Barrier dysfunction is well recognised as an important pathogenic factor in UC, and an impaired barrier function has become evident also in IBS. The aim of this study was to compare differences and similarities in epithelial barrier function between UC patients in remission, IBS patients and healthy controls (HCs).
Methods: Colonic biopsies were collected from 13 patients with UC in remission, 15 patients with IBS-mixed (Rome III) with moderate to severe symptoms (median IBS-SSS score 343 (range 167–462), and 15 HCs. UC patients had recently been treated for relapse and biopsies were taken from earlier inflamed areas but all patients had a macroscopically healed mucosa. IBS patients had no anti-inflammatory medication while UC patients had the following maintenance treatment: 5-ASA (n = 10), Remicade (n = 1) and azathioprine (n = 3). Biopsies were mounted in Ussing chambers directly after colonoscopy to measure paracellular permeability to 51chromium (Cr)-EDTA. Serosal samples were collected over time and permeability to 51Cr-EDTA was measured by γ-counting. In addition, biopsies were fixed in 4% PFA directly after dissection and further analysed for mast cells by tryptase immunofluorescence staining. Plasma was collected for measurements of TNF-levels by ELISA.
Results: Ussing chamber experiments revealed an increased 51Cr-EDTA permeability in both UC (2.18 ± 0.28, cm/s $\times 10^{-6}$, $p < 0.0005$) and IBS (1.24 ± 0.13, $p < 0.05$) compared with HCs (0.89 ± 0.1). Paracellular permeability was higher in UC compared with IBS, $p < 0.005$. Moreover, there were more mucosal mast cells present in the colon of UC (144.7 ± 19.2, cells/mm^2) and IBS (132.1 ± 12.7) compared with HCs (79.0 ± 12.2), $p < 0.05$. ELISA revealed higher TNF-levels in plasma of UC (8.93 ± 0.34, pg/ml) compared with both IBS (6.18 ± 0.54) and HCs (5.5 ± 0.48), $p < 0.0005$. Results were presented as mean ± SEM and medications had no significant effect on the results.
Conclusions: The present results contribute to a better understanding of colonic paracellular permeability in patients with UC and IBS. Our findings indicate a more permeable mucosa in both UC patients in remission and IBS patients with moderate to severe disease compared with HCs. Interestingly, the UC patients, even during remission, possess a leakier barrier compared with the IBS patients. The increased TNF-levels in plasma of UC probably refers to the underlying inflammation, however, the leakier barrier in UC compared with IBS seems to be independent on mast cell numbers.

P092

Circulating classical monocytes and intestinal macrophages exhibit reduced response to IL-10 in IBD

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Background: Mice in which the IL-10 receptor (IL-10R) is knocked out in macrophages (Mφs) alone develop bacterially driven colitis, demonstrating that IL-10 mediated control of these cells is essential to prevent intestinal inflammation. Humans who have loss-of-function IL-10R mutations develop severe early-onset IBD; these individuals may represent the end of a spectrum in which suboptimal control of Mφs by IL-10 leads to gut inflammation. Our aim was to investigate whether monocytes and monocyte-derived intestinal Mφs from adult-onset IBD patients exhibit a diminished response to IL-10.
Methods: Blood monocyte subsets (CD14++CD16– classical; CD14++CD16+ intermediate; CD14+CD16++ non-classical) and monocyte-derived intestinal Mφs in IBD patients and controls were identified by flow cytometry. Inhibition of LPS-induced TNFα production by IL-10 was measured by intracellular cytokine staining.
Results: LPS-induced TNFα production by classical monocytes (78 ± 4.46% TNFα+) was significantly ($p < 0.001$) inhibited by

IL-10 in healthy controls. A similar frequency (89 ± 2.39%) of intermediate monocytes produced TNFα. However, compared with classical monocytes, this response was significantly (p = 0.009) less well controlled by IL-10 despite higher IL-10R expression and similar IL-10-induced STAT3 phosphorylation. Fewer LPS-stimulated non-classical monocytes produced TNFα (33 ± 6.24%; p < 0.001), which was poorly inhibited by IL-10 due to poor IL-10-induced STAT3 phosphorylation as a consequence of low STAT3 availability. IL-10 was significantly less effective at inhibiting TNFα production by classical monocytes from IBD patients than from controls (p = 0.026) (Figure 1), despite increased expression of IL-10Rα and IL-10-induced STAT3 phosphorylation. The implications of a suboptimal response to IL-10 in classical monocytes was investigated in CD14+ monocyte-derived Mφs in the intestine. Two populations of CD45+HLA-DRhi cells were identified based on CD14 expression: CD14hi (P1) and CD14lo (P2). Both populations spontaneously produced TNFα, which was enhanced with LPS stimulation. Inhibition of LPS-induced TNFα by IL-10 was reduced in IBD patients compared with controls.

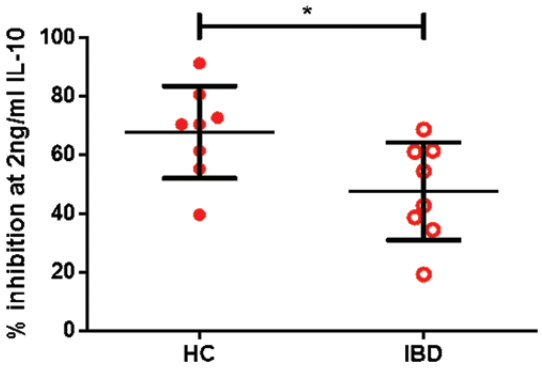

Figure 1. Inhibition of LPS-induced TNFα production in classical monocyte in health and IBD.

Conclusions: TNFα production by intermediate and non-classical monocytes is poorly controlled by IL-10 and these populations may contribute to inflammation in the IL-10-rich intestine. A lower responsive to IL-10 observed in both classical monocytes and monocyte-derived intestinal Mφs from IBD patients and may contribute to inflammation.

P093

CD4 T-cell transcriptome analysis at baseline predicts clinical remission to anti-TNF agents in ulcerative colitis (UC)

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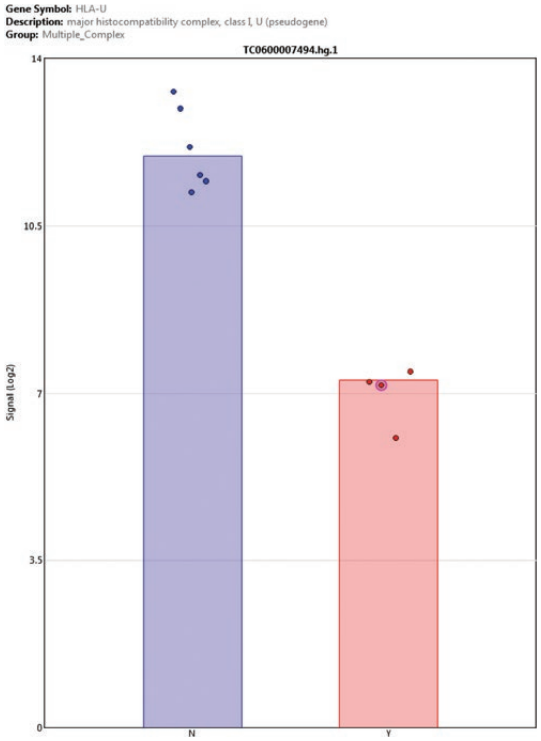
Background: Anti-tumour necrosis factor (TNF) agents are used to treat UC but response is variable. Apart from concurrent immunomodulatory therapy and there are no clear predictors of efficacy. Analysis of transcriptome from peripheral blood CD4 and CD8 T cells (1) has been shown to predict disease outcome in IBD but this strategy has not been tested to predict response to biological therapy. We investigated the utility of baseline CD4 and CD8 transcriptome in predicting response to anti-TNF agents in UC.

Methods: Patients who were commenced on any anti-TNF therapy for ambulant UC were included in this single-centre cohort study. Clinical response and remission was defined using full or partial Mayo score at Week 14. RNA was extracted from peripheral blood CD-4 and CD-8 populations and subjected to transcriptome analysis using human Clariom D analysis. Transcriptome Analysis Console (TAC) 4.0 from ThermoFisher Scientific was used to analyse Expression Array feature intensity (CEL) files. The analysis was carried out with the Clariom_D_Human NetAffx Library. Statistical analysis to detect differential expressed genes was carried out with default settings of TAC, except that the use of FDR p-values was set from false to true.

Results: Ten patients with UC with a median age of 35 (range 19–69) and median Mayo score of 8 (range 2–12) were included. Three (30%) had pancolitis and 6 (60%) of patients were on concomitant immunomodulators. At Week 14, six (60%) and 4 (40%) patients achieved clinical response and remission, respectively. Of the 135 750 genes tested, differential expression was noted in over 900 genes between responders and non-responders at a p-value of <0.05. However, there was only one differentially expressed gene in the CD4 cell population in patients who achieved clinical remission with an FDR p-value < 0.05. There was a 25.87-fold higher expression of the major histocompatibility complex, class I, U (pseudogene) in patients who failed to achieve remission.



Using a cut-off of 10 fold expression of MHC class I U predicted lack of clinical remission with high sensitivity and specificity (>90%, p < 0.05).

Conclusions: CD4 transcriptome analysis at baseline identified differentially expressed genes in patients with lack of clinical remission. Specifically, MHC class I U pseudogene at baseline strongly coorelated with remission status at end of induction therapy. This has potential utility as a novel non-invasive biomarker of resposne

to anti-TNF therapy in UC. Our findings require further validation in a larger cohort.

Reference

1. Lee JC, Lyons PA, McKinney EF, *et al*. Gene expression profiling of CD8+ T cells predicts prognosis in patients with Crohn's disease and ulcerative colitis. *J Clin Invest* 2011;121:4170–9.

P094

Polyphenolic extract from Chilean berry attenuates intestinal damage and improves clinical indicators in an animal model of Crohn's disease

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Background: Crohn's disease (CD) is an inflammatory bowel disease (IBD), whose pathogenesis and aetiology remains unclear. Trinitrobenzenesulfonic acid (TNBS)-induced colitis is a commonly utilised animal model because it shares features of human CD. Polyphenols have been studied widely by their anti-inflammatory, antioxidant and immunomodulatory properties. Chilean berry Aristotelia chilensis (*ACh*) belongs to the 'super fruit' family due to its high content of phenolic antioxidants. Our objective was to investigate the clinical and histopathological impact of *ACh* extract on TNBS-induced colitis.

Methods: Male Balb/c mice of 8 months old were used for CD induction, administrating via intracolonic 125 mg/kg of TNBS with 50% ethanol (EtOH). Control group received only 50% ethanol. Ach extract was administered by orogastric tube (500 mg/kg/day) for 1 week prior to the induction of disease (Preventive group) and 4 days after TNBS administration (Treatment group).

Results: TNBS treated mice exhibited significantly body weight loss compared with the Control group (EtOH). The administration of *ACh* extract significantly improved the body weight in Preventive and Treatment groups (Figure 1). For the histopathological analysis, we used the whole colon in the same slide (Figure 2). Colonic tissue of the different groups showed colon shortening as a marker of tissue inflammation (Figure 3). Microscopically, we observed transmural inflammation with cell infiltration, ulcerations and loss of goblet cells in the TNBS group. *ACh* extract largely restored the normal histological structure of the colonic mucosa and submucosa (Figure 4).

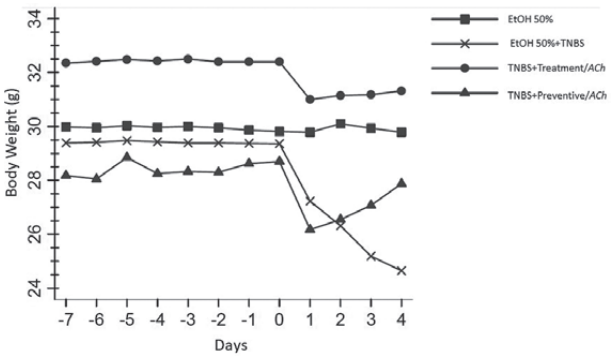

Figure 1. Effect of ACh extract on body weight.

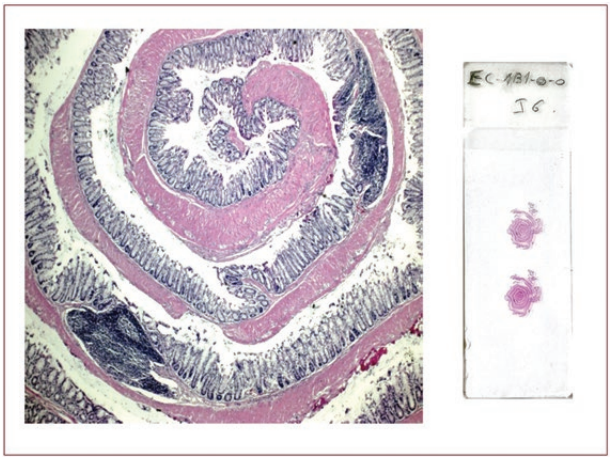

Figure 2. Rolled colon for the microscopic evaluation of the whole organ. H&E, 4×.

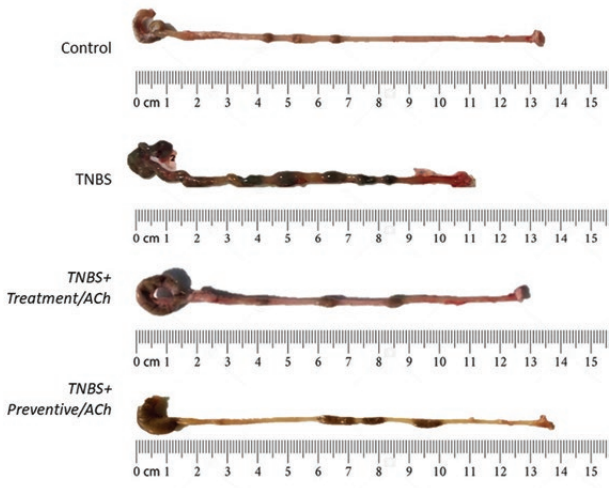

Figure 3. Ach extract prevents shortening of large intestine.

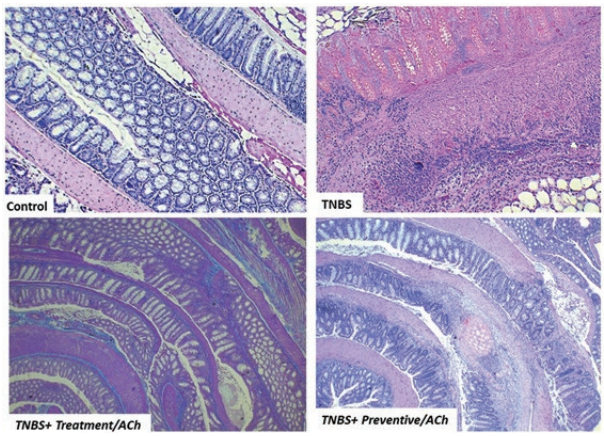

Figure 4. Microscopic evaluation of colonic tissue.

Conclusions: This animal model shows the progress of a transmural inflammation with tissue damage that resembles the development of human CD. The administration of polyphenolic *ACh* extract may exert protective effects and therapeutic against TNBS-induced colitis.

P095

Association between tissue oncostatin M expression and infliximab response in corticosteroid refractory acute severe ulcerative colitis

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Background: Infliximab (IFX) is a rescue therapy for corticosteroid refractory acute severe ulcerative colitis (ASUC). A significant proportion of ASUC patients fail to respond to IFX or require accelerated dosing. Oncostatin M (OSM) is a member of the gp130 cytokine family this includes IL-6, LIF, IL-11, Cardiotrophin -1. It is receptor is a member of JAK STAT pathway. It is expressed in macrophages, monocytes, T cells and dendritic cells and is a marker on inflammation. High pre-treatment expression of the cytokine oncostatinM (OSM) has been associated with anti-TNF therapy failure. We aimed to evaluate whether OSM had utility as a tissue biomarker of IFX response in a cohort of patients with ASUC.
Methods: A colonic formalin-fixed paraffin-embedded (FFPE) specimen from a patient who had colectomy for ASUC was used to optimise anti-OSM antibody for immunohistochemistry and determine staining pattern is severely inflamed tissue in patients refractory to IFX treatment. Patients attending St James's Hospital with ASUC who received rescue IFX for IV corticosteroid refractory disease were selected for inclusion. Included patients had an endoscopic assessment prior to IFX initiation. Colonic tissue slides from biopsies collected during this procedure were retrieved. Immunohistochemistry for OSM was performed on these FFPE slides and scoring performed to quantify epithelial and stromal immunostaining by two blinded investigators. The association between OSM immunostaining and colectomy and requirement for accelerated IFX dosing was assessed. p-values <0.05 were considered significant
Results: In total, 21 patients were included [median age 38.3 years (21.1–28.8), median endoscopic Mayo score 3(2–3). Median follow-up 47.2 weeks (0.6–117.1). Sixty-five per cent received standard IFX induction. 7/21 (33%) required colectomy. There was no association between epithelial or stromal OSM staining and requirement for colectomy or accelerated dosing($p > 0.6$ for all comparisons). Neither epithelial nor stromal OSM staining were associated with time to colectomy, $p = 0.99$ and 0.44, respectively.
Conclusions: Tissue OSM expression was not associated with IFX response or requirement for accelerated IFX dosing in a small cohort of corticosteroid refractory ASUC patients. Further studies are required to definitively assess the utility of this biomarker in ASUC.

P096

The anti-inflammatory effects of niclosamide on cytokines produced by PBMCs derived from IBD patients

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Background: Even after considerable progress in IBD therapies, at least half of the treated patients fail to reach remission. Monoclonal antibody therapies are associated with immunogenicity. Niclosamide is a salicylide which has been used as an anti-helminthic drug and minimally absorbed from the gastrointestinal tract. It has been shown to have anti-inflammatory properties and is currently repurposed for use in head and neck cancer. We aimed to study its effects on immune cells *ex vivo* and potential for repurposing in IBD.
Methods: Peripheral blood mononuclear cells (PBMCs) from the bloods of 6 IBD patients were cultured with or without stimulation with 0.5 μg/ml anti-CD3 (clone OKT3). Niclosamide was prepared in dimethyl sulfoxide (DMSO) and diluted into culture medium at 0.25 μM and 0.5 μM. Effect of niclosamide upon cell survival and T-cell activation was measured at 1 day by flow cytometry analysis of activation markers CD69, CD25, and CTLA-4. At 6 days, cells were re-stimulated with PMA and ionomycin in the presence of Brefeldin A and expression of cytokines IL-17A, TNFα, IFNγ and IL-2 measured by flow cytometry. Data were analysed by Flowjo and significance tested by Friedman Analysis.
Results: Niclosamide was not toxic to cells at the concentrations tested and did not alter the frequencies of CD4+ and CD8+ T cells, CD19+ B cells or CD14+ monocytes in unstimulated cells. However, niclosamide reduced CD4 and CD8 T-cell activation indicated by a significant decrease in the frequency of CD4+ cells expressing CTLA-4 and CD25 and CD69 and CD25 by CD8+ cells (Figure 1A). This resulted in a significant decrease in T-cell number at 6 days ($p = 0.0120$). Furthermore, it significantly inhibited expression of pro-inflammatory cytokines IL-17, IFNγ, TNFα and IL-2 by CD4 and CD8+ T cells (Figure 1B).
Conclusions: Our results suggest a strong anti-inflammatory action of niclosamide when tested on T cells from IBD patients with no significant cell toxicity seen at concentrations used. The significant reduction in cytokine levels known to be involved in IBD make it a potential drug that could be used for treatment of IBD in the future.

P097

Intestinal barrier dysfunction in association with fibrosis during experimental acute and chronic colitis in mice

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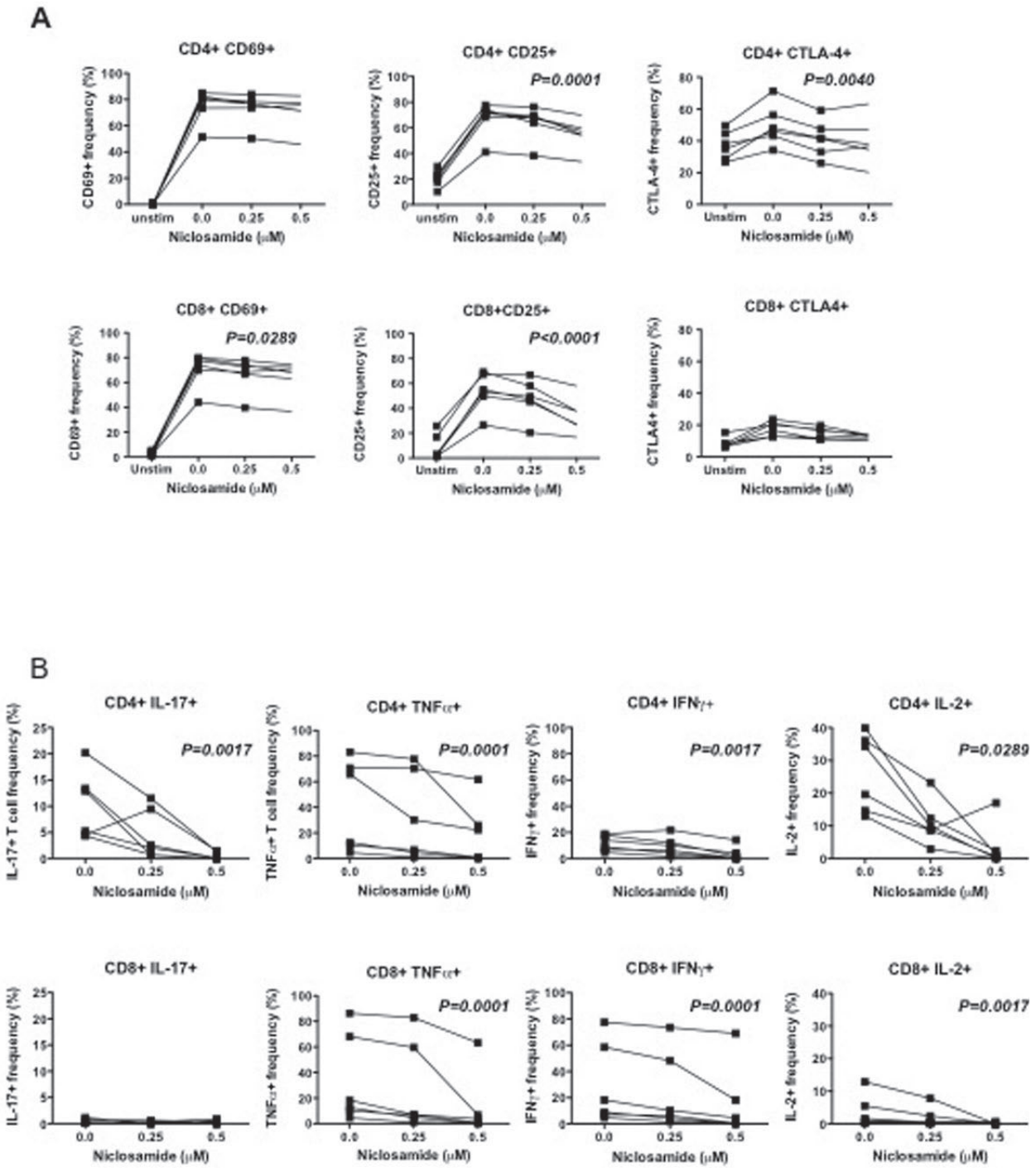
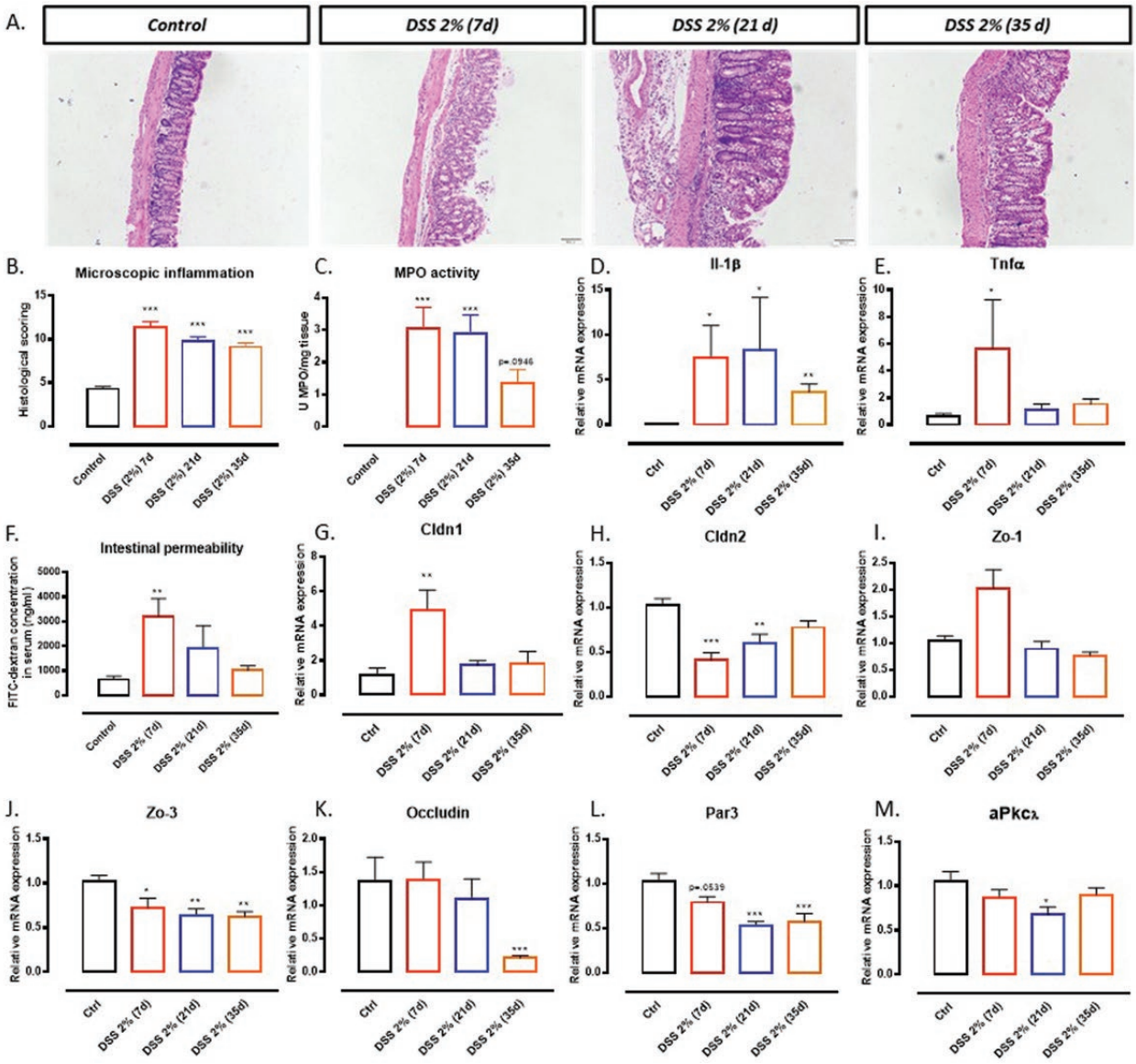
Background: Intestinal barrier dysfunction is a significant contributor to the pathophysiology of Inflammatory bowel diseases (IBD). Furthermore, chronic inflammation and barrier dysfunction may result in the mucosal and submucosal deposition of the extracellular matrix, which progressively leads to structural fibrosis, a major complication in IBD. Here, we aimed at investigating intestinal inflammation, barrier function and the development of fibrosis using the dextran sodium sulphate (DSS) colitis mouse model.
Methods: Seven-week old C57BL6/J mice were treated with 3 subsequent cycles of 2% DSS in their drinking water for 7 days followed by a recovery phase of 7 days with normal drinking water to induce acute (cycle 1) and chronic colitis (cycle 2 and 3). Control animals



Abstract P096 – Effect of niclosamide on T cells and cytokines.

received only drinking water. Disease activity was daily monitored. At the end of each DSS treatment (Day 7, 21 and 35), mice were used for compliance measurements to investigate the viscoelastic properties of the colon. Thereafter, at euthanasia, colonic tissue was collected to investigate inflammation (H&E), fibrosis (Masson's trichrome), MPO activity and expression of tight junctions (Cldn1, Cldn2, Ocln, Cdh1, Zo-1, Zo-3), cell polarity proteins (Par3-Par6-aPKC, Crb3) and cytokines (Tnf-α, Il-1β, Il-6, Il-10, Il-22). Intestinal permeability was determined via oral gavage (4 h before euthanasia) of 4 kDa FITC-dextran, followed by measuring the fluorescence in the blood.

Results: Acute colitis in mice was correlated with marked intestinal inflammation (Figure 1A-C), increased expression of several pro-inflammatory cytokines (Tnf-α, Il-1β and Il-22; Figure 1D-E), increased intestinal permeability (Figure 1F), aberrant expression of Cldn1, Cldn2, Zo-3 and Par3 (Figure 1G-M) and a remarkable



Abstract P097 – Figure 1. (A) Representative H&E stained colon sections of control and DSS-treated mice. (B) Scoring of microscopic inflammation which was based on immune cell infiltration, goblet cell loss and epithelial damage. (C) MPO measurement to analyse colonic neutrophil activation. (D-E) Colonic mRNA expression of Il-Ib and Tnf-α cytokines analysed by qPCR. (F) FITC-dextran intestinal permeability assay. (G–M) Colonic mRNA expression of the polarity protein genes Par3 and aPkcλ and tight junction protein genes Cldnl and 2, Zo-1 and -3 and Occludin analysed by qPCR. One-way ANOVA $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .401$ vs. control (Ctrl) (n = 3–10 mice/group)

decrease in colonic compliance at lower balloon distension volumes (<80 µl, $p < 0.05$). Progression towards chronic colitis resulted in intestinal inflammation (Figure 1A–C) with marked bowel wall thickening, reduced colonic compliance at higher distension volumes (>120 µl, $p < 0.05$) and fibrotic lesions. Although intestinal permeability was not significantly altered anymore at Day 21 and 35 (Figure 1F), barrier mediators, such as Cldn2, Zo-3 and Par3 (Figure 1G–M), were still changed.

Conclusions: Colitis progression investigated in the DSS mouse model was associated with intestinal inflammation and barrier dysfunction in the acute phase and the additional development of fibrosis in the chronic phase. The underlying mechanisms involved in barrier dysfunction and existence of fibrosis, require further investigation.

P098

Role of serum lysol oxidase like 2 in Crohn's disease and modulation to biological treatment.

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Background: Lysyl oxidase-like 2 (LOXL-2) expression at the level of the mucosa is elevated in diseases with fibrotic component, and also, has been involved in the biogenesis of connective tissue after the activation of the signalling pathway of TGF β-1. The aim of our

study is the evaluation of serum levels of LOXL-2 in patients with Crohn's disease (CD) and assess the variability of the levels after the start of biological treatments.
Methods: We performed a cross-sectional study to determine the serum levels of LOXL-2 by enzyme-linked immunosorbent assay (ELISA) in patients with CD defined according to the European Crohn's and Colitis Organisation (ECCO). For this, 24 patients with Crohn's disease and 24 healthy controls were analysed matched by age and sex. The baseline characteristics of the patients were collected and biochemical parameters were also measured at baseline and 6 months after the start of the biological therapy. The patients were classified according to the response in responders and no responders.
Results: LOXL 2 levels were higher in patients with CD (72.81 pg/ml (SD 24.65)) compared with healthy controls (31.40 pg/ml (SD 19.39)) in a significant way (p = 0 0.0001). No significant differences were observed related to smoking, age or years of disease evolution. Higher levels were observed in those who required surgery prior to inclusion in the study with regards to those without surgery [(80.53 pg/ml (SD 22.66) vs. 60.53 pg/ml (SD 22.23) (p = 0.02]. Regarding the characteristics of Crohn's disease, no significant differences were found in LOXL-2 levels in relation to behaviour or location, although a tendency of higher levels of LOXL-2 was observed in patients with intestinal involvement respect to colonic involvement. (78.92 pg/ml (SD 24.83) vs. 55.19 pg/ml (SD 13.14)). As found in those patients with penetrating or stenosing behaviour with regards to inflammatory (78.92 pg/ml (SD 32.08) vs. 60.53 pg/ml (SD 20.03)). No differences were observed in the levels according to the response 6 months after starting biological treatment. A positive correlation was observed between albumin and haemoglobin levels with LOXL2 levels (r = 0.45, r = 0.54, p < 0.05) while a negative correlation was observed with the Harvey Index (r = –0.51, p = <0.05). A positive correlation was observed with faecal calprotectin at 6 months after inclusion (r = 0.58, p < 0.05)
Conclusions: Serum levels of LOXL2 were elevated in patients with Crohn's disease and were significantly higher than the healthy control group. Patients who required previous surgery showed higher levels than those without surgery. More studies are needed to corroborate these results with a larger sample size to know the real involvement of LOXL2 in CD.

P099

Patients with ulcerative colitis show increased Treg number in peripheral blood after 1 year of anti-TNF therapy

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Background: Tregs are cells with well-known immunosuppressive functions realised by contact-dependent mechanisms (expression of CTLA-4 and PD-L1) and cytokine secretion (TGFβ and IL-10). These cells are often found on the bowel mucosa, where they suppress excessive T-cell mediated immune reactions. The aim of our study was to investigate the dynamics of changes in peripheral blood of Treg population in patients with ulcerative colitis (UC) before and after anti-TNF therapy.
Methods: Eight patients on anti-TNF therapy and 15 healthy controls are enrolled in the study. Using flow cytometry the percentage of Tregs was detected before and after 1 year on anti-TNF therapy.
Results: Our results demonstrate that before anti-TNF therapy the mean percentage of Tregs in UC patients is lower than in healthy persons. In six patients after 1 year of anti-TNF treatment the number of Tregs increased reaching that of the healthy persons. In the same patients the activity of the disease (Mayo score) strongly decrease. Two of the patients are non-responders. They did not show up-regulation of Tregs as well as clinical improvement.
Conclusions: Our results demonstrate that anti-TNFα therapy may lead to a significant rise in the number of peripheral blood Tregs in UC patients responding to this therapy.

Clinical: Diagnosis and outcome

P100

Real-world data: the incidence, diagnosis, and management outcomes of patients with immunotherapy-related colitis in two tertiary centres

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Background: Checkpoint inhibitors are a novel anti-cancer therapy that are standard of care in metastatic melanoma, non-small cell lung and renal cancer. CTLA-4 inhibitors (eg, Ipilimumab) and PD-1 inhibitors (Nivolumab, Pembrolizumab) can be used separately or in combination for melanoma, whereas single PD-1 inhibitors are the norm for others. Their immune inhibition is non-specific, leading to a number of immune-related adverse events (irAEs), including colitis, hepatitis, and pancreatitis. Combination therapy is known to cause more irAEs than single-agent PD-1 inhibition. There are limited real-world clinical data describing the incidence and management of these GI irAEs.
Methods: Retrospective two–centre (John Radcliffe Hospital in Oxford and Clatterbridge Cancer Centre in Liverpool) review. Melanoma, renal and lung cancer patients receiving Ipilimumab ± Nivolumab ± Pembrolizumab between December 2011 and June 2018 were identified from the oncology prescribing database. The electronic patient record (EPR) was used to determine the incidence of GI side effects. Investigations, treatment, and outcome data were collated.
Results: Of 1125 patients who had immunotherapy, 130 developed colitis (11.6%). In our cohort: (1) Median age was 66 (Males-Median 67, range 24–88; females: 64.5 range 27–86); (2) 60% were male; (3) 63.0% patients required admission (75% combination); (4) median length of admission is 4–7 days (6 combination); (5) presence of erosions or ulcers at endoscopy tended to predict a more severe outcome; (6) faecal calprotectin in steroid refractory cases was

>300 in all patients where measured; (7) high proportion of patients receiving IV methylprednisolone 43.8% (66.7% combination); (8) significant proportion of patients requiring infliximab 21.5% (35% in combination therapy); (9) of those requiring infliximab, 64.3% (18/28) were male; (10) two patients with refractoriness to steroids and infliximab had vedolizumab; (11) colectomy rate 2.3% (3/130). Complete management and outcome data will be presented.
Conclusions: Immunotherapy-related colitis is one of the more severe adverse events related to immunotherapy and a significant proportion of patients will require hospital admission. Steroid refractoriness is a significant problem and studies are required to elucidate optimum treatment regimens and escalation strategies. This has implications for standardisation of care and healthcare provision on already stretched budgets. Complete management and outcome data will be presented.

P101

Simple five-point classification of MR enterocolonography for Crohn's disease based on enteroscopic findings

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Background: Crohn's disease (CD) is a chronic progressive inflammatory bowel disease. Assessing the severity and extent of the disease is critical to determine appropriate therapeutic strategies in patients with CD. Magnetic resonance (MR) enterography can assess both intestinal walls and extraintestinal structures without radiation exposure and anaesthesia, which makes it appropriate for repeated evaluation in CD patients. We developed novel MR enterocolonography (MREC) for simultaneously evaluating large and small intesntinal lesions of CD. The aim of this study was to establish the efficacy of the simplified 5-point MREC classification for assessing CD activity, comparing to the validated MR score of magnetic resonance index of activity (MaRIA) and endoscopic findings.
Methods: A total of 120 patients (70 for derivation cohort and 50 for validation cohort) with CD were enrolled and undergone MREC and ileocolonoscopy or balloon-assisted enteroscopy (BAE). MREC results were evaluated for each bowel segment; rectum, sigmoid, descending, transverse, ascending colon, terminal, proximal ileum, and jejunum, by one observer in the derivation phase, and independently by three observers in the validation phase, using the simplified 5-point MREC (sMREC) classification lexicon and MaRIA. Areas under the receiver-operating characteristic curves (AUCs) were obtained to assess the accuracy of discriminating deep ulcers. Inter-observer reproducibility was assessed using weighted Kappa coefficients.
Results: The AUCs of sMREC classification were 89.0% in the derivation phase and 88.5, 81.0, and 77.3% for three observers in the validation phase. The AUCs of MREC classification were statistically non-inferior to those of MaRIA ($p < 0.001$). The cross-validation accuracy was 81.9% in the derivation and 81.5% in the validation phase. sMREC classification showed enough reproducibility.
Conclusions: In clinical practice, scoring systems should be simple and provide appropriate levels of accuracy and reproducibility. sMREC classification met these requirements, and was demonstrated to be useful for evaluating CD activity in the large and small intestine.

P102

Subclinical atherosclerosis assessed by coronary artery calcium score in patients with Crohn's disease

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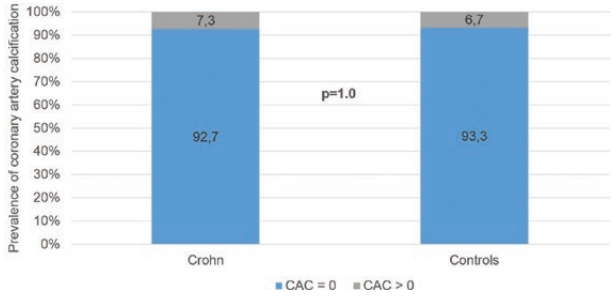
Background: Several immune-mediated diseases such as rheumatoid arthritis, systemic lupus erythematosus and psoriasis are associated with an increased risk of cardiovascular disease (CVD).[1] However, there are conflicting data as to whether inflammatory bowel diseases (IBD) increase risk for CVD.[2] We aimed to evaluate coronary artery calcium (CAC) score as an accurate predictor of cardiovascular event in patients with Crohn's disease.
Methods: We investigated 150 patients with Crohn's disease (mean age, 43.4 ± 5.9 years) and 75 age- and sex-matched controls (mean age, 43.6 ± 5.6 years) without prior known CVD and traditional risk factors for atherosclerosis such as hypertension, dyslipidemia, diabetes, smoking, obesity, and family history of coronary disease. All participants underwent a computed tomography for the measurement of CAC and the calcification extent was measured by means of the Agatston score. CAC was considered a qualitative variable (CAC = 0 and CAC > 0).
Results: The two groups were similar in respect to age, sex and Framingham risk score. Nevertheless, there were differences in body mass index, systolic blood pressure and lipid profile, even though all these parameters were within normal range in both groups. Serum C reactive protein and albumin differed between groups.

Table 1. General characteristics of patients with Crohn and control subjects

	Patients (n = 150)	Controls (n = 75)	p-value
Age (years)	43.4 ± 5.9	43.6 ± 5.6	0.72
Male	78 (52%)	39 (52%)	1.00
Body mass index (kg/m^2)	23 ± 3	24 ± 2	0.007
Systolic blood pressure (mmHg)	115 ± 14	119 ± 13	0.05
C reactive protein (mg/l)	6.24 ± 11.0	1.99 ± 3.17	0.0003
Low-density lipoprotein (mg/dl)	88 ± 33	107 ± 26	<0.001
High-density lipoprotein (mg/dl)	53 ± 14	57 ± 15	0.05
Triglycerides (mg/dl)	103 ± 38	97 ± 40	0.19
Framingham risk score (%)	1.6 ± 1.6	1.7 ± 1.4	0.38

CAC score > 0 was observed in 11 of 150 patients and in 5 of 75 control subjects with no significant difference between groups (p = 1.0).

Abstract P102 – Figure 1. Prevalence of coronary artery calcification (CAC) among patients with Crohn's disease and control subjects



Among patients with Crohn, disease activity scores, years since diagnosis and the use of immunomodulators and/or biologic therapy were similar in those with and without coronary artery calcification. Those with calcification were older (p = 0.022) and more likely to be male (p = 0.058).

Abstract P102 – Table 2. Characteristics of patients with Crohn according to the CAC score

	CAC = 0 (n = 139)	CAC > 0 (n = 11)	p-value
Age (years)	43.1 ± 5.9	48.1 ± 5.2	0.022
Male	69 (50%)	9 (82%)	0.058
Duration of disease (years)	15 ± 6	17 ± 5	0.13
C reactive protein (mg/l)	6.1 ± 11.1	6.9 ± 10.8	0.80
CDAI* (mean)	129 ± 96	102 ± 75	0.39
Harvey–Bradshaw (mean)	3 ± 3	2 ± 2	0.80
Under Azathioprine or Methotrexate therapy	94 (68%)	7 (64%)	0.74
Under anti-TNF therapy	76 (55%)	7 (64%)	0.74

*Crohn's disease activity index.

Conclusions: The current findings show that patients with Crohn's disease without traditional cardiovascular risk factors do not exhibit higher coronary artery calcification. Cardiovascular risk is still a conflicting issue in IBD and further studies are needed to clarify the relationship between CVD and IBD.

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P103

Degradation and formation of type III, IV and V collagen are associated with disease activity, disease severity and disease extension in patients with ulcerative colitis

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Background: Ulcerative colitis (UC) is an idiopathic chronic inflammatory bowel disease, where increased matrix metalloproteinases are the major contributor to the intestinal tissue remodelling UC. The intestinal basement membrane (main constituent is type IV collagen) is directly positioned underneath the epithelial cells. The supportive interstitial matrix (main constituent are type I, III and V collagens) is mainly produced by fibroblasts. Both matrices are important for intestinal health and are highly affected in UC. We investigated serum biomarkers of collagen degradation and formation of the respective extracellular matrix (ECM) compartments and their association with disease activity, severity and extension in UC.
Methods: In total, 29 UC patients and 29 healthy donors (HD) were included. A combination of the partial mayo score and biochemical activity was used to determine disease activity (p_{Mayo} > 1 and CRP >5). Disease severity and extension was assessed by Montreal classification. Biomarkers of type III collagen degradation (C3M) and formation (PRO-C3), type IV collagen degradation (C4M) and formation (PRO-C4), type V collagen formation (PRO-C5) and C-reactive protein (CRP) were measured in serum by ELISA. One-way ANOVA (Tukey's multiple comparisons test), and spearman rho correlations were applied for statistical analyses.
Results: C4M was significantly elevated in active UC compared with UC in remission (p < 0.05) and HD (p < 0.001), and PRO-C4 was also significantly elevated in active UC compared with UC in remission (p < 0.01) and HD (p < 0.001). C3M was significantly elevated in active UC compared with UC in remission (p < 0.05) and HD (p < 0.05), whereas PRO-C3 was significantly elevated in active UC and UC in remission compared with HD (p < 0.001). PRO-C5 was elevated in active UC compared with HD (p < 0.01).
In addition, C3M (r = 56, p < 0.01), C4M (r = 0.41, p < 0.05), PRO-C4 (r = 58, p < 0.001), PRO-C5 (r = 49, p < 0.01), and CRP (r = 47, p < 0.01) correlated with disease severity, and PRO-C4 (r = 48, p < 0.01), PRO-C5 (r = 0.38, p < 0.05), and CRP (r = 45, p < 0.01) correlated with disease extension.
Conclusions: The biomarkers C3M and C4M were associated with disease activity in UC and disease severity in addition to PRO-C4 and PRO-C5. PRO-C4 and PRO-C5 also correlated with disease extension. These data demonstrated that ECM remodelling of the intestinal basement membrane and interstitial matrix are associated with disease status and progression, which can be used to optimise treatment strategies for UC patients.

P104

Monitoring inflammatory activity in Crohn's disease: simple ultrasonographic score vs. CEUS which one to use?

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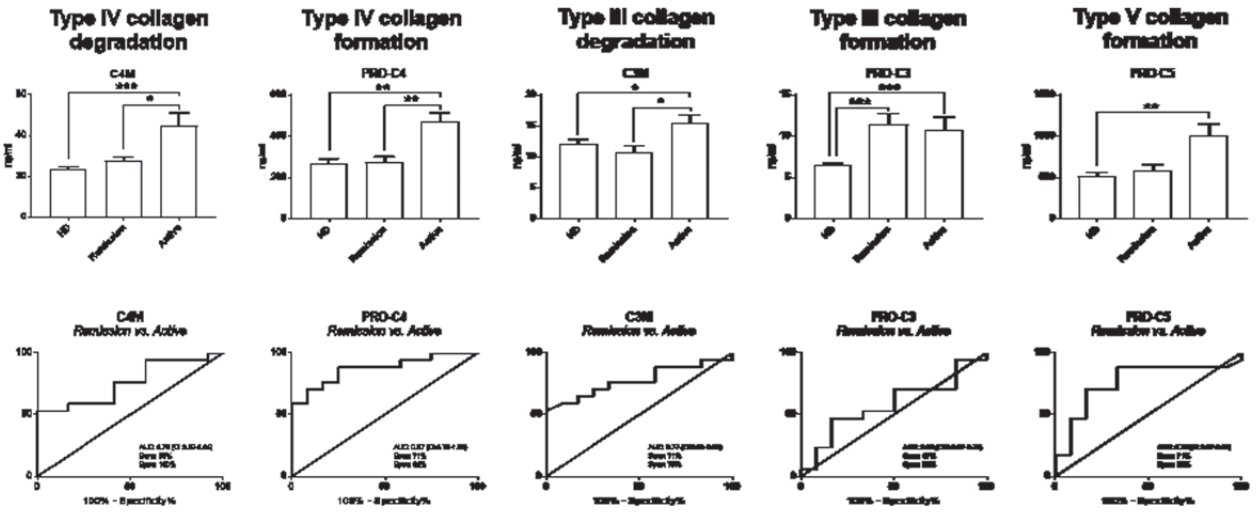
Background: Gastrointestinal Ultrasound (GIUS) is increasingly being used in Crohn's disease (CD) as an essential tool in monitoring inflammatory activity, given its low cost and the absence of ionising radiation exposure. In 2017 emerged a simple ultrasonographic score (SUS) that allows the accurate non-invasive assessment of



Abstract P103 – Figure 1. The figure depict type III, IV, and V collagen remodelling in UC, and differences between healthy donors, UC in remission and active UC.

inflammatory activity based on two parameters: bowel wall thickness (bwt) and colour Doppler.

The aim of this study was therefore to compare the accuracy of bowel GIUS with SUS vs. Contrast Enhanced Ultrasound (CEUS) in predicting inflammatory activity in ileocolonoscopy.

Methods: All CD patients underwent a conventional GIUS directed to terminal ileum followed by a CEUS using a microbubble contrast agent (SonoVue®). GIUS examinations were performed using a Hitachi HI VISION Avius®, employing a linear abdominal transducer. Qualitative and quantitative parameters from the sonographic analysis included maximum bowel wall thickness (bwt), semi-quantitative analysis of vascularity pattern by Doppler GIUS and quantitative measurement of contrast bowel wall enhancement using CEUS (peak intensity). SUS was calculated according to the authors = (0.0563xbw1) + (2.0047xbtw2) + (3.0881xbwt3) + (1.0204xDoppler1) + (1.5460xDoppler2). Disease activity was assessed by ileocolonoscopy (reference) and patients were graded as inactive (normal or mild disease) or active (moderate or severe inflammation).

Results: Thirty known CD patients were included, 60% female with median age 33.5 (17–63) years. Regarding endoscopic disease severity, 14 (46.7%) patients presented inactive disease and 16 (53.3%) patients were classified as active disease. Median bwt was 6.1 (3–13) mm and Doppler intensity was absent in 1 patient (3.3%), mild in 7 patients (23.3%) and moderate to severe in 22 patients (73.3%). Patients presented a median SUS of 5.1 (0.1–12.4) and was not different between patients with active or inactive disease (p = 0.50) with a poor capability to predict endoscopic activity in ileoscopy (AUROC 0.6, 95% CI 0.38–0.75). Regarding CEUS, the median peak intensity was 10.9 (2.5–44) and was related with disease severity (p = 0.005) with a good capability to predict endoscopic activity in ileoscopy (AUROC 0.8, 95% CI 0.61–0.92). We found that peak intensity of 7.8 is the optimal cut-off point predicting active disease with a sensitivity of 87.5% and a specificity of 71.4%.

Conclusions: Although SUS is a validated score including bowel wall thickness and colour Doppler parameters, in our population was not capable to predict with good accuracy endoscopic activity. CEUS is an emerging technique that must be considered routinely part of the entire sonographic evaluation in CD with good diagnostic accuracy for bowel inflammation.

P105

Can patients enter the 'Standard Set' ICHOM parameters by completing electronic questionnaires?

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Background: The International Consortium for Health Outcomes Measurement (ICHOM) has created a 'Standard Set' for Inflammatory Bowel disease outcomes, but there is currently no system in place to collect these data. The ICHOM Standard Set for IBD is one of 26 ICHOM Standards in different disease areas established through a common methodology.[1]

Methods: TrueColours ulcerative colitis (TCUC) is a comprehensive real-time web-based programme that, among other things, collects ICHOM parameters. 342 patients registered with TCUC were prompted (through email) to complete the ICHOM questionnaire.

Results: 287/342 (84%) adherence rates to the ICHOM questionnaire: male 41%, distribution disease (proctitis 19%, left-sided colitis 21% and extensive colitis 30%, unsure 30%), level of education (none 5%, primary 2%, secondary 33% and tertiary 60%), smoking status (never 60%, ex-smoker 35% and current 5%). Extraintestinal manifestations included arthritis 15%, eye disease 2.4%, skin disease 1.4%, liver disease 1.4%. Hepatitis B was reported in 0.3%, previous tuberculosis in 1.4% and HIV in 0%. Over the previous 12 months, prednisolone use was reported in 22% for < 3 months and 15% for >3 months. Complications due to IBD interventions were reported in 10% (adverse reactions n = 21 (including 6 with pancreatitis), surgical complications n = 4, infection n = 4, malignancy n = 1, thrombosis n = 1, dermatological n = 2, diabetes n = 1). Complications resulting in hospitalisation occurred in n = 8 and prolonged hospitalisation (>10 days) in n = 4. Hospital admissions in the past 12 months: nil in 80%, 1 in 16%, 2 in 3%, ≥3 in 1%. The median estimated total length of stay was 5 days (IQR 6.0). Emergency Department visits in the past 12 months: nil in 78%, 1 in 13%, 2 in 7%, ≥ 3 in 2%. Colorectal cancer was reported by 2 (0.7%): neither patient was on a colorectal cancer surveillance scheme prior to this diagnosis.

Conclusions: Collecting ICHOM parameters through patient-reported electronic questionnaires is possible. Adherence rates were good at 84%. Outcomes (eg, steroid use) are revealing. Used on a larger scale, this method would allow collection of ICHOM data and audit of quality improvement at an individual centre as well as comparison between centres.

Reference

1. Kim A, Roberts C, Feagan BG, *et al.* Defining a standard set of patient-centred outcomes for inflammatory bowel disease—an international, cross-disciplinary consensus. *J Crohns Colitis* 2018;12:408–18.

P106

Successful outcome of the transitional process of inflammatory bowel disease from paediatric to adult age: a 5-year experience

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Background: The transitional process of young patients affected by inflammatory bowel disease (IBD) from pediatric to adult care is a crucial step. Our study aimed to investigate the 1-year success outcome of the transitional process of IBD patients.

Methods: From 2013 to 2018, we evaluated the transitional process of patients with Crohn's disease (CD) or ulcerative colitis (UC), from the Pediatric to the Adult IBD Center. For each patient, the following parameters 12 months before and 12 months after the transition were evaluated: body mass index (BMI), disease activity and smoker status, number of outpatient visits and the pharmacological therapy, the number of disease exacerbations, hospitalisations, and surgical interventions.

Results: We enrolled 106 patients with IBD (43 CD and 63 UC). No statistically significant difference was found between patients' BMI before and after transition. There was a significant reduction in the number of exacerbations and hospitalisations in the 12 months post-transition (pre-transition exacerbations: 0.74 ± 0.79, post-transition exacerbations: 0.35 ± 0.57, $p < 0.001$; pre-transition hospitalisations: 0.28 ± 0.44, post-transition hospitalisations: 0.1 ± 0.3, $p < 0.001$). In contrast, there was no significant difference in the number of outpatient visits (3.40 ± 1.4 vs. 3.25 ± 1.2; p = ns) and of patients undergoing surgery (0.9% vs. 1.8%, p = ns). We also found a significant difference ($p < 0.01$) in the use of nutritional therapy between the pre-transition (18.8%) and the post-transition phase (0%). Moreover, in the post-transition period there was a reduction in immunosuppressant use (methotrexate: 9% vs. 2%, $p = 0.03$; azathioprine: 36% vs. 23%, $p < 0.01$).

Conclusions: The parameters used as success indicators of the transition Programme confirm the achievement of a continuity of care from Pediatrics to adult Gastroenterology, such as the maintenance of a state of well-being, in a generally critical phase of the natural history of IBD patients.

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Value of faecal biomarkers are affected by extension of inflammation in ulcerative colitis

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Background: Faecal biomarkers are non-invasive markers of inflammation activity in patients with ulcerative colitis (UC) and reflect intestinal inflammation activity. However, whether disease extension affects the value of faecal biomarkers has not been fully investigated. In the present study, to identify the effect of disease extension on faecal biomarkers we assessed the correlation between faecal biomarkers and endoscopic activity in each inflammatory location type.

Methods: We conducted a retrospective observational study. 108 UC patients from February 2017 to March 2018 in Kyorin University hospital who underwent faecal biomarkers test within 2 months of colonoscopy were studied. Faecal calprotectin level (FC), faecal lactoferrin level (FL) and faecal immunochemical test (FIT) were measured simultaneously in the same sample. We examined the correlation between Mayo Endoscopic Subscore (MES), and faecal biomarkers in inflammatory location of Montreal classification (proctitis, left sided colitis, total colitis). Correlation was analysed using the Spearman's rank correlation index (SPSS).

Results: In all cases, all faecal biomarkers were correlated with MES (FC: $\rho = 0.645$, $p < 0.001$, FIT: $\rho = 0.627$, $p < 0.001$, FL: $\rho = 0.646$, $p < 0.001$). In proctitis, all faecal biomarkers were not correlated with MES (FC: $\rho = 0.148$, $p = 0.613$, FIT: $\rho = 0.542$, $p < 0.045$, FL: $\rho = 0.342$, $p < 0.231$). On the other hand, in left colitis and total colitis, all faecal biomarkers were correlated with MES (FC: $\rho = 0.554$, $p < 0.001$, FIT: $\rho = 0.736$, $p < 0.001$, FL: $\rho = 0.567$, $p < 0.001$ and FC: $\rho = 0.741$, $p < 0.001$, FIT: $\rho = 0.563$, $p < 0.001$, FL: $\rho = 0.713$, $p < 0.001$). The correlation coefficients of FC and FL were higher in pancolitis than in left sided colitis (Table 1).

	Proctitis	Left-sided colitis	Pancolitis	All cases
FC (μg/g)	0.148, $p = 0.613$	0.554, $p < 0.001$	0.741, $p < 0.001$	0.645, $p < 0.001$
FIT (ng/ml)	0.542, $p = 0.045$	0.736, $p < 0.001$	0.563, $p < 0.001$	0.627, $p < 0.001$
FL (μg/g)	0.342, $p = 0.231$	0.567, $p < 0.001$	0.713, $p < 0.001$	0.646, $p < 0.001$

Spearman's rank correlations between faecal biomarkers and MES by extension of inflammation.

Conclusions: Faecal biomarkers showed correlation satisfactory in overall patients, except for in proctitis patients. These results suggested that value of faecal biomarkers is affected by extension of inflammation.

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Validation of a new score for paediatric Crohn's disease on a paediatric tertiary hospital: the MINI-Index (Mucosal Inflammation Non-Invasive Index)

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Background: The incidence of paediatric Crohn's disease has increased in the last years. New non-invasive tools for the prediction of endoscopic activity have been proposed to improve the selection of patients who require an ileocolonoscopy. In 2017, Turner *et al*., developed the MINI-INDEX (Mucosal Inflammation Non-Invasive Index) as a new clinical–analytical index in paediatric patients with high correlation with the endoscopic activity assessed by SES-CD (Simplified Endoscopic Activity Score for Crohn's Disease). Our study aims to validate the Mini-Index in our paediatric Crohn's disease patients.
Methods: Retrospective cohort study of patients with Crohn's disease who underwent ileocolonoscopy between 2015 and 2017 in a paediatric tertiary hospital. We performed the endoscopic index SES-CD and the MINI INDEX, which evaluates in each patient the stool pattern, faecal calprotectin (mg/kg), C-reactive protein (mg/l) and erythrocyte sedimentation rate (mm/h), obtaining a total score index between –3 and 25.
Results: A total of 96 ileocolonoscopies performed on Crohn's disease patients were included in the study (69.8% males and 30.2% females), with an average age of 13.65 ± 2.78 years. Overall, the mean SES-CD score was 13.26 ± 9.25 and the median (IQR) of the Mini-Index was 16.5 (10). 15.6% had an SES-CD score < 3 (remission), 21.9% between 3 and 10 (mild activity) and 62.5% > 10 (moderate–severe activity). The median of the Mini-Index for each group of SES-CD was: – (7) in patients with SES-CD < 3, 14 (8) in SES-CD 3–10 and 18.5 (5) in the group of SES-CD > 10, obtaining statistically significant differences ($p < 0.001$). Furthermore, Pearson correlation was performed between the Mini-Index and SES-CD values, which was statistically significant ($p < 0.001$, $r = 0.701$). Selecting mucosal healing as an SES-CD value of <3 we performed a ROC curve for the Mini-Index obtaining an AUC of 0.985 ($p < 0.001$). In our cohort, the best cut-off point was a Mini-Index value <6 ($p < 0.001$), with a sensitivity of 100%, specificity 96%, positive predictive value 83% and negative predictive value 100%.
Conclusions: Our results confirm the Mini-Index as a useful non-invasive tool in paediatric Crohn's disease to predict the inflammatory status of the mucosa with high precision. The Mini-Index could be incorporated into the clinical practice of paediatric Crohn's disease to help us to select those patients that require an ileocolonoscopy. However, further prospective studies are needed to confirm these results.

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Analysis of the clinical, gastroscopic, and pathological features of upper gastrointestinal lesions in Crohn's disease

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Background: With the increasing incidence of Crohn's disease (CD) of the upper gastrointestinal (UGI) tract, whether gastroscopy should be routinely performed in asymptomatic adult CD patients is controversial. We aimed to assess the prevalence of UGI involvement, determine the role of gastroscopy in the diagnosis, and assess whether UGI symptoms should be used as guidelines for gastroscopy.
Methods: This cross-sectional study included consecutive patients diagnosed with CD at our centre between June 2017 and May 2018. gastroscopies and histological reviews were performed by designated endoscopists and pathologists. Ten specimens were obtained from six areas of the UGI tract (the oesophagus, gastric body, antrum and angulus, duodenal bulb, and descending duodenum). Both demographic and clinical data were collected.
Results: Among the 169 included patients, endoscopic and histological lesions suspected to be of UGI CD were found in 74 (43.79%) and 106 (62.72%) patients, respectively. Seven (4.14%) patients had non-caseating granulomas, 15 (8.88%) patients had focally enhanced gastritis, and 36 (21.3%) patients had focal active gastritis. 137 (81.1%) patients had no UGI symptoms, among these, endoscopic and/or pathological abnormalities were observed in 108 (78.8%) patients. Twenty-four (75%) patients with UGI symptoms did not have any endoscopic or histological abnormalities. In total, the rates of non-caseating granulomas, focally enhanced gastritis, and focal active inflammation were significantly higher in the asymptomatic group ($p = 0.033$). According to the endoscopic and histological features, 26 patients (15.4%) were identified having UGI CD involvement among 169 CD patients, and among these, 24 patients (17.5%) were asymptomatic, whereas 2 (6.3%) were symptomatic. We further observed that the frequency of characteristic histological lesions was significantly higher in the gastric antrum and angulus than in any other biopsy site ($p = 0.028$). Focally enhanced gastritis and focal active inflammation had significantly higher frequencies than non-caseating granulomas in the stomach ($p < 0.01$). There were no significant differences in the basic data between patients with or without endoscopic or pathological abnormalities ($p > 0.05$).
Conclusions: There was a high frequency of UGI involvement in adult CD patients, irrespective of the presence or absence of UGI symptoms. Confirmable characteristic UGI lesions of CD are also common, and routine gastroscopy and biopsy may be recommended for patients suspected of having or diagnosed with CD. Focally enhanced gastritis and focal active inflammation were observed to be more common than non-caseating granulomas which may helpful in the diagnosis of CD and are worth focussing on.

P110

Inter-rater validity of a new scoring index for Crohn's disease (Crohn's disease activity in capsule endoscopy)

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Background: The Lewis Score (LS) and the Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) are scoring indices for small bowel capsule endoscopy (SBCE) in patients with Crohn's disease (CD) and small bowel lesions. We proposed the new capsule endoscopic scoring index (CDACE) correlated with existing scores. CDACE is evaluated by dividing the small intestine into four sections, determining the sum (range: 0–16) of the degree of inflammation at each section (range: 0–4; inflammatory score: (A) the number of sections with inflammation (range: 0–4; zone score: (B) and the degree of stenosis (range: 0–3; stenosis score: (C) and using the equation CDACE = A × 100 + B × 10 + C (range: 0–1643).
Methods: In purpose, we evaluate the validity and rate of concordance of CDACE. An expert with experience calculated CDACE scores of 184 SBCE sessions performed on 102 patients with CD. Twenty patients forming a representative score range were included in the analysis (CDAI 168 ± 115, LS 566 ± 1191; range: 0–3961), CECDAI 6.6 ± 4.4 (range: 0–13). After anonymizing and randomising these cases, two gastroenterologists (reader A, B) independently interpreted the image records, determined the LS, CECDAI, and CDACE score, and we determined the concordance between the three gastroenterologists including the original expert. We evaluated the concordance using the intraclass correlation coefficient (ICC) (2.1). We also compared the correlation between the scores.
Results: The average CDACE scores for the expert were 594 ± 395 (range: 0–1243), for reader A, 760 ± 351 (ranging: 110–1342), and for reader B, 546 ± 357 (range 0–1340). The ICC (2.1) equalled 0.618, indicating a somewhat strong concordance. In addition, CDACE exhibited a correlation with the existing scores, and was strongly correlated with CECDAI (expert: CDACE:LS (r = 0.662, p < 0.0001), CDACE:CECDAI (r = 0.911, p < 0.0001), LS:CECDAI (r = 0.784, p < 0.0001).
Conclusions: The CDACE can be used to determine the range of inflammation of the small bowel (second digit of the score) and the presence or absence of stenosis (first digit of the score). Moreover, to some degree, it is possible to infer inflammation morphology (third and fourth digits of the score) from these results. CDACE scores were found to have a somewhat strong concordance among readers, as well as a correlation with existing scores.

P111

Clinical validation of a blood-based prognostic biomarker in Inflammatory bowel disease; towards personalised medicine in IBD

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Background: The inherent patient to patient variability in disease course observed in inflammatory bowel disease (IBD incorporating both Crohn's disease and ulcerative colitis) has a direct impact on disease management; patients with aggressive disease are undertreated by conventional 'step-up' therapy, whilst those with indolent disease would be exposed to the risks and side-effects of unnecessary immunosuppression if a 'top-down' approach was indiscriminately used. We previously described, a transcriptional signature detectable within peripheral blood CD8+ T cells of IBD patients at diagnosis, which correlates with subsequent disease course (McKinney et al. *Nat Med* 2010). We have now developed a whole blood, qPCR-based biomarker test that can re-capitulate the CD8+ subgroups without the need for cell separation, and overcomes the technical challenges of separating cell populations, which would not be possible in a routine clinical setting. Here we describe the development and validation of this biomarker and its use in the first biomarker-stratified clinical trial for Crohn's disease. Successful completion of the trial should provide the first step towards personalised medicine in IBD.
Methods: We simultaneously obtained a whole blood PAXgene RNA tube and peripheral blood CD8+ T-cell sample from a training cohort of 69 newly diagnosed IBD patients, Gene expression in both samples was measured by microarray and machine learning used to identify a transcriptional classifier in whole blood gene expression data that would re-capitulate the CD8+ transcriptional subgroups and correlated with prognosis. The classifier was initially trained using leave-one-out cross-validation, and the genes identified were subsequently tested by qPCR and an optimised qPCR assay developed. Independent validation of the biomarker was established using a second, independent validation cohort of 84 newly diagnosed patients with IBD from 4 sites around the UK.
Results: This validated the biomarker and confirmed that the subgroups it identified had significantly different disease courses (analogous to those observed with the CD8+ T-cell subgroups). We have now extended this data set and embarked on the PROFILE trial: PRedicting Outcomes For Crohn's dIsease using a moLecular biomarker.
Conclusions: We have developed, optimised and validated a whole blood qPCR classifier that is able to predict disease course from diagnosis in IBD patients. This represents a major step towards personalised therapy in IBD, and is currently being used investigate whether this could make personalised medicine a reality in CD.

P112

Long-term outcome of immunomodulators use in paediatric patients with inflammatory bowel disease

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Background: In the era where new powerful biologicals are entering the market, the place of conventional immunomodulators (IMM) in treatment of paediatric inflammatory bowel disease (IBD) is questioned. We studied the long-term outcome of paediatric IBD patients receiving conventional therapy.
Methods: All children with Crohn's disease (CD) or ulcerative colitis (UC) followed at our centre between July 2008 and July 2018 were retrospectively included. Only children receiving conventional therapy including mesalazine, steroids and IMM (thiopurine, methotrexate) at start were studied. Patients requiring rescue therapy (either biologics or surgery) around diagnosis or with a follow-up (FU) <6 months were excluded. The primary outcome of interest was steroid-free clinical remission without need for rescue therapy at 6 and 12 months after diagnosis and at last FU visit. Cox proportional hazard modelling was performed (Hazard risk: HR (95% CI) to determine variables associated with outcomes.
Results: A total of 221 patients (149 CD and 72 UC; median age at diagnosis 12 [10–14] years) were included (Table 1). We excluded 45 (20%) patients due to insufficient FU (n = 21), need of biologics (n

= 22) or surgery around diagnosis (n = 2). The median FU duration was 5 [2–8] years. Steroid-free clinical remission rates decreased from 80% at month 6, and 58% at month 12, to 32% at last FU visit. The likelihood of remaining free of rescue therapy was 53% and 72% at 1 year and 27% and 31% at 5 years for CD and UC patients, respectively (Figure 1). For CD patients, higher CRP [HR 1.007 (1.002–1.011), p = 0.002], lower albumin [1.045 (1.008–1.080), p = 0.016] and growth failure [1.206 (1.011–1.362), p = 0.040] at diagnosis were associated with an increased risk of need of rescue therapy. For UC patients, higher PUCAI score at diagnosis [1.037 (1.009–1.065), p = 0.008] was determined as a risk factor for rescue therapy.

Conclusions: These real-life data in paediatric IBD show that only 32% of children remain free of biologic or surgery 5-years after diagnosis. Especially children with a high disease burden at diagnosis as witnessed by higher CRP, lower albumin and growth failure for CD and higher PUCAI score for UC were more likely to fail conventional therapy. This type of risk stratification algorithms will help to determine which patients will benefit from accelerated step-up therapy.

Table 1. Patients' characteristics.

Number of patients	221
Sex, male, n (%)	109 (49.3)
Age at diagnosis, year, median (IQR)	12.3 (9.9-14.3)
IBD subtype, n (%): CD, UC	149 (67.4), 72 (32.6)
Paris classification for CD at diagnosis	
Age at diagnosis, n (%): A1a, A1b	36 (24.2), 113 (75.8)
Disease location, n (%): L1, L2, L3	38 (25.9), 26 (17.7), 83 (56.5)
Upper GI involvement, n (%): no, L4a, L4b	59 (40.1), 83 (56.5), 5 (3.4)
Disease behaviour, n (%): B1, B2, B3	133 (90.5), 11 (7.5), 3 (2.0)
Perianal disease modifier, n (%)	18 (12.2)
Growth, n (%): G0, G1	112 (76.2), 35 (23.8)
PCDAI score at diagnosis, median (IQR)	30.0 (21.9-42.5)
Paris classification for UC at diagnosis	
Disease extent, n (%): E1, E2, E3, E4	4 (5.7), 16 (22.9), 8 (11.4), 42 (60.0)
Disease severity, n (%): S0, S1	53 (75.7), 17 (24.3)
PUCAI score at diagnosis, median (IQR)	50.0 (30.0-60.0)
IMM, n (%): started during FU, continued at last visit	194 (87.8), 99 (44.8)
Thiopurine, n (%): during FU, at last visit	192 (86.9), 95 (43.0)
Methotrexate, n (%): during FU, at last visit	24 (10.9), 4 (1.8)
Disease duration till start of IMM, months, median (IQR)	0.9 (0.3-2.5)
Reason to start rescue therapy at diagnosis	
Steroid resistant patients, n (%)	10 (4.5)
Peri-anal Crohn's disease, n (%)	7 (3.2)
Severe disease at presentation and TPMT mutation, n (%)	5 (2.3)
Ileocaecal abscess at presentation	1 (0.5)
Intestinal obstruction with stricture	1 (0.5)
Need of rescue therapy at last FU visit, n (%)	120 (68.2%)
Biological therapy, n (%)	112 (63.6%)
Surgery, n (%)	8 (4.5%)

Legend: CD: Crohn's disease; FU: follow-up; GI: gastrointestinal tract; IMM: Immunomodulation; IQR: interquartile range; n: number; PCDAI: Paediatric Crohn's Disease Activity Index; PUCAI: Paediatric Ulcerative Colitis Activity Index; UC: ulcerative colitis.

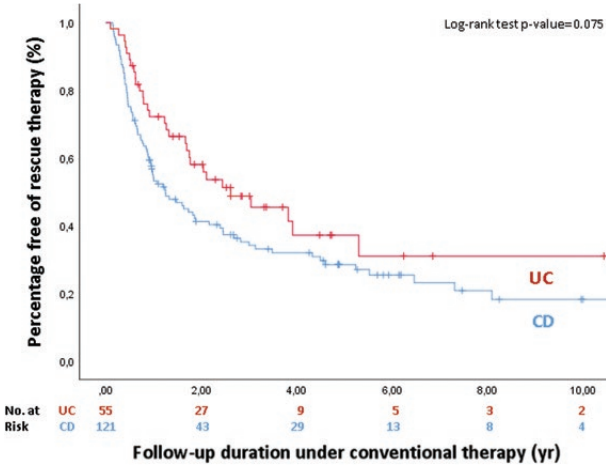

Figure 1. Kaplan–Meier analysis showing the likelihood of remaining free of rescue therapy in paediatric IBD patients receiving conventional therapy from diagnosis.

P113

Accuracy of a new rapid test assay for monitoring adalimumab levels

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Background: Low serum concentrations at trough levels have been related with loss of response in inflammatory bowel disease (IBD) patients under Adalimumab (ADA) therapy. Most of the methods commercially available in the market for the quantification of ADA are ELISA-based, with a turnaround time of approximately 8 h, delaying the target dosage adjustment to following infusion. A new rapid test device (RT-ADA) was recently launched for monitoring serum ADA levels. The aim of this study was to evaluate the performance of a new rapid test for ADL quantification by comparing it with three well-established methods.

Methods: Sera from 120 IBD patients undergoing ADA therapy were quantified by four assays: rapid test lateral flow Quantum Blue® from Buhlmann (RT-ADA) and three ELISA formats: commercials assay from Immundiagnostik (ELISA A) and from R-Biopharm (ELISA B) and an in-house assay. Moreover, donor's serum samples were spiked with known concentrations of ADA and the percentage of recovery of each assay was evaluated.

Results: Spiked samples showed an excellent Intraclass Correlation Coefficient (ICC) between theoretical and measured concentrations for all the assays 0.927, 0.984, 0.982 and 0.989 and a good recovery 111%, 113%, 86%, 110%, respectively, ELISA A, ELISA B, RT-ADA, and in-house ELISA. Regarding the clinical samples, the ICC of the RT-ADA assay vs. the three ELISA-based established methods was 0.590, 0.761, and 0.864, respectively, RT-ADA/ELISA A, RT-ADA/in-house ELISA and RT-ADA/Elisa B. When using different cut-offs for a qualitative comparison, RT-ADA showed accuracy between 73 and 89% and the kappa statistics revealed mostly a good agreement (0.492 and 0.682).

Conclusions: The new RT-ADA assay, which is able to deliver results within 15 min, can safely replace the commonly used ELISA-based ADA quantification kits and it is reliable alternative to these methods. This new assay is perfect for immediate concentration adjusted dosing avoiding delays cause by ELISA assays with a turnaround time of approximately 8 h.

P114

Risk factors and clinical characteristics for *Pneumocystis jirovecii* pneumonia in Japanese patients with ulcerative colitis

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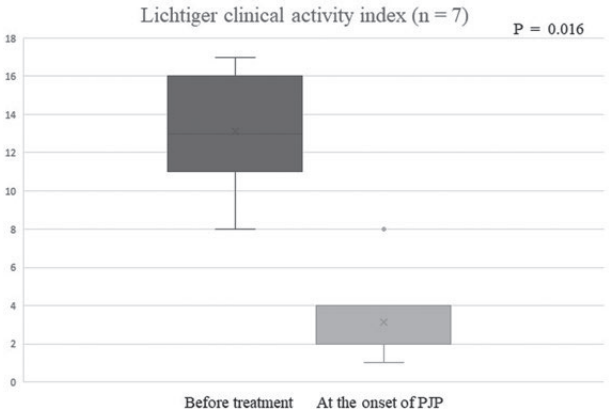
Background: *Pneumocystis jirovecii* pneumonia (PJP) is usually classified into two types: PJP with HIV (HIV-PJP) and PJP without HIV (non-HIV-PJP: NH-PJP). Respiratory failures progress more rapidly and require more artificial respiratory control, falling in poor prognosis in NH-PJP than in HIV-PJP.[1–3] There is no consensus in the approach to prophylaxis against NH-PJP in patients with ulcerative colitis (UC) despite prophylaxis with sulfamethoxazole/trimethoprim (TPM-SMX) reduces NH-PJP infections.[4] The purpose of this study was to determine the clinical characteristics and risk factors for NH-PJP in patients with UC treated with immunosuppressants.

Methods: Of the 3927 patients with UC between April 2007 and March 2017 received immunosuppressive drugs. Seventy patients experienced pneumonia, including nine patients with NH-PJP. A retrospective case–control study was conducted in these patients, with an NH-PJP group (n = 9) and a non-NH-PJP group (n = 36). The Lichtiger clinical activity index (LCI) was compared between the initiation of treatment and the onset of NH-PJP. The day of NH-PJP onset after immunosuppressant therapy was calculated with the Kaplan–Meier estimator.

Results: Two patients in the NH-PJP group died. The median LCI (range) at the initiation of treatment was 13 (8–17), whereas that at NH-PJP onset was 2 (1–8) (p = 0.016)



Comparison of Lichtiger clinical activity index before treatment and at the onset of PJP. Median score 13 (range 8–17) before treatment decreased significantly to 2 (1–8) at the onset of PCP. *Wilcoxon's signed-rank test.

The median period to NH-PJP onset was 83 days from the beginning of immunosuppressive treatment. Age and the dose of prednisolone (PSL; mg/day) were significantly greater (p = 0.02 and p = 0.002, respectively), three immunosuppressants were used significantly more frequently (p = 0.004), and the lymphocyte counts during treatment were significantly lower (p < 0.01) in the NH-PJP group than in the non-NH-PJP group. The cut-off value, sensitivity, and specificity for the lowest lymphocyte count to predict NH-PCP during treatment were 570/μl, 0.81, and 0.89, respectively, according to a receiver-operating characteristic curve.

Conclusions: NH-PJP occurred when the symptoms of UC were stabilising, when the immunosuppressive drugs were reduced. Senior age, a higher dose of PSL (mg/day), and lower lymphocyte counts during treatment are risk factors for NH-PJP. Prophylactic treatment with TPM-SMX should be used for UC patients with these risk factors.

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P115

Monitoring faecal calprotectin at 3 months post-surgery is useful to predict further postoperative endoscopic recurrence in Crohn's disease

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Background: Most of the patients with Crohn's diseases (CD) underwent surgery and the risk of postoperative recurrence remains high. An ileocolonoscopy is recommended within the first year post-surgery to detect postoperative endoscopic recurrence (POR) that precedes clinical recurrence. Faecal Calprotectin (fCal) monitoring within the first year post-surgery is useful to predict POR and could avoid performing some colonoscopies. However, the usefulness of an early postoperative monitoring of fCal as soon as 3 months post-surgery to detect the occurrence of further POR within 1 year after surgery remains unknown.

Methods: Stool samples were collected 3 months post-surgery in a cohort of 55 consecutive CD patients who had undergone an ileocolonic resection to measure fCal concentrations by an immunoenzymatic assay (Bühlmann). An ileocolonoscopy was performed within the first year post-surgery and endoscopic recurrence, graded by the Rutgeerts score (POR defined as Rutgeerts >i1) was assessed. The performance, sensitivity, specificity, predictive values of fCal levels to predict further POR as well as the optimal cut-off point capable to predict POR has been determined by ROC curves.

Results: At 3 months post-surgery, the mean fCal levels were significantly higher in patients with endoscopic recurrence, when compared with those in endoscopic remission (204.9 μg/g; 95% CI [124–660 μg/g] vs. 102.9 μg/g [61–207 μg/g] respectively; p = 0.0071). Based on the AUROC, the accuracy of fCal measured at 3 months post-surgery was 0.712. The respective sensitivities, specificities, positive and negative predictive values according to various cut-off points are summarised in Table 1. The fCal value of 65 μg/g was the best cut-off point to accurately distinguish the patients who will further experience a POR from those who will stay in endoscopic remission, and this could allow avoiding around 20% of colonoscopies given the high NPV of fCal in this setting.

fCal (g/kg) cut-off	Sen (%)	Spe (%)	PPV (%)	NPV (%)
50	96	19	46	86
65	96	31	50	91
75	87	34	49	79
105	78	53	55	77

Conclusions: The present study reports the usefulness of monitoring fCal as soon as 3 months post-surgery to predict accurately POR in CD patients. FCal levels below 65 µg/g at 3 months post-surgery could help making decision to avoid performing an ileocolonoscopy within 1 year post-surgery.

P116

The investigation of colonic mucosal inflammation of ulcerative colitis by linked colour imaging

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Background: Recently, it has been reported that not only mucosal healing but also histological assessment of inflammation is important to predict prognosis of the patients of ulcerative colitis. However, it has not been established the endoscopic classification to reflect mucosal inflammation. In the present study, we investigated the possibility of linked colour imaging (LCI) to diagnose mucosal inflammation such as inflammatory cell infiltration and cytokine expression.
Methods: All examinations were carried out with an EG-L590WR endoscope and a LASEREO endoscopic system (FUJIFILM Co., Tokyo, Japan) including 78 UC patients with clinically remission (Under 4 of Lichtiger CAI score). Endoscopic images and biopsy samples were taken at caecum, sigmoid colon, rectum, and additional area with mucosal redness and diagnosed by endoscopic LCI classification (LCI-A, -B, -C)(Uchiyama K, et al., *J Crohns Colitis* 2017;11(8):963–969). Inflammation in the biopsy specimens were evaluated according to Geboes score and cytokine expression was evaluated by real-time PCR. The patients were observed for 30 months at longest.
Results: Total number of images was 365, and biopsy samples were taken from all of these areas. Geboes score was significantly higher in LCI-C area compared with LCI-B, and LCI-A. Cytokine mRNA expression such as TNF-α, IL-6, IFN-γ, IL-1b, IL-8, and IL-23 were well correlated with LCI classification. But IL-12, IL-17, and IL-10 were not significantly correlated with LCI classification. No relapse was observed in the group with LCI-A (n = 8). The relapse rate of LCI-B, and -C was 35.7% (15/42) and 46.4% (13/28). Geboes score was higher at relapse group, but there was no difference of mucosal cytokine expression between relapse group and non-relapse group.
Conclusions: The LCI classification is considered as a practical approach to diagnose mucosal inflammation in UC patients. However, further study is necessary to reveal the relation between relapse of UC and mucosal cytokine profile.

P117

Can we identify risk factors for the progression of bowel damage in Crohn's disease using the Lémann index?

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Background: Prediction of disease course in Crohn's disease is inaccurate, resulting in either over or under treatment. The Lemann index (LI) evaluates extent of structural bowel damage (SBD) based on clinical, endoscopic and imaging data from computerised tomography or magnetic resonance imaging. We aimed to identify demographic and disease parameters that are associated with worsening of LI
Methods: This is a comparative retrospective study of adult patients diagnosed with Crohn's disease at Meir Medical Center between 2004 and 2016. Patients were included if they had two imaging studies (CT or MRI) at least 1 year apart. Imaging were evaluated by an experienced radiologist for degree of bowel damage using the LI. Significant SBD was defined as LI score >4.8. SBD progression was identified as Delta LI(DLI)>0.3. Variables of interest included gender, age at diagnosis, disease duration and location, smoking, surgical history, family history of IBD and treatment.
Results: Sixty patients were recruited. Significant SBD was detected in 13 (21.7%) on the first LI evaluation. Disease location (colonic and perianal, p = 0.015, p = 0.008,, respectively) and previous surgeries (bowel resection and perianal surgery, p = 0.006, p = 0.009, respectively) were associated with significant SBD. Disease duration and smoking were not associated with significant SBD.

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		DLI < 0.3 (n = 31)	DLI > 0.3 (n = 29)	p-value
Disease duration, years		2.8 ± 2.7	2.8 ± 3.1	0.841
Smoking (current and previous)		9 (34.6%)	6 (24.0%)	0.406
Current treatment	None	9(29.0%)	6(20.7%)	0.456
	Immunomodulators	9 (29.0%)	6 (20.7%)	0.456
	Immunomodulators + anti-TNFs	8 (25.8%)	8 (27.6%)	0.876
	Any biological	13 (41.9%)	17 (58.6%)	0.196
first Lémann score		3.9 ± 4.5	2.9 ± 2.6	0.278
Bowel resection (Betweenfirst and second Lémanns)		0 (0.0%)	12 (41.4%)	<0.0001
Months between first and second Lémann		35.2 ± 22.4	46.8 ± 24.1	0.043

Comparison of patients with and without significant progression of structural bowel damage as measured by delta Lemann index (DLI).

Data of SBD progression are summarised in Table 1.

Significant progression of SBD (DLI >0.3) was detected in 29 (48.3%) patients in an average time of 40.8 ± 23.8 months. DLI >0.3 was associated with history of bowel resection ($p < 0.001$) and time elapsed from one imaging to the next ($p = 0.043$). Both parameters are embedded in the LI scoring system. Other parameters including: initial LI score, smoking status and medical treatment (specifically with biologic agents) were not associated with significant SBD progression.

Conclusions: Perianal disease predicted intestinal structural damage as reflected by a higher initial LI. Involvement of the distal gastrointestinal system (colonic and perianal) was associated with an initially higher LI, reflecting more sever SBD. Smoking, medical treatment or initial LI did not predict progression of LI. Despite the long time difference between the two imaging studies no parameters predicted the accumulation of SBD other than those embedded in the LI scoring system. A longer interval between the two studies was associated with further progression of LI. Surprisingly, medical treatment, and specifically biologic treatment, between the two studies did not prevent progression of LI.

P118

Magnetic resonance enterograghy in operative planning for patients with Crohn's disease of the small bowel: does timing matter?

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Background: Cross-sectional imaging is often utilised in the preoperative evaluation of Crohn's disease to enable planning of surgical approach and to counsel patients effectively regarding the nature of surgery. The aim of this study was to determine the diagnostic accuracy of MRE in patients having imaging within 6 months of surgery compared with those who had it 7–12 months prior to surgery.

Methods: Retrospective review of consecutive patients who underwent surgical resection for Crohn's disease of the small bowel between March 2015 and August 2018. Data obtained from electronic clinical records. MRE predicted disease location, extent and nature (either stricturing or fistulating) were correlated with operative findings. The sensitivity and positive predictive value (PPV) of MRE across these three domains was calculated for both groups. If the predicted length of disease was within 5 cm of the length described at time of surgery, the MRE length assessment was considered to be accurate. As no patients with negative imaging underwent surgery (true negatives), it is not possible to calculate specificity.

Results: In total, 39 patients were included (M:F 20:19, median age 44 years), of which, 28 had undergone MRE within 6 months prior to surgery (Group 1). There were 7/39 (18%) patients where there was underdistension of the small bowel and 2/39 (5%) where the images were distorted secondary to motion artefact. The table below demonstrates the differences between the two groups across the three domains.

	Group 1 ($n = 28$ patients)	Group 2 ($n = 11$ patients)
Number of males	12	6
Median Age (years)	48	43
Number of diseased segments	40	15
Sensitivity (location)	89.7%	91.7%
Sensitivity (length)	47.1%	14.3%
Sensitivity (nature)	79.5%	72.7%
PPV (location)	97.2%	78.6%
PPV (length)	94.1%	25.0%
PPV (nature)	96.9%	66.7%

Comparison of diagnostic accuracy of MRE in Groups 1 and 2.

There were three patients in Group 2 where the MRE suggested a small bowel stricture, however, at time of surgery, there was no evidence of a stricture and a resection was not performed. In comparison, all patients in Group 1 had procedures in keeping with pre-operative planning.

Conclusions: Our study suggests that the sensitivity and PPV of MRE decreases with time. MRI small bowel within 6 months of surgery is advocated to enable accurate pre-operative planning for these patients and to counsel them appropriately about the extent of surgical resection.

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Surgical recurrence in Crohn's disease patients with severe post-operative endoscopic recurrence: risk difference between purely anastomotic lesions and lesions limited to the neoterminal ileum

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Background: Seventy per cent of patients with Crohn's disease (CD) require surgery. Post-operative endoscopic recurrence (POR) is up to 100% at 5 years with severe POR at 6-month around 50% as reported in an Italian study. Surgical recurrence is strongly related to the severity of POR with higher rate in those with 'very severe' POR (i3 and i4) lesions. It is quite unclear if lesions limited to the neoterminal ileum modify the risk of surgical recurrence compared with purely anastomotic lesions. The STRIDE study tried to stress the difference between 2a (purely anastomotic lesions) and 2b (>5 aphthous ulcers in the neoterminal ileum) lesions to better identify POR with worst prognosis. We performed a pilot study to compare 2a and 2b lesions in terms of surgical recurrence.

Methods: We reviewed all colonoscopies performed in CD patients who have undergone ileocolonic resection regardless of the year of surgery. We analysed data from endoscopies performed in 2016, to reach an adequate follow-up until the end of 2018. POR was

evaluated according to the Rutgeerts' score classifying severe POR in those with a score ≥ i2. The main outcome was surgical recurrence.
Results: After reviewing the electronic medical records, 64 CD patients were identified: 6 with a Rutgeerts' score ≤ i1 and 58 (91%) with a score ≥ i2 . Considering only those with severe POR, 43/58 (74%) presented a score of i3 or i4 (very severe POR): 33 male (57%) with overall mean age of 46.8 ± 14.9 year, 42 (72%) and 16 (28%) were treated, respectively, with biological therapies or immunosuppressants. Thirty-nine patients (67%) presented both neoterminal ileum and anastomotic lesions, 14 (24%) presented purely anastomotic lesions (2a), and 5(9%) presented only lesions in the neoterminal ileum (2b). At the end of the follow-up (2 years), 5 patients of 58(9%) underwent new surgery and those with 2b lesions presented a significantly increased risk compared with those with 2a lesions ($p < 0.0001$).
Conclusions: This pilot retrospective study seems to confirm that in CD patients, with severe POR, only 2b lesions should be considered the worst prognostic factor for surgical recurrence. POR that involves neoterminal ileum probably increases the risk of surgery during the follow-up. Lesions limited to the anastomosis cannot be considered severe POR deserving of an aggressive medical treatment.

P120

Usefulness of the faecal calprotectin for the diagnosis of inflammatory bowel disease in patients with spondylorarthritis and no digestive symptoms

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Background: Faecal calprotectin (FC) is a biomarker of bowel inflammation widely spread in diagnosis and follow-up of inflammatory bowel disease (IBD). It is classically estimated that 5% of patients with axial spondyloarthritis (SpA) also have IBD; coexistence of both conditions has definite impact in clinical decisions. Proactive detection of both diseases should be advisable, though appropriate screening tools are still lacking. Our aim was to evaluate the usefulness of FC for the diagnosis of IBD in patients diagnosed with SpA without suggestive manifestations or previous diagnosis of IBD.
Methods: Patients from a Rheumatology clinic diagnosed with SpA who met ASAS criteria and did not present digestive symptoms suggestive of IBD were consecutively included. Demographics, clinical and analytical data of SpA (uveitis, HLA B27, acute phase reactants) at the time of inclusion, and treatment history were collected. Patients with a positive FC (> 50 mg/kg) underwent ileocolonoscopy with biopsies of colon and terminal ileum. Patients who were recommended to avoid NSAIDs 2-4 weeks before stool collection and endoscopy.
Results: In total, 98 patients included; 47% male, mean age 46.1 (20–74) years. BASDAI 3.6 + 2.5. HLA B27 positive in 78% of patients, high ESR in 31.6%, high CRP in 9.2%. FC positive in 49 patients (50%): mean 147 mg/kg (range 0–3038). Forty-seven underwent ileocolonoscopy: in 13 cases (26.5%), endoscopic findings were suggestive of IBD although confirmed in 8 cases (16.3%) (7 Crohn's disease and 1 ulcerative colitis). Microscopic inflammation was found in 2 additional cases. In patients with high FC levels, those with high CRP and ESR were more likely to have IBD (29% vs. 16% and 29% vs. 12%, respectively). Patients with a history of uveitis (18% vs. 12%) or psoriasis (33% vs. 16%) also had a higher prevalence of IBD, although none of those differences reached statistical significance. FC was higher in smokers (72% vs. 44%; $p = 0.03$). There were no significant differences regarding HLA B27. No statistically significant differences were found in FC between patients with high FC who were diagnosed with IBD and those who were not.
Conclusions: In our study, patients with FC >50 mg/kg had a high prevalence of IBD, which could indicate the usefulness of FC determination as screening tool for IBD in patients with SpA and no clinical feature suggestive of IBD.

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Correlation between histological activity and endoscopy in patients with UC, seen in a tertiary centre of gastroenterology in Romania

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Background: Histological activity is important in the choice of drug treatment and the patients with residual microscopic acute inflammation are more likely to relapse. The aim of this study was to see if there is any correlation between the macroscopic aspect of the colon and the degree of histological activity in patients with ulcerative colitis.
Methods: The medical charts of a total 84 patients were reviewed with a median age of 39.8 years old (18–78 years); 55 of them were males and 29 were females, most of them from the urban area/ nonsmokers and 154 biopsies were analysed by a histopathologist with experience in IBD. Colonoscopies or sigmoidoscopies with biopsies were performed once in 65 patients, twice in 11 patients, three times in 4 patients, and four times in 3 patients. Total number of endoscopies performed are 102. To make a difference between histologically active or inactive disease, we considered a Geboes score >3.1 and regarding endoscopy, the optimal cut-off Mayo endoscopic subscore to be a score of 1. Extent of disease: E1–28 (22%); E2–33 (40%); E3–31 (38%).
Results: In 61% of all endoscopies, the mucosa was inflamed, but anyway 15% did not show an important histological inflammation (Geboes score <3.1). Endoscopic remission was observed in the other 35.4% of procedures; however, in biopsies, 22% exhibited histological inflammation.
Conclusions: Our results indicate that histological activity was correlated with endoscopic activity in patients with UC. Focal active inflammation is likely to be missed by endoscopy and biopsies thus add an additional dimension regarding the presence of inflammation. Therefore, it seems appropriate to use both endoscopy and histology for the assessment of disease activity and extent.

P122

Longitudinal follow-up of body mass index as a predictor for severe disease course in children with inflammatory bowel disease

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Background: Recent studies have shown that obesity may be associated with severe disease course in inflammatory bowel disease (IBD). The aims of this study were to present the longitudinal course of height, weight and body mass index (BMI) in children with IBD and to describe the impact of BMI on the clinical course of the disease.
Methods: We reviewed the medical records of children with IBD from the database of the 'Dana-Dwek' Children's Hospital between June 2010 and August 2018. Anthropometric data were longitudinally collected every 6 months as were disease characteristics, course and therapy. Patients were categorised in quartiles according to BMI percentile.
Results: Of 152 children, 85 had Crohn's disease (CD) and 67 had ulcerative colitis (UC). The median age (IQR) at diagnosis was 14 (12–15.5) years. During a median (IQR) follow-up of 2.95 (1.73–4.5) years, height Z-scores in the study population have not significantly changed. Weight and BMI Z-scores increased in the first 18 months since diagnosis in CD ($p < 0.001$) and UC ($p = 0.021$). BMI in the lower and upper quartiles at diagnosis was associated with higher risk of hospital admission (HR = 2.72, $p = 0.021$). BMI in the lower quartile at diagnosis and at 6, 12 and 18 months was associated with higher risk of disease exacerbation (HR = 3.25, 2.18, 2.01, 2.50, respectively, $p < 0.013$). BMI in the upper quartile at diagnosis and at 6 and 12 months was associated with higher risk of disease exacerbation (HR = 3.98, 2.98, 2.39, respectively, $p < 0.012$). In a multivariate analysis, BMI in the lower and upper quartiles at diagnosis was associated with higher risk of disease exacerbation (HR = 2.36 and 2.59, respectively, $p = 0.006$).
Conclusions: BMI in the lower and upper quartiles in 18 months since diagnosis was associated with more severe disease course in children with IBD. The results support using BMI as a predictor of IBD course and prognosis.

P123

The fully-automated LIAISON Calprotectin immunoassay from DiaSorin can distinguish between IBD and IBS patients

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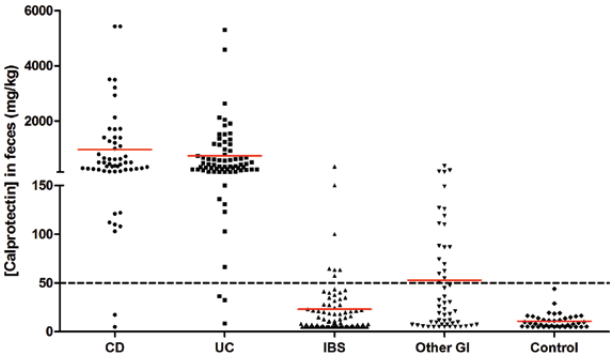
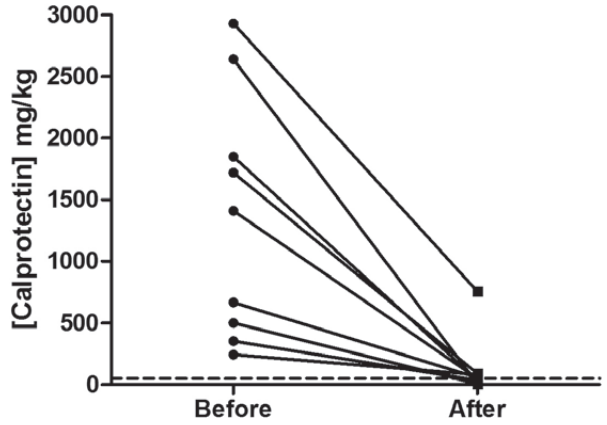
Background: inflammatory bowel disease (IBD) comprises two major disorders: ulcerative colitis (UC) and Crohn's disease (CD). These two disorders can be distinguished from irritable bowel syndrome (IBS). In this study, we assessed the performance of the quicker, fully automated calprotectin immunoassay from DiaSorin in IBD diagnosis and follow-up.
Methods: The LIAISON Calprotectin assay from DiaSorin run on the LIAISON XL was analytically and clinically validated and compared with the EliA Calprotectin immunoassay from Thermo Fisher Scientific run on the ImmunoCAP250. The immunoassay from DiaSorin uses recombinant human antigen standards. For the clinical validation, 303 samples were measured from 5 patient groups: UC, CD, IBS, other gastrointestinal diseases (GI) and controls, which consisted of healthy patients with no intestinal disease.
Results: The calprotectin immunoassay of DiaSorin showed good analytical performance. Regarding diagnostic accuracy, patients suffering from an active disease state of IBD showed significant higher concentrations of faecal calprotectin compared with controls as shown in Figure 1



Clinical validation of the DiaSorin LIAISON® Calprotectin assay on the LIAISON®XL.
(UC: 710 ± 921 mg/kg; CD: 967 ± 1243 mg/kg; controls: 11 ± 8 mg/kg). The remaining non-IBD groups showed no significant difference compared with controls (IBS: 23 ± 43 mg/kg; 53 ± 68 mg/kg). Follow-up patients ($n = 9$) showed a significant decrease in faecal calprotectin after treatment (Figure 2).



Follow-up results before and after treatment.
At the 50 mg/kg cut-off value, the negative predictive value (NPV) for the LIAISON Calprotectin for detecting IBD was 95% and, respectively, the positive predictive value (PPV) 96% (sensitivity and specificity of 96%) with an area under the curve was 0.97 ($p < 0.001$).
Conclusions: The LIAISON Calprotectin immunoassay can be used both to distinguish between IBD and non-IBD patients as well as for follow-up of IBD patients.

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Latent and active tuberculosis in patients with inflammatory bowel disease under anti-TNF—data from a centre with high incidence of tuberculosis

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Background: Portugal is one of the countries with the highest tuberculosis burden in the European Union, with a reporting rate in the North region registered in 2016 of 21.6 cases per 100 000 inhabitants. Anti-TNF can increase up to five times the reactivation of tuberculosis in patients with latent infection (LT). Therefore, it is recommended its diagnosis and treatment before starting biological therapies.
Methods: A single-centre retrospective study in the North region of Portugal included patients with inflammatory bowel disease (IBD) who started anti-TNF treatment between 2013 and 2017. The aim was to evaluate the prevalence of LT before initiating anti-TNF and the percentage of active infection during treatment. Screening of LT was considered positive if the tuberculin test (TST) ≥ 5 mm in immunocompromised patients or TST ≥ 10 mm in immunocompetent patients, positive/indeterminate Interferon Gamma Release Test (IGRA) or history of contacts. Active infection was excluded using chest X-ray and clinical history.
Results: One hundred and seventeen patients were identified—56% female, mean age 40 years, 91% Crohn's disease, 9% ulcerative colitis; 79% started infliximab, 21% adalimumab and 1% golimumab. The prevalence of LT was 32% (n = 37)—TST positive in 18 patients (51%); IGRA positive in 14 patients (40%) and undetermined in 7 (6%); history of contacts in 11 patients (31%). During screening 61% of the patients were under immunosuppressive therapy. All patients screened with LT performed isoniazid for 9 months. During follow-up (mean 21.6 months), one patient under infliximab developed pleural tuberculosis 5 years after receiving treatment with isoniazid. None of the patients with negative LT screening had active tuberculosis.
Conclusions: In this sample of patients with IBD, the occurrence of LT before starting biological treatment was significant (32%) but only 1 patient had active tuberculosis after TL treatment.

P125

Role of UCEIS vs. MES in predicting patients unresponsive to biological therapy and need for surgery: a retrospective single-centre analysis

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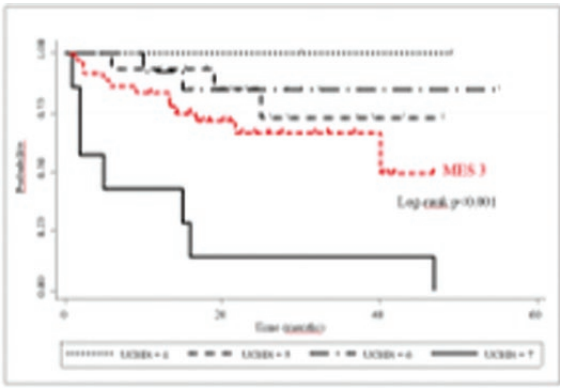
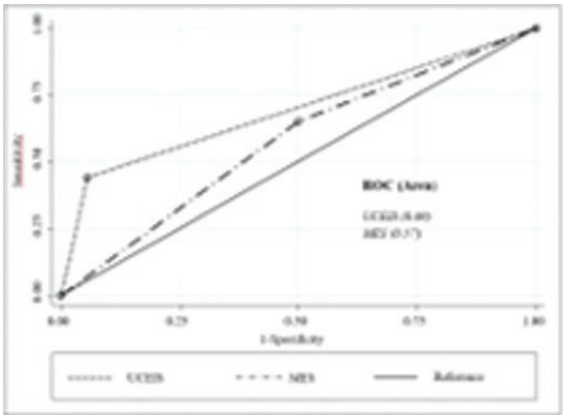
Background: Biological drugs represent the best choice for treating patients with moderate to severe ulcerative colitis (UC). About 60% of patients fail to achieve clinical and endoscopic remission and about 20% undergo colectomy. The ulcerative colitis Endoscopic Index of Severity (UCEIS) is a new validated score but the Mayo Endoscopic Subscore (MES) still represents the most used index. The aim of this study was to evaluate the predictive role of UCEIS and MES in identifying patients not responding to biological therapy and their need for surgery.
Methods: We retrospectively evaluated patients enrolled between 2014 and 2018. Endoscopic disease activity was assessed with MES and UCEIS at baseline and at Week 48. Unresponsiveness was defined as UCEIS ≥ 2. Statistical analysis included Fisher exact test, receiver-operator characteristic (ROC) curves and log-rank test for Kaplan–Meier plots. A p-value of <0.05 was considered significant.
Results: Sixty-one patients were included (28 infliximab, 10 adalimumab, 20 golimumab, 3 vedolizumab). Forty-three patients (70.5%) were unresponsive to therapy. The UCEIS, unlike the MES, was found to be significantly associated with unresponsiveness (p = 0.003 vs. p = 0.389). The area under the ROC curves (AUROC) of UCEIS were 0.58, 0.69 and 0.60, using cut-off value of 7, 6 and 5. Specificity was 94% and sensitivity was 44% using cut-off value of 6. The AUROC of MES was 0.57 with specificity and sensitivity of 50% and 65%, respectively, using a cut-off value of 3. Among unresponsive patients, 13 (30.2%) underwent colectomy for treatment failure. Twelve (92.3%) patients were MES = 3 at baseline with an overall colectomy-free survival rate significantly lower compared with MES = 2 (p = 0.007). According to the UCEIS at baseline, 6 patients (46.2%) with UCEIS 5-6 and 7 (53.8%) with UCEIS ≥ 7 needed for surgery. When the UCEIS ≥ 7, 100% of patients underwent colectomy (log-rank test for UCEIS p < 0.001).



Colectomy-free survival rates according to the UCEIS score (all patients with MES = 3 at baseline).



ROC curves of UCEIS (cut-off value of 6) vs. MES (cut-off value of 3) in predicting response to treatment.

Conclusions: The UCEIS score, compared with MES, better predict UC patients unresponsive to biological therapy. It is also useful for identifying patients needing colectomy.

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Low reproductive knowledge and fertility in patients with inflammatory bowel disease in Serbia—results of pilot study

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Background: Inflammatory bowel diseases (IBD) are predominantly diagnosed in young patients who are in the reproductive period. Misconceptions associated with the lack of adequate information can force patients to ignore available medical evidence of pregnancy safety leading to voluntary childlessness.
Methods: In this pilot study, 80 female IBD patients (aged 18–67) treated in the Clinic for Gastroenterology and Hepatology Clinical Center of Serbia, completed standardised questionnaire consisting of demographic characteristics, pregnancy and abortion data, IBD phenotype and therapy. Disease related pregnancy knowledge was assessed using previously described Crohn's and colitis pregnancy knowledge score (CCPKnow). CCPKnow consists of 18 questions and scores lower than 7 are considered poor. Patients were divided according to the diagnosis into the group with ulcerative colitis (UC) and Crohn's disease (CD). These two groups were further stratified according to the presence of pregnancy after IBD diagnosis.
Results: We analysed data from 80 IBD patients (42 UC, 38 CD). In UC group 8 (19%) and in CD group 8(21%) were childless. After IBD was diagnosed 33 (78.6%) UC and 32 (84.6%) CD patients were not pregnant. Six patients (3 UC, 3 CD) stated that IBD diagnosis was the sole reason for voluntary childlessness. Total of 14 pregnancies was found in 9 UC patients while in CD patients total of 6 women had 10 pregnancies after IBD diagnosis. Statistically significant difference was shown only in UC patients when average number of children was compared between groups with and without pregnancy after IBD diagnosis (2.00 vs. 1.03, $p < 0.05$).In CD there was the same trend but significant difference was not observed. Average CCPKnow scores were poor in both groups (5.44 in UC vs. 4.38 in CD). CCPKnow scores showed better knowledge, both in UC and CD patients, among women who gave birth after IBD diagnosis compared with those who did not (UC: 6.44 vs. 5.16; CD: 5.83 vs. 4.11, respectively). Better knowledge in UC than in CD patients about the chances of pregnancy during IBD ($p < 0.001$) and regarding mesalazine safety in pregnancy was demonstrated ($p < 0.013$).
Conclusions: Our study confirmed that voluntary childlessness is a common occurrence in female patients with IBD. The CCPKnow score is extremely low in the examined population and specific reproductive knowledge in IBD is lower in CD patients, which points to the great need for fertility related education of IBD patients in our country.

P127

Anti-TNFs patterns of use in clinical practice in inflammatory bowel disease (VERNE study)

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Background: Anti-TNFs represent one of the main treatment strategies for the management of IBD. One of the aims of this study was to learn about the patterns of the use of anti-TNFs therapies in Spain when used in biologic-naïve patients for the treatment of IBD.
Methods: VERNE was a retrospective, non-interventional study, conducted in 24 hospitals in Spain. 310 adult patients who started first treatment with anti-TNFs between June 2011 and June 2013 (194 with CD and 116 with UC) were consecutive recruited. Data about patient characteristics (including comorbidities and extraintestinal manifestations) and anti-TNF management were collected. Studied variables were analysed descriptively. Kaplan–Meier analyses were used to evaluate time to treatment intensification and time to discontinuation.
Results: Median time from diagnosis to first anti-TNF use was 45.5 months (IQR 25–75: 11.1–150.2) (45.5 months in CD and 43.8 months in UC), and median follow-up time after administration of the anti-TNFs was 59.8 months (IQR 25–75: 53.3–65.6) (59.8 months in both CD and UC). Comparable fractions of patients used infliximab and adalimumab in CD (43.8% vs. 56.2%). However, in UC infliximab was preferred to adalimumab use (87.1% vs. 12.9%).
Treatment intensification was needed for 31.9% of patients (28.9% in CD and 37.1% in UC). The most common treatment intensification approach was the combination of dose escalation and interval shortening; it was reported in 43.4% of intensified patients (41.1% in CD and 46.5% in UC). The median time to intensification was 9.2 months (IQR 25–75: 3.5–23.3) (14.3 months in CD and 5.3 months in UC). Treatment intensification rates were similar for infliximab and adalimumab, and median time to intensification was longer for adalimumab than for infliximab (10.6 vs. 8.2 months).
Treatment discontinuation occurred in 50.6% of patients (47.4% in CD and 56.0% in UC). The most common cause for discontinuation was loss of response, reported in 29.9% of patients (30.4% in CD and 29.2% in UC). Adverse events accounted for 20.4% of discontinuations (21.7% in CD and 18.5% in UC). Median time to discontinuation was 20.9 months (IQR 25–75: 7.2-37-3) (24.7% in CD and 17.4% in UC).

Conclusions: Around one third of bio-naïve patients who started anti-TNF treatment required intensification, and one in every two discontinued therapy, with loss of response as the most common cause for discontinuation. Further investigations are needed to optimise anti-TNF management and to identify patients' groups which can benefit from alternative biologic therapies.

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Histological activity predicts clinical relapse in patients with ulcerative colitis in endoscopic remission

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Background: Mucosal healing (MH) is a current target in the treatment of ulcerative colitis (UC), as it reduces the risk of surgery and hospitalisation. However, some patients with MH relapse. Persistent histological lesions (HL) beyond MH could probably explain some of these cases. Our aim was to assess the presence of histological disease in patients with MH and if it is associated with clinical relapse.
Methods: We retrospectively enrolled 100 UC patients showing MH, expressed as Mayo 0 and 1 at colonoscopy, and undergone multiple biopsies during the same examination. We evaluated whether clinical relapse was reported in patients charts up to 12 months after colonoscopy.
Results: Only 2% of patients showed the absence of HL. Chronic and acute inflammatory infiltrate and basal lymphoid aggregates were the most common (89%, 65%, and 64% of patients, respectively). Twenty-seven per cent of patients showed clinical relapse (mean time for relapse 6.5 months from baseline). At the univariate analysis, an older age (OR 0.96, $p = 0.028$ [95% IC 0.93–0.99]) and a longer disease duration were protective factors for relapse (OR 0.9, $p = 0.014$ [95% IC 0.83–0.98]). Patients with higher number of HL at baseline relapsed more frequently (OR 1.25, $p = 0.012$ [95% IC 1.05–1.49]), similarly to patients with basal plasmacytosis (OR 4.3, $p = 0.005$ [95% IC 1.57–11.98]), lamina propria eosinophils (OR 2.9, $p = 0.047$ [95% IC 1.02–8.83]) and surface irregularity (OR 4.7, $p = 0.010$ [95% IC 1.45–15.22]). At the multivariate analysis, basal plasmacytosis (OR 3.07, $p = 0.045$ [95% IC 1.03–9.17]) and surface irregularity (OR 4.45, $p = 0.025$ [95% IC 1.20–16.48]) were confirmed as risk factors, and disease duration as a protective factor (OR 0.89, $p = 0.021$ [95% IC 0.81–0.98]). However, basal plasmacytosis and surface irregularity were relatively infrequent lesions, as they were found in 21% and 14% of patients, respectively.
Conclusions: HL persist in the major part of patients with MH. Basal plasmacytosis and surface irregularity correlated with clinical relapse.

P129

Endoscopy and inflammatory bowel disease: data from a pilot experience to investigate the gap between the current guidelines and the real clinical practice

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Background: Endoscopy plays an essential role in inflammatory bowel disease (IBD). ECCO promoted specific consensus on the appropriate indication and application of endoscopy in IBD patients. Nevertheless, up to know endoscopy risks being under or overused. We explored whether the use of colonoscopy is appropriate in a real clinical setting.
Methods: We collected data from 150 consecutive colonoscopy performed in our unit (referral centre for endoscopy in IBD). In Table 1 we reported the kind of the collected data.

Table 1

Collected data on	- Type of IBD - Medical center that was treating the patient - Indication to endoscopy - Bowel preparation and final Boston scale
Patients' characteristics	- The median time from the last endoscopy was 2 years - 60% had an adequate degree (at least upper secondary school) - 28% reported having at least one comorbidity - 85% were followed-up in a IBD referral center
Indication to colonoscopy	- 1.3% of patients underwent colonoscopy to perform chromoendoscopy due to mild dysplasia evidence - 5.3% to confirm the diagnosis of IBD - 12% to evaluate post-operative recurrence - 22.7% to evaluate mucosal healing after therapy - 26.7% to evaluate endoscopic severity after symptomatic relapse - 32% to perform "bioptic mapping" in light of long-standing colitis

Results: We analysed 72 males and 78 females (mean age of 45.4 ± 16.7 years): 49.3% were Crohn's disease (CD) patients and 50.7% ulcerative colitis patients. Table 1 shows patients' characteristics.

Fifty-seven per cent of patients preferred a 'low-volume" bowel preparation, especially those with CD ($p = 0.005$), an adequate degree ($p < 0.001$), and < 40 years-old ($p = 0.01$); 28% of all patients chose the 'split' modality (bowel preparation in 2 days) especially those with an adequate degree ($p = 0.05$). At the final analysis 84.6% of patients reached an adequate intestinal cleansing: patients with comorbidities presented a greater risk of intestinal cleanliness ($p = 0.04$). No difference between low and high volume bowel preparation was observed

concerning the adequate intestinal cleansing as well as between split and non-split methods. Fourteen per cent of patients underwent endoscopy with a 'weak' clinical indication and patients followed-up in a non-IBD referral centre were more exposed to this risk ($p = 0.03$). Thirty-two per cent of patients with long-standing colonic involvement underwent colonoscopy for dysplasia surveillance: 16 patients out of 48 (33.3%) underwent colonoscopy after 1–2 years from last endoscopy, 18 (37.5%) after 3–4 year and the remaining 14 patients (29.2%) after more the 4 years. Patients followed-up in a non-IBD referral centre were more exposed to risk of late endoscopies ($p = 0.05$).

Conclusions: This pilot experience shows that, despite the current guidelines, there are some 'gaps' in prescribing endoscopy in IBD patients with a risk of underuse and overuse of colonoscopy also in referral centres. Patients followed-up in referral centres are more likely to have adequate indication for endoscopy. More careful observance of timing for surveillance colonoscopy remains one of the main issue on which to improve.

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Delay in diagnosis of inflammatory bowel diseases and associated factors since the 1980s

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Background: There is an increase in IBD (Crohn's disease-CD and ulcerative colitis-UC) diagnosis during the last decades. Also the importance of early treatment commencement has been highlighted by several studies. The aim of the present study was to investigate whether there is a change in the time delay between symptom initiation and diagnosis nowadays in comparison to the past and to search for possible associated factors.

Methods: The medical records of patients of the outpatient IBD clinic of 'Tzaneion' General Hospital from the beginning of patient recording up to present were revised and were classified in 4 time periods (1980–1989, 1990–1999, 2000–2009 and 2010 until 2018). Data regarding time of initiation of symptoms and time of diagnosis of IBD as well as data regarding age at diagnosis (according to Montreal classification), gender, disease type (ulcerative colitis-UC and Crohn's disease-CD) and educational level were collected excluding patients with missing data.

Results: In total, 483 patients in total (UC: 240, CD 243) were studied. The results regarding delay of diagnosis from initiation of symptoms are shown in Table 1.

Decades	1980–1989	1990–1999	2000–2009	2010–2017	*p*-value
Delay (months)	8.55 ± 14.7	11.2 ± 21.2	9.3 ± 15.1	9.1 ± 15.9	0.74
UC	10.8 ± 19.1	6.3 ± 12.4	7.7 ± 12.7	6.7 ± 14.3	0.61
CD	5.6 ± 4.9	17.6 ± 27.9	10.5 ± 16.7	11.8 ± 17.3	0.1

The results regarding delay of diagnosis from initiation of symptoms and the aforementioned factors are shown in Table 2.

	Delay (months)	*p*-value
Men vs. women	7.8 ± 14.9 vs. 12 ± 18.8	0.021
UC vs. CD	7.3 ± 13.6 vs. 11.8 ± 19.1	0.003
Education (primary vs. secondary vs. tertiary)	8.6 ± 16.1 vs. 9 ± 14.6 vs. 12.3 ± 24.1	0.31
Age (≤16 vs. 17–40 vs. ≥41)	7.8 ± 13.4 vs. 10 ± 17 vs. 9.1 ± 17.2	0.71

Conclusions: According to the results, it seems that despite the constantly increasing interest in IBD and the evolution of diagnostic means, there has been no improvement as far as the delay between initiation of symptoms and diagnosis is concerned. The results are similar for both UC and CD. As for associated factors it was found that male patients and patients with UC are diagnosed earlier compared with females and patients with CD, whereas age at time of diagnosis and educational level are not associated with the time delay.

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Effectiveness and safety of vedolizumab maintenance therapy for inflammatory bowel disease: findings from a Belgian registry

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Background: Clinical trials have demonstrated the efficacy and safety of vedolizumab (VDZ) as maintenance therapy for Crohn's disease (CD) and ulcerative colitis (UC). This report presents outcome data for VDZ maintenance therapy in real life practice in Belgium.

Methods: The Belgium VDZ Registry includes 202 VDZ-treated adult patients from 19 Belgian centres. Inclusion criteria were on-going VDZ therapy started 15+ days prior to recruitment and patient not in a clinical trial or VDZ PASS study. This interim analysis presents safety data for the all 202 registry participants, and clinical remission rates on the subset of 156 participants with at least one 6-monthly investigator update on clinical management and outcomes. Clinical

remission was defined as Harvey–Bradshaw Index <5 or partial Mayo score < 3 with no sub-score >1. Patients who discontinued VDZ were considered not in remission from that point forwards. An imputation analysis was included to account for missing disease activity scores, where a missing activity score was assumed not in remission, thereby giving a minimum imputation estimate.

Results: The characteristics of the 202 participants were 52% female, 66% had CD, predominantly ileal or ileocolonic CD, and 34% had UC, predominantly left-sided UC. Median age at onset of IBD was 28 years, and median duration of IBD prior to starting VDZ was 10 years. At recruitment, median length of on-going VDZ therapy was 11 months, and 63% of UC and 60% of CD patients were in remission. Median duration of follow-up in the outcomes subset was 11 months (range 4–18 months). Clinical remission rates are shown below. The corresponding rates of corticosteroid-free clinical remission were 30–40% for both CD and UC.

Duration of VDZ maintenance therapy	CD remission rate (Observed)	CD remission rate (imputation)	UC remission rate (observed)	UC remission rate (imputation)
1–6 months	64% (18/28)	47%	54% (7/13)	33%
7–12 months	48% (29/61)	36%	80% (20/25)	51%
13–24 months	40% (31/78)	34%	70% (26/37)	55%
25–36 months	30% (13/44)	23%	52% (11/21)	42%

Clinical Remission

All reported serious adverse events (SAEs) and non-serious AEs were considered un-related to VDZ therapy. Thirty-four patients (16.8%) had a SAE, the most frequent being worsening of CD/UC (4.0%) and small intestine obstruction (1.5%). Eighty patients (39.6%) had a non-serious AE, the most frequent being constipation (2.5%), gastroenteritis (2.0%), nasopharyngitis (2.0%), and upper respiratory tract infection (2%). There were no reports of hepatic injury, infusion-related reactions, hypersensitivity or opportunistic infection.

Conclusions: These real-life data collected from 19 gastroenterology centres across Belgium demonstrate sustained clinical benefit with up to 36 months of VDZ maintenance therapy in everyday clinical practice.

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Detection and monitoring of IBD based on faecal volatile organic compounds

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Background: The gold standard to detect and monitor inflammatory bowel disease (IBD) remains endoscopic assessment which is invasive and costly. Faecal calprotectin (FCP) is the most commonly used non-invasive biomarker to assess IBD but lacks specificity. Faecal volatile organic compounds (VOC) are molecular end-products thought to represent both metabolic processes in the human body and the interaction between microbiota and host. The aim of the current study was to evaluate the potential of faecal VOC patterns to detect IBD and to identify disease exacerbation.

Methods: Patients aged 18 years and older with an established diagnosis of IBD collected a faecal sample prior to their scheduled consult at the outpatient clinic of either the Maastricht University Medical Centre (MUMC+) or the Amsterdam University Medical Centres (Amsterdam UMC). The healthy control (HC) group consisted of patients without mucosal abnormalities observed during their scheduled colonoscopy at the Amsterdam UMC. Active disease was defined as an FCP level of ≥250 mg/g, remission was defined as FCP <100 mg/g combined with a Harvey–Bradshaw Index <4 points for Crohn's disease (CD) or Simple Clinical Colitis Activity Index <3 points for ulcerative colitis (UC). Faecal samples were measured by means of gas chromatography-ion mobility spectrometry (G.A.S. Flavourspec). The data were split into three sets, 70% for training and validation and the remaining 30% as test set. A Wilcoxon rank-sum test was used to find the 100 most discriminatory features and Random Forest classification was used to provide statistical results.

Results: A total of 497 faecal samples were provided by 281 IBD patients and compared with 224 samples from 224 HC. Of these, 294 were CD samples (107 active disease, 84 remission) and 203 were UC samples (83 active disease, 64 remission). Outcomes of the Random Forest classification are given in Table 1. IBD, UC and CD could be discriminated from HC with high accuracy both in active state and remission. No difference in VOC pattern was observed between UC and CD, and between active disease state and remission.

Conclusions: We demonstrated that faecal VOC patterns can discriminate IBD, CD and UC from HC both during active disease state and remission, though there is no difference between UC and CD. These characteristics imply that faecal VOC patterns may hold potential as non-invasive biomarkers for IBD disease detection. Based on clinical activity, active disease could not be discriminated from remission, which hamper its potential to detect disease exacerbation.

Table 1. Differences in VOC pattern between groups of inflammatory bowel disease patients and healthy controls

	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	p-value
IBD vs. HC	0.97 (0.94–1)	0.97	0.95	0.99	0.88	<0.0001
CD active vs. HC	0.98 (0.96–1)	1	0.95	0.84	1	<0.0001
CD remission vs. HC	0.97 (0.95–1)	1	0.93	0.74	1	<0.0001
CD active vs. CD remission	0.49 (0.36–0.62)	0.33	0.77	0.73	0.38	0.562
UC active vs. HC	0.97 (0.95–1)	1	0.91	0.88	1	<0.0001
UC remission vs. HC	0.97 (0.95–0.99)	0.96	0.95	0.70	1	<0.0001
UC active vs. UC remission	0.62 (0.43–0.81)	0.85	0.43	0.78	0.55	0.094
CD active vs. UC active	0.55 (0.41–0.68)	0.54	0.67	0.74	0.46	0.228
CD remission vs. UC remission	0.52 (0.33–0.72)	0.53	0.62	0.78	0.36	0.393

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Comparison of accuracy between faecal immunochemical test and faecal calprotectin for predicting mucosal healing in quiescent ulcerative colitis patients: a prospective multi-centre study

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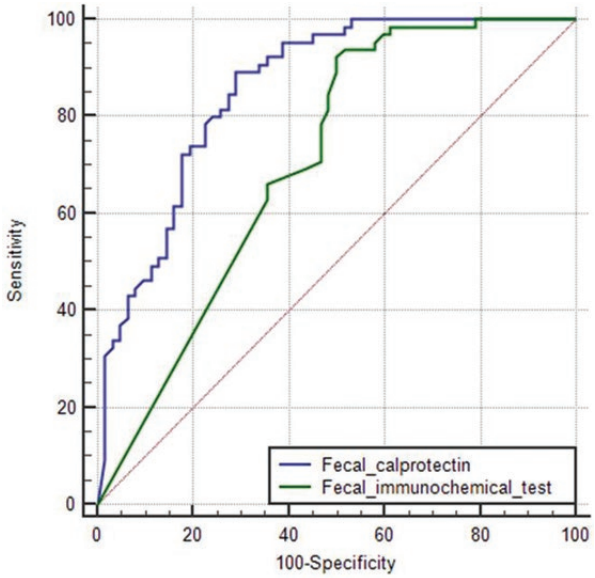
Background: Non-invasive stool tests including faecal immunochemical test (FIT) and faecal calprotectin (FC) are known to be a reliable biomarker for mucosal healing (MH) in UC. However, direct comparison of these faecal tests for predicting mucosal healing in inactive UC patients has yet to be evaluated. We aimed to compare accuracy of FIT and FC for predicting MH in UC patients in clinical remission.

Methods: This was a prospective, multi-centre study conducted in 3 tertiary hospitals between February 2016 and January 2018. UC patients in clinical remission for at least 3 months underwent colonoscopy and MH was evaluated using Mayo endoscopic subscore (MES). Faecal samples were collected for FIT and FC 24 h before colonoscopy. Receiver-operating characteristic (ROC) curve and cut-off value of the best accuracy for predicting MH was assessed in each test. Independent predictive factors for MH were identified by logistic regression analysis.

Results: Of all 127 patients (male 86, median age of diagnosis 44 (range 14–77)), 65 (51.2%) showed complete MH (MES = 0). Area under curve (AUC) of FC was significantly higher than FIT (AUC 0.858 vs. 0.707, $p < 0.001$) (Figure 1) whereas this difference disappeared when MH was defined as MES 0 or 1 (AUC 0.820 vs. 0.813, $p = 0.891$). When cut-off value was set as 70 μg/g for FC and 10 mg/ml for FIT, sensitivity, specificity, positive predictive value and negative predictive value were 89.2, 71, 76.3, and 86.3 and 92.3, 50, 65.9, and 86.1, respectively. Multi-variate logistic regression analysis showed that age of diagnosis >45, haematocrit >44, FC <70 μg/g, and FIT <10 mg/ml were identified as independent predictive factors for MH (MES = 0).



Comparison of ROC curves for predicting MH (MES = 0).

Conclusions: Our study demonstrated that FC is more sensitive than FIT for predicting complete MH in quiescent UC patients. The best cut-off value of FC and FIT for MH in these patients is found as 70 μg/g and 10 mg/ml, respectively. Age of diagnosis and haematocrit are additional predictors for MH.

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Long-term bowel function and fate of the ileal pouch after restorative proctocolectomy in patients with Crohn's disease: a systematic review and meta-analysis

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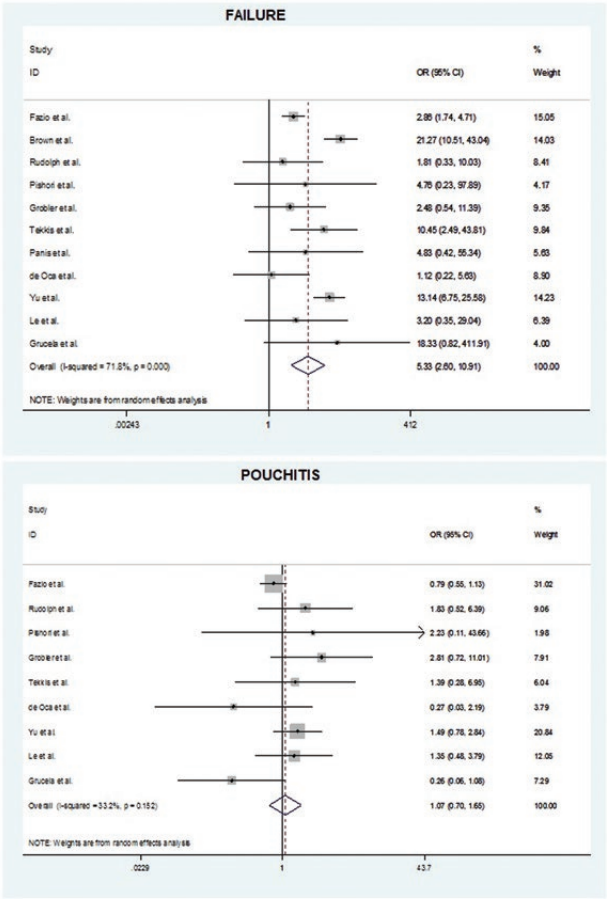
Background: Debate exists on whether restorative proctocolectomy with ileal pouch anal anastomosis (RPC) can be safely offered to patients diagnosed with Crohn's disease (CD). Few studies have been published on the topic. Our aim was to systematically review the literature for study reporting on RPC in CD compared with patients who underwent the procedure for ulcerative colitis (UC).

Methods: This is a Cochrane Collaboration QUORUM-compliant meta-analysis. All studies published between 1993 and 2018 were evaluated for inclusion. Only studies comparing the outcome of RPC in CD and UC and with more than 2 years of follow-up were included. In the event of studies from the same Centre, only the most recent or the one with more complete data were included. Two screeners performed the literature screening and review (GuS and DV); discrepancies were addressed by agreement with a third screener (GiS). Searches were performed on PubMed, EMBASE, Ovid and Cochrane Database (last search 19 October 2018). Primary endpoints included complications. Secondary endpoints included functional outcome (PROSPERO registry 116811).

Results: Eleven studies comprising 6770 patients (CD = 352, UC = 6418) were included in the quantitative analysis. Follow-up ranged between 44 and 120 months. Preoperative diagnosis of CD was made in 30% of patients. Pouch fistulae were more common in CD patients (CD vs. UC; OR 5.62; 95% CI, 2.01–15.76, $p = 0.001$), as well as strictures (CD vs. UC; OR 1.83; 95% CI, 1.13–2.97, $p = 0.015$) and failure (CD vs. UC; OR 5.33; 95% CI, 2.60–10.61, $p > 0.001$). Heterogeneity was acceptable in the analysis of strictures (I2 = 36%), whereas it was high in fistulae and failure (I2 = 85% and 72%, respectively). Pelvic sepsis and bowel obstruction were more common in CD, but they did not reach statistical significance. Interestingly, there was no significant difference in the incidence of pouchitis between CD and UC (OR 1.07, $p > 0.05$). In patients who preserved their pouch, there were no differences in terms of incontinence, urgency and use of pads; however, CD patients were at higher risk of seepage (CD vs. UC; OR 2.28; 95% CI, 1.22-4.26; $p = 0.010$, I2 = 34%).



Forest plot of failure (up) and pouchitis (down). Description in the text.

Conclusions: Patients with CD have 5-fold higher risk of fistulae and failure, and 2-fold risk of strictures after RPC compared with UC. However, in those who retain the pouch function might be similar to that of patients with UC. CD does not increase the risk of pouchitis. RPC could be offered to a very selected population of patients with CD, motivated not to have a definitive stoma, and after proper pre-operative counselling.

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Altered body composition profiles in young adults with childhood-onset inflammatory bowel disease

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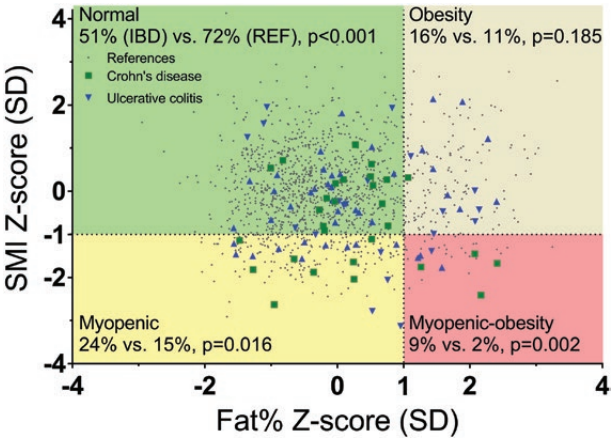
Background: Patients with inflammatory bowel disease (IBD) have an increased risk to develop lean mass and bone mass deficits. However, there are scarce data about the outcome in young adult patients with childhood-onset IBD. The aim of this study was to investigate body composition profiles with focus on skeletal muscle index (SMI) and fat percentage (fat %) and bone mineral density (BMD) in young adults with childhood-onset IBD. A second aim was to evaluate whether eventual body composition disturbances in young adulthood could be predicted from measurements in childhood.

Methods: A total of 94 out of 144 included patients in this prospective longitudinal study with median follow-up time of 8.4 years, had when these measurements were done reached adulthood (age ≥18 years). Body composition profiles in young adulthood were defined from dual X-ray absorptiometry estimated SMI and fat %. Normative age- and gender-matched data from the same region (N = 2480, age 6–30 years) were used to calculate individual Z-scores. Study participants were then classified based on a model proposed by Baumgartner (*Ann N Y Acad Sci*, 2000) as being (i) normal, (ii) obese (fat % Z-score >1SD), (iii) myopenic (SMI Z-score <–1 SD), or (iv) myopenic-obese. Risk of myopenia in adulthood was estimated with a logistic regression, based on a previous childhood SMI measurements available for 77 out of 94 patients.

Results: A higher proportion of young adults with childhood-onset IBD had a myopenic (24% vs. 15%, p = 0.016) or myopenic–obese (9% vs. 2%, p = 0.002) profile than age- and gender-matched healthy references (Figure 1).



Body composition profiles in young adulthood in 94 patients with childhood-onset IBD compared with reference data (M = 1181, F = 108). The proportional differences within each profile between patients and references were tested with Fisher's exact test.

In patients with childhood-onset IBD, SMI Z-score correlated to whole body BMD Z-score (R = 0.61, p < 0.001). Patients with childhood-onset IBD had in young adulthood 0.3 SD (95% CI [0.15–0.51], p < 0.001) lower whole body BMD Z-score, than healthy age- and gender-matched controls after adjusting for SMI Z-score in a linear regression model. A SMI Z-score of 0 SD, –0.5 SD or –1 SD in children with IBD could predict the risk for myopenia to occur in young adulthood corresponding to 6%, 25%, and 64%, respectively.

Conclusions: A larger proportion of young adults with childhood-onset IBD had a myopenic or myopenic-obese body composition profile and lower BMD then healthy references. SMI measures in

children with IBD could predict the risk for myopenia in young adulthood.

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Association between histological indices and ulcerative colitis activity measures among patients in the HICKORY (etrolizumab) open-label induction cohort

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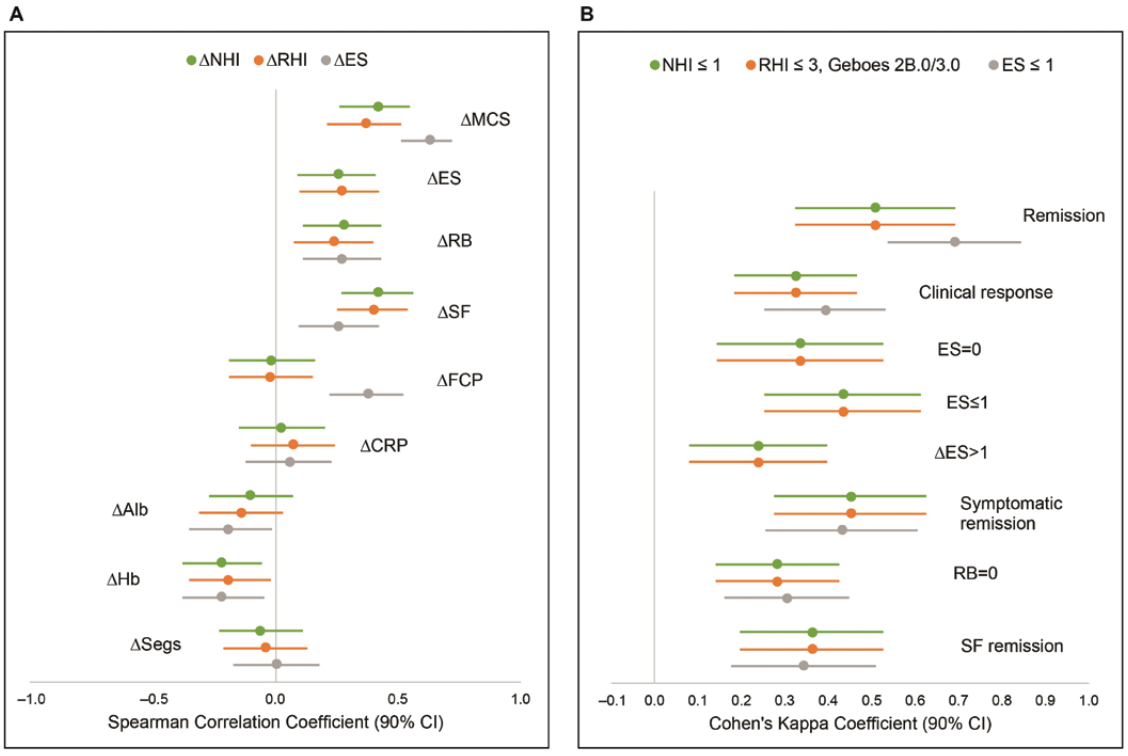
Background: Cross-sectional studies in UC have shown an association between histological and clinical measures of disease activity, but few longitudinal studies have evaluated this relationship.[1,2] Using data from the open-label induction (OLI) cohort of HICKORY,[3] we evaluated the correlation between histological changes and established disease activity measures at end of induction (Week 14).

Methods: Baseline and Week 14 biopsies were scored by 4 central readers using the Robarts histopathology index (RHI) and the Nancy histological index (NHI) in patients who had active baseline histology (NHI > 1 and RHI > 3) and complete scoring at Week 14 (n = 97). Binary Week 14 histological outcomes were characterised by presence or absence of neutrophils (NHI ≤ 1 or RHI ≤ 3 and Geboes subgrades 2B.0/3.0). Pairwise associations were quantified by Spearman correlation (ρ; for correlation between change from baseline scores) and Cohen's kappa coefficients (κ; for agreement among Week 14 outcomes). ΔRHI and ΔNHI were compared with determine the presence of a minimal clinically important difference (MCID) in Mayo Clinic score (MCS; ΔMCS ≥ 3). MCS endoscopic subscore (ES) was used to assess endoscopy.

Results: At Week 14, 22% (21/97), 23% (22/97) and 8% (8/97) of patients achieved resolution of neutrophilic inflammation, endoscopic improvement (ES ≤ 1) and endoscopic remission (ES=0), respectively; NHI ≤ 1 was achieved in 55% (12/22) of patients with ES ≤ 1 and 75% (6/8) of patients with ES = 0. ΔNHI and ΔRHI were highly correlated (ρ = 0.91). There was little to no association between laboratory results and ΔNHI/ΔRHI/ΔES (Figure 1A). A weak correlation was seen between ΔNHI/ΔRHI and ΔES (ρ = 0.26–0.27) and between ΔNHI/ΔRHI and change in rectal bleeding and stool frequency. NHI, RHI and ES agreement with symptomatic outcomes were weak to moderate (κ = 0.28–0.45; Figure 1B). Difference in the mean grouped by achievement of ΔMCS ≥3 suggests MCIDs in ΔNHI and ΔRHI of 1 and 9, respectively (Table 1).



Remission = MCS ≤ 2, RB = 0, remaining individual subscores ≤ 1; Clinical response = ΔMCS ≥ max (3, 0.3 baseline MCS) and either ΔRB ≥ 1 or RB ≤ 1; Symptomatic remission = RB = 0 and either SF = 0 or SF remission; SF remission = ΔSF ≥ 1 and SF ≤ 1.
Δ = change from baseline to week 14; NHI = Nancy histological index; RHI = Robarts histopathological index; MCS = Mayo clinic score; ES = endoscopic subscore; RB = rectal bleeding subscore; SF = stool frequency subscore; FCP = fecal calprotectin; CRP = C-reactive protein; Alb = albumin; Hb = hemoglobin; Segs = segmented neutrophils.

Figure 1. (A) Pairwise Spearman correlation coefficients between change from baseline scores at Week 14 and disease activity measures and (B) Pairwise Cohen's kappa coefficients among Week 14 outcomes.

Abstract PO136 – Table 1. Baseline and Change from Baseline in NHI and RHI by Achievement of MCID in MCS (ΔMCS≥3) in NHI- and RHI-evaluable Patients

		ΔMCS<3 n=48	ΔMCS≥3 n=49	Difference in Mean
NHI				
Baseline NHI	Mean (SD)	3.1 (0.9)	3.1 (0.8)	
	Median (IQR)	3.5 (2-4)	3.0 (2-4)	
	Range	2-4	2-4	
ΔNHI	Mean (SD)	0.2 (1.4)	1.4 (1.5)	1.2
	Median (IQR)	0 (–0.5-1)	2 (0-2)	
	Range	–2-3	–1-4	
RHI				
Baseline RHI	Mean (SD)	20.2 (8.5)	20.0 (7.6)	
	Median (IQR)	21 (11-28)	21 (14-26)	
	Range	6-33	5-33	
ΔRHI	Mean (SD)	2.3 (12.1)	10.9 (11.0)	8.6
	Median (IQR)	2.5 (–7-12)	13 (2-19)	
	Range	–23-30	–12-29	

IQR, interquartile range; MCID, minimal clinically important difference; MCS, Mayo Clinic score; NHI, Nancy histological index score; RHI, Robarts histopathology index score; SD, standard deviation.

Conclusions: The analysis showed no associations between changes in histological scores and changes in laboratory results, a weak correlation between changes in histological and endoscopic scores, and a weak to modest correlation between histological scores and symptoms at the end of induction.

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3 Rubin DT, Feagan BG, Peyrin-Biroulet L, *et al.* Tu2006—etrolizumab induction therapy improves histologic outcomes in anti-TNF-failed patients with ulcerative colitis: results from the Hickory Open-Label Induction cohort. *Gastroenterology*. 2018;S-1366

P137

Serum biomarkers of degradation and formation of type III, IV and V collagen are associated with disease activity in patients with Crohn's disease

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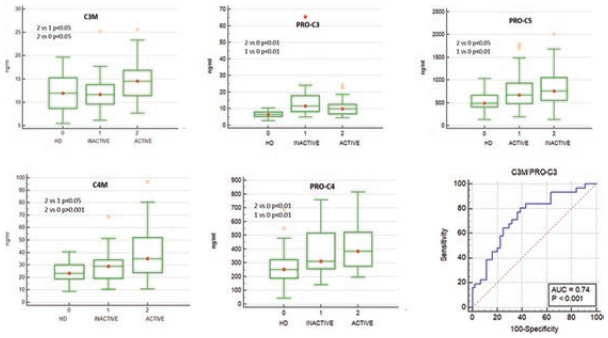
Background: Crohn's disease (CD) is characterised by episodes of relapse and remission and therefore requires continuous evaluation of disease activity. Extra Cellular Matrix (ECM) consists of basement membrane (BM) and interstitial matrix (IM). BM is positioned directly underneath the epithelial cells and consists mainly of type IV collagen, while IM consists mainly of type I, III and V collagen, and is produced by fibroblasts. Pathological environment, such as inflammation and fibrosis, leads to impaired remodelling, structure, quality and function of the collagen in the ECM. We investigated biomarkers of collagen degradation and formation and their association with disease activity and in patients with CD.

Methods: In this cross-sectional study we measured five biomarkers of ECM remodelling in 75 patients with CD (60% males, age 35 (IQR 26.5–43.5)), and 29 healthy controls matched by age and gender. Biomarkers of type III collagen degradation (C3M) and formation (PRO-C3), type IV collagen degradation (C4M) and formation (PRO-C4) and type V collagen formation (PRO-C5) were measured in serum by ELISA. Inflammatory activity was defined as combination of clinical or biochemical activity (CDAI ≥150 or CRP >5). One-way ANOVA (Tukey's multiple comparisons test), and ROC analysis was applied in statistical analysis.

Results: Biomarkers of interstitial matrix remodelling showed that C3M was significantly elevated in active CD compared with inactive CD ($p < 0.05$) and HD ($p < 0.05$), whereas PRO-C3 and PRO-C5 were significantly elevated in active CD and inactive CD compared with HD ($p < 0.001$, $p < 0.05$)(Figure 1). Turnover type III collagen showed highest diagnostic accuracy for active disease (AUC=0.74). Area under curve was for C3M 0.63, PRO-C3 0.36 and PRO-C5 0.52. Biomarkers of BM remodelling showed significantly higher C4M in active CD compared inactive ($p < 0.05$) and HD ($p < 0.001$), whereas PRO-C4 was significantly elevated in active and inactive CD compared with HD ($p < 0.01$). Area under curve was for C4M 0.64, C4M/PRO-C4 ratio 0.57 and PRO-C4 0.56.



Depiction of type III, IV, and V collagen remodelling in CD, and differences between healthy donors, CD in remission and active CD.

Conclusions: Both biomarkers of interstitial matrix (C3M) and basement membrane (C4M) were associated with disease activity. PRO-C3, PRO-C5 and PRO-C4 were associated with CD regardless of disease activity. Interstitial matrix biomarkers of turnover type III collagen C3M/PRO-C3 showed highest diagnostic accuracy for disease activity. In conclusion, these biomarkers may be used in monitoring and prediction of disease activity and in differentiation between patients with CD and healthy individuals.

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Prediction model to safely cease anti-TNF therapy in Crohn's disease: individual patient data meta-analysis (IPD-MA)

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Background: Tools for patient stratification to safely cease anti-TNF therapy in Crohn's disease (CD) are urgently needed. This IPD-MA aims at development of a predictive diagnostic tool for a personalised approach towards anti-TNF cessation in CD.
Methods: A systematic literature search was conducted to identify studies investigating the risk of relapse and risk factors in CD patients after anti-TNF therapy cessation by using Medline Ovid, Embase, Cochrane, Web of Science and Google Scholar. Cohort studies with >50 CD patients in remission (clinical or biochemical or endoscopic/radiological) were selected. IPD from the original study databases were used for analysis. Inclusion criteria: luminal CD as indication for anti-TNF therapy, duration of treatment ≥6 months. We associated baseline demographic and clinical data (age, gender, smoking, disease duration, Montreal classification, history of surgical resection, type of anti-TNF medication, concomitant immunosuppressants, corticosteroids prior to cessation and previous anti-TNF therapy) with time to relapse using a Cox model. A prediction model was constructed following the 'TRIPOD' statement, with backward selection and $p > 0.2$ as selection criterion. To investigate the predictive performance internal-external validation was applied.
Results: A total of 10 cohort studies were identified, IPD were available from 6 studies. Anti-TNF was withdrawn in 1006 patients, who experienced 474 relapses after a median FU time of 14 months (IQR 8–28). At 1-year relapse rate was 36%, ranging from 24% to 44%. At 2-year relapse rate was 54% (41%-82%). Risk factors for relapse were age (HR 0.98, CI 0.97–0.99), smoking at baseline (HR 1.19 (CI 0.96–1.48), disease duration (HR 1.06, CI 1.03–1.10), disease location (L2) (HR 1.04, CI 0.77–1.41), disease location (L3) (HR 1.25, CI 0.96–1.62), +L4 (HR 1.50, CI 1.00–2.27), type of anti-TNF therapy (adalimumab vs. infliximab) (HR 1.18, CI 0.95–1.48), immunosuppressant use (HR 0.68, CI 0.54–0.85), steroid used 6–12 months prior to cessation (HR 1.24, CI 0.72–2.13), ≥1 anti-TNF therapy in medical history (HR 1.37, CI 1.04–1.80). The prediction model had a discriminative ability with a C-statistic of 0.62 (0.58–0.64). Biochemical parameters of remission (CRP, FC, haemoglobin, leucocytes), anti-TNF trough level and endoscopic data will be added to this preliminary prediction model.
Conclusions: The overall risk of relapse in CD patients in remission is 37% within 1 year after anti-TNF cessation. Despite associations between clinical parameters and relapse risk, individualised prediction solely based on clinical parameters remains challenging. Improvement of the discriminative ability of the prediction model may be anticipated after insertion of biochemical and endoscopic data.

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Advance of medical therapies may improve outcome of ulcerative colitis with cytomegalovirus infection

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Background: Cytomegalovirus (CMV) reactivation often makes ulcerative colitis (UC) refractory. Despite recent advance of medical treatment for UC, few studies evaluated whether change of UC management affected clinical course of UC with CMV infection.
Methods: A total of 140 CMV-IgG positive UC patients, who underwent colonoscopy with the polymerase chain reaction assay using colonic biopsy specimen (mucosal-PCR) to investigate CMV reactivation between October 2003 and December 2017, were enrolled in this retrospective observational study. We divided those patients into two cohorts, the early (October 2003–June 2009, $n = 44$) and the late period (July 2009–December 2017, $n = 96$), according to the timing of colonoscopy. We compared cumulative colectomy-free rate between two periods.
Results: There was no significant difference in baseline characteristics between two groups. The 5-year cumulative colectomy-free rate in the late period was higher than that in the early period (72.4% vs. 91.2%; $p < 0.05$, Figure 1). Of note, while approximately 70% of CMV seropositive patients had CMV reactivation in the early cohort, less than half patients did in the late cohort (68.2% vs. 42.7%; $p < 0.05$). Significantly less patients in the later period received corticosteroids at enrolment compared with those in the early period (40.9% vs. 22.9%; $p < 0.05$). Usage of other immunosuppressant including tacrolimus, TNF-α antagonist, and thiopurine at baseline was similar between two groups. The proportion of patients with initiation or dose escalation of corticosteroids after colonoscopy was significantly lower in the late period than in the early period (27.3% vs. 12.5%; $p < 0.05$). Tacrolimus was also administered after colonoscopy less frequently in the late period than in the early period (47.7% vs. 30.2%; $p < 0.05$). Furthermore, the 5-year cumulative colectomy-free rate of patients with CMV reactivation in the late period was higher than that in the early period (66.0% vs. 92.7%; $p < 0.05$, Figure 1), although anti-viral therapy was more frequently performed in the early period than the late period (80% vs. 22.0%; $p < 0.01$). The proportion of patients who received corticosteroids

after CMV reactivation were significantly lower in the late period (60% vs. 29.3%; $p < 0.01$).

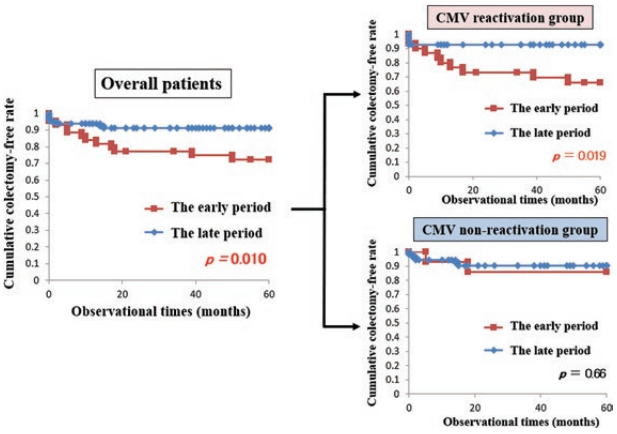

Figure 1. Cumulative colectomy-free rate.

Conclusions: Our results suggest that recent medical management for UC patients, especially optimisation of corticosteroid use, could not only decrease CMV reactivation, but avoid colectomy in patients with CMV reactivation, both of which results in improvement of the long-term outcome of UC patients with CMV seropositivity.

P140

Challenges in colonoscopic surveillance in chronic IBD

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Background: Chronic inflammatory bowel disease (IBD) is associated with a 2- to 4-fold elevation of lifetime risk of colorectal cancer (CRC). Regular colonoscopic surveillance and the detection of colonic epithelial dysplasia are the gold standard for the early detection of CRC. Despite this, up to a third of patients will develop CRC within 3 years of a normal colonoscopy. We therefore aimed to calculate our post-colonoscopy CRC rate and identify the root causes for these cancers to inform where practice could be improved.

Methods: Surveillance colonoscopy procedures were extracted from Unisoft® from April 2008 to December 2015 to allow determination of the 3-year post colonoscopy cancer rate.

Results: 1460 procedures were undertaken including 845 males (58%) with a mean age of 53 years (range 17–88 years). The IBD diagnosis was: 1051 ulcerative colitis, 337 Crohn's disease and 72 IBD-Unclassified. Chromoendoscopy was adopted in 2012 and is achieved in approximately 50% of these procedures. Reasons for non-compliance with the use of chromoendoscopy include patient factors (poor bowel preparation, concurrent colonic inflammation and extensive pseudopolyposis), equipment factors (no dye spray) and endoscopist skill. Chromoendoscopy led to a significant reduction in the mean number of random colonic biopsies from 17 to 11 ($p < 0.05$). The post-colonoscopy cancer rate was <10% in our unit. Low-grade dysplasia was not a robust marker of future CRC compared with high-grade dysplasia.

Conclusions: We demonstrate the challenges in detecting CRC in patients with chronic IBD and confirm the poor clinical utility of low-grade dysplasia in predicting future CRC. There is an urgent need to develop more objective predictive biomarkers of future CRC risk.

P141

Faecal calprotectin correlates to UCEIS and can predict short-term recurrence in patients with ulcerative colitis

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Background: We recently reported that ulcerative colitis Index of Severity (UCEIS) of 0–1 is associated with better long-term prognosis while faecal calprotectin is a valuable biomarker for assessing the severity of UC. However, there have been only few large multi-centre cohort studies trying to predict short-term recurrences using faecal calprotectin (FCP).

Methods: The multi-centre prospective cohort study was conducted in 756 UC patients from 14 Japanese academic institutions. Median FCP level on each score of UCEIS (range 0–7) was calculated (Cohort 1) and the correlation between FCP and UCEIS was assessed using Kruskal–Wallis analysis. We also assessed the association of FCP level and clinical recurrence (partial Mayo score>2) in quiescent UC patients (partial Mayo score of 0–1) using the log-rank test and cox proportional hazard model(Cohort 2). A receiver-operating characteristic curve analysis was conducted to determine the cut-off value of the FCP at baseline for predicting mucosal healing and clinical recurrence. FC was measured by Fluoro Enzyme Immunoassay using EliA Calprotectin 2.

Results: The median FCP level increased gradually as UCEIS become higher ($p < 0.001$) although FCP level is difficult to distinct between UCEIS of 0 (IQR:18.8–143.8) and 1 (IQR: 32.9–222.8) or UCEIS of 2 (IQR: 39.8–862.0) and 3 (IQR: 81.4–858.3). Each UCEIS subscore (vessel, bleeding, and erosion/ulcers) strongly correlated to FCP level (all items; $p < 0.001$). A cut-off value of 131 mg/kg for FCP level had a sensitivity of 75% and a specificity of 71% to predict UCEIS of 0-1. In Cohort 2, 24 (6.3%) and 90 (23.7%) of 379 quiescent patients had recurrences within 3 and 12 months, respectively. A cut-off value of 156 mg/kg for FCP level had a sensitivity of 68% and a specificity of 82% to predict recurrence within 12 months. The recurrence rate in patients with FCP ≥ 156 mg/kg (55.4%) was significantly higher ($p < 0.001$) than those with FCP < 156 mg/kg (12.2%). In a multi-variate analysis, FCP ≥ 156 mg/kg was an independent risk for recurrence (HR 6.2; 95% CI 3.6–10.6). Regarding the recurrence within 3 months, a cut-off value of 263.5 mg/kg for FCP had a sensitivity of 56% and a specificity of 84% to predict recurrence. The recurrence rate within 3 months in patients with FCP ≥ 263.5 mg/g (31.6%) was significantly higher ($p < 0.001$) than those with FCP < 263.5 mg/kg (5.7%). Only 2 (1.4%) 144 patients with FCP < 30.6 mg/kg had recurrences within 3 months.

Conclusions: FCP levels are strongly correlated to UCEIS and appears to be predictors of both short- and middle-term of recurrence in quiescent UC patients.

P142

Ulcerative colitis: risk factors for relapse in clinical remission patients

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Background: Ulcerative colitis (UC) is a chronic inflammatory bowel disease, characterised by periods of remission and relapse. The aim of this study was to identify factors associated with a higher risk of relapse in patients in clinical remission.
Methods: Retrospective study, including UC patients in clinical remission with minimum follow-up of 2 years. Clinical relapse was defined as a need for therapeutic escalation and UC-related hospitalisation or surgery. Statistical analysis was carried out by means of t-test and chi-square (univariate analysis) and logistic regression (multi-variate analysis). A p-value < 0.05 was considered statistically significant.
Results: In total, 169 patients were included, 51.5% female. Clinical relapse was observed in 30.2% of the patients. In the univariate analysis, relapse was more frequent in patients with higher number of previous relapses (2.7 vs. 1.0; $p < 0.001$), younger age at diagnosis (36.6 vs. 41.2 years ;$p = 0.045$) and with therapeutic non-adherence (82.4% vs. 17.6%; $p < 0.001$). Patients who presented at clinical remission with a Mayo Endoscopic Score (MES) of 0 had a recurrence rate of 5.6%, significantly lower than the rate of 43.2% presented by the group with mild endoscopic disease activity (MES 1) and also lower than the rate of relapse of 73.3% presented by the group with moderate endoscopic disease activity (MES 2) ($p < 0.001$). In the multi-variate analysis, therapeutic non-adherence (HR 24.6 CI 95% 2.0–296.6; $p = 0.012$) and MES >0 (HR 16.6; CI 95% 2.9–94.2; $p = 0.002$) were the only independent risk factors associated with relapse.
Conclusions: Presented results suggest that therapeutic non-adherence and MES at clinical remission may be helpful factors in identifying patients with inactive clinical disease at a higher risk of disease relapse.

P143

Measuring the mediating effects of tofacitinib on health status in ulcerative colitis: data from the OCTAVE programme

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Background: The Mayo score (MS) is typically used to calculate ulcerative colitis (UC) clinical trial efficacy endpoints and includes four components: stool frequency, rectal bleeding, endoscopic appearance, and physician assessment. Although generic patient-reported outcome measures (PROMs) like the Short Form-36 (SF-36) are also frequently included in UC trials, it is unclear whether treatment effects on these measures are fully explained by MS changes or whether other unobserved variables are in play. Here, we explored the interrelationship among treatment, SF-36 domains and MS using a mediation modelling framework.
Methods: Pooled data at the end (Week 8) of the two double-blind, identically designed induction studies of tofacitinib (OCTAVE Induction 1 and 2, NCT01465763 and NCT01458951) were used. Tofacitinib is an oral, small-molecule Janus kinase inhibitor approved in several countries for the treatment of ulcerative colitis (UC). A mediation model was specified such that the MS components served as mediators between treatments (active treatment vs. placebo) and the eight SF-36 domain scores (bodily pain, general health, mental health, physical functioning, emotional role limitations, physical role limitations, social functioning, and vitality), which served as the outcomes. Our primary interest was the extent to which treatment affects the SF-36 domain outside of any change in MS components (ie the direct path).
Results: In total, 1079 patients with moderately to severely active UC were included. For all SF-36 domains, the indirect path (ie the pathways from treatment to the MS components and then to each SF-36 domain score) was significant (all $p < 0.05$) and explained 65.6% (bodily pain) to 92.9% (mental health) of the total effect of the treatment on SF-36 domain scores. In other words, the majority of the total effect of treatment on the SF-36 scores was explained by changes in Mayo score components. Yet, for bodily pain (34.4%), physical role limitations (31.2%) and vitality (32.7%), the direct paths (ie, the pathway from treatment directly to each SF-36 domain outside of any effect from changes in MS components) were also significant (all $p < 0.05$). No other direct effects were observed.
Conclusions: Our study suggests that the MS, while important in capturing disease activity, does not fully mediate treatment effects on all SF-36 domains. Hence, the results indicate that tofacitinib can directly improve certain aspects of general health status—specifically, bodily pain, physical role limitation and vitality—outside of any benefit of improving stool frequency, rectal bleeding, endoscopic assessment, or physician assessment. These results reinforce the value of health status PROMs such as the SF-36 in capturing the full benefit of UC treatment.

P144

Correlation between clinical, endoscopic, histological activity scores in a cohort of patients with ulcerative colitis: a prospective study

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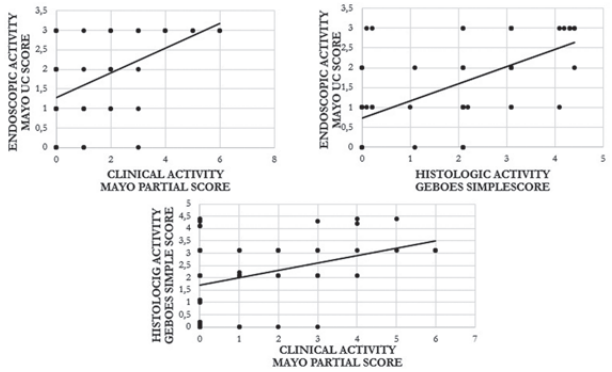
Background: The relationship between clinical, endoscopic and histological scores used in ulcerative colitis (UC) is debated. Primary aim was to assess, in a prospective study, the correlation between clinical, endoscopic, and histological scores of activity in a cohort of UC patients undergoing colonoscopy. Secondary aim was to assess the role of histological scores in clinical practice.
Methods: From February 2016 to February 2017 UC patients undergoing colonoscopy according to clinical indication were enrolled. Inclusion criteria: (1) diagnosis of IBD; (2) age> 18, <80 years; (3) regular follow-up; (4) indication for colonoscopy. During colonoscopy ≥2 biopsies were taken from ≥1 macroscopically involved area

and, possibly, from ≥1 uninvolved area. All colonoscopies were performed by the same IBD-dedicated gastroenterologist. Clinical activity was assessed with Mayo partial score (activity ≥3),[1] endoscopic activity with the Mayo endoscopic score (activity ≥2).[1] Histological activity was assessed by the same IBD-dedicated pathologist using the Geboes Simplified Score for UC (activity ≥3.1).[2] Scores were blindly assessed. Follow-up was planned at 1 year. Data expressed as median [range]; coefficient of correlation; T-test.

Results: UC cohort included 91 patients (M 52 [57%], age 51 [24–80] years, UC duration 15 years [1–48] years). UC extent was *n* (%): pancolitis 43(47%), left sided 25(28%), proctitis 22(25%) patients. The day of colonoscopy UC was clinically active in 16 (18%), inactive in 75 (82%) patients. Endoscopic activity was observed in 46(51%) patients (Mayo score: [*n*]: 0[17];1[28]; 2[21], 3[25]). In UC, microscopic activity (GSS ≥ 3.1) was observed in 39/91 (43%) patients: 5 of these 39 patients were in endoscopic remission. Significant correlation was observed between clinical vs. endoscopic scores ($r = 0.486$; $p < 0.0001$); clinical vs. histological scores ($r = 0.35$; $p < 0.0001$). At 1-year clinical follow-up data were available in 77 UC patients (75%). In 1 year, UC has been clinically active in 24 (31%) patients, inactive in 53 (69%) patients. 11/24 (46%) patients were clinically active at baseline, 15/24 (63%) patients endoscopically and 16/24 (67%) patients histologically. Of the 5 patients in endoscopic remission and histological activity at baseline, 1 had a clinical relapse.

Conclusions: In a prospective study, significant correlation was observed between clinical, endoscopic and histological activity in UC. Histological activity observed in UC patients in endoscopic remission may represent a predictive marker of clinical relapse.



Correlation between clinical and endoscopic, endoscopic and histological, clinical and histological activity scores

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P145

Telephone straight-to-test (tSTT) improves early diagnosis of inflammatory bowel disease (IBD)

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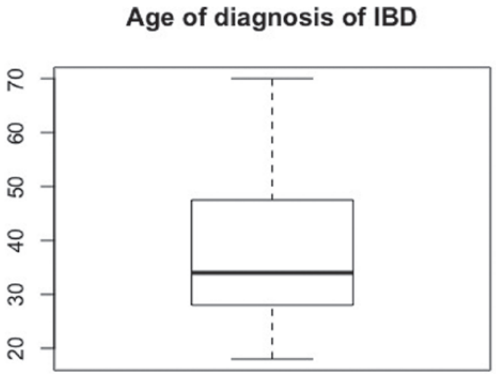
Background: ISBEN study showed that the average time to reach a diagnosis in IBD is 8.3 months in Crohn's disease (CD) and 4.5 months in ulcerative colitis (UC), highlighting a challenge in establishing an early diagnosis. In IBD, early diagnosis and treatment has a positive impact on the disease outcome. Barts health NHS trust is one of the hospitals pioneered in tSTT service aiming to reduce the waiting time in patients referred by primary care GPs with lower GI symptoms. Our study aims to assess whether tSTT pathway reduces the delay in diagnosing IBD.

Methods: In tSTT pathway, specialist colorectal nurses scrutinise routine (18-week wait) and urgent (2-week wait) referrals. The priorities of the investigations are based on the information on referral letters and patient history during telephone assessment. The endoscopic assessment can be expedited in patients with features suggestive of IBD such as family history, raised faecal calprotectin and weight loss.

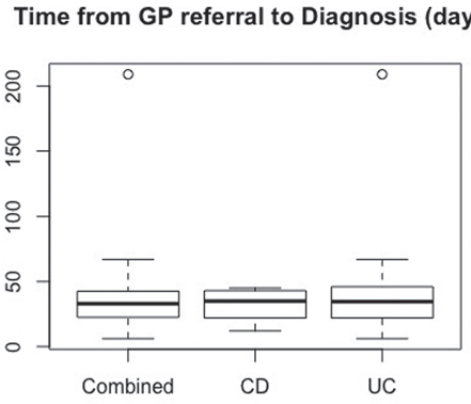
Results: During a 4-year period from 1 July 2013 to 1 July 2018, a total of 1757 referrals were received. Seventy-eight (4.4%) patients were identified to have findings such as inflammation or ulcers suspicious of inflammatory bowel disease on flexible sigmoidoscopy or colonoscopy. Of them, 47/78 patients were found to have a new diagnosis of IBD. The remaining patients were eventually diagnosed as drug induced, infective, bowel prep-related or diverticular-related colitis.

Of 47 new diagnosis of IBD, 24 (51%) were UC, 12 (25.5%) Crohn's disease (CD) and 11 (23.5%) indeterminate colitis. There is an equal male to female ratio (25:22). Mean age of diagnosis is 39 (range 18–70).



Boxplot of age of diagnosis.

Average time from GP referral to diagnosis is 37 days (32.4days in CD and 41.5 days in UC)



Boxplot of time to diagnosis.

There is a significant difference in time to diagnosis between 2 week wait and 18 week wait referral (25.2 days vs. 45.7 days, $p = 0.004$).

Conclusions: Our tSTT data shows a significant improvement in diagnosing inflammatory bowel disease in patients presenting to GP

with lower GI symptoms compared with ISBEN study. When triaged with tSTT, even routine 18 week referral reaches much earlier diagnosis of IBD. Even though, there is a statistically significant difference between 2 week and 18 week referral, since 2 week wait is resource intensive, its clinical significance in earlier detection is debatable.

P146

Dysplasia Surveillance in inflammatory bowel disease—a cohort study

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Background: Patients with inflammatory bowel disease (IBD) are at increased risk for developing colorectal cancer (CRC). Currently, surveillance colonoscopy is recommended to detect and treat neoplastic lesions.
Methods: A cohort study was conducted to determine clinical and endoscopic variables associated with dysplasia in IBD patients who were part of a colonoscopy surveillance programme between 2011 and 2016.
Results: In total, 162 patients (51.2% men, mean age at diagnosis 36.8 ± 13.5 years, mean duration of IBD at the start of the Programme: 11.0 ± 8.9 years) were included. 105 patients had ulcerative colitis (UC) and 57 had Crohn's Disease (CD). Six patients had concurrent primary sclerosing cholangitis (PSC), 18 had a family history of CRC and 6 had personal history of colorectal dysplastic lesions. 342 colonoscopies were performed during the 5 years period (2.1 ± 1.2 colonoscopies/patient). Random biopsies were performed at least once in 81.5% of patients with a mean 27.5 ± 6.4 biopsy samples per colonoscopy and 33.3% of the patients underwent chromoendoscopy (CE) at least once. Endoscopically resectable lesions were detected in 55 patients (34%) and visible lesions deemed unfit for endoscopic resection were found in 5 patients (3.1%). Overall, 61 dysplastic visible lesions (58 with low-grade dysplasia and 3 with high-grade dysplasia) and 1 adenocarcinoma were found in 34 patients. Dysplasia in random biopsies was present in 3 patients, the yield of random biopsies for dysplasia being 1.85% per-patient (3/162), 1.75% per-colonoscopy (6/342) and 0.25% per-biopsy (9/3637). Dysplasia detected in random biopsies was associated with a personal history of visible dysplasia ($p = 0.006$). The presence of dysplasia, either in targeted samples or random biopsies, was significantly associated, on univariate analysis, with type of IBD (26.7% in UC vs. 10.5% in CD) ($p = 0.016$), with the performance of random biopsies ($p = 0.009$), and CE ($p = 0.05$) and with previous ileocolonic surgeries ($p = 0.002$). On multi-variate analysis, dysplasia was associated with type of IBD ($p = 0.034$), with the performance of random biopsies ($p = 0.09$) and with previous ileo-colonic surgeries ($p = 0.001$). Median disease duration was superior in patients with dysplasia compared with those without dysplasia (14.0 (IQR 5.75–21.0) vs. 9.0 (IQR 3.25–15.0) years, $p = 0.03$). There was no significant association between the presence of dysplasia and family history of CCR or personal history of PSC.
Conclusions: Our data confirm that patients with longstanding IBD, in particular UC, should be enrolled in dysplasia surveillance Programmes and that performing CE and random biopsies helps in the detection of colonic neoplastic lesions.

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Thromboembolic complications in patients with Inflammatory bowel disease predict poor prognosis: a large North Indian cohort study

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Background: Inflammatory bowel disease (IBD) is associated with increased risk of thromboembolic (TE) complications. However, the information on exact burden of TE in IBD and its predictors are lacking, especially from developing countries, where IBD is on the rise. The present study aimed to find out the prevalence and predictors of TE in patients with IBD and their prognosis.
Methods: A cohort of 3597 patients with IBD (UC $n = 2752$, CD $n = 845$) under follow-up from 2004 to 2018 was analysed and this case–control study included 35 IBD patients (ulcerative colitis [UC, $n = 25$]; Crohn's disease [CD] $n = 10$) with history of TE. Details on demographics, extra intestinal manifestations (EIMs), patients status at the time of TE, type and outcome of TE including recurrence, treatment details before and after TE and disease course before and after TE were collected and compared with IBD patients without history of TE in the ratio of 1:4.
Results: The prevalence of TE in patients of IBD was 1% (UC 0.9%, CD 1.2%). Among patients with TE (mean age, 39.6 ± 14 years, 48.6% males), mean duration from disease onset to TE for UC and CD was 35.3 ± 37.4 and 120.2 ± 147.9 months, respectively. More UC patients with TE had severe disease (80% vs. 10%, $p < 0.001$), pancolitis (79.2% vs. 40%, $p = 0.001$), other EIMs(44% vs. 22%, $p = 0.026$), chronic continuous disease course (44% vs. 13%, $p < 0.001$), steroid dependent disease (60% vs. 13%, $p < 0.001$),H/o surgery (12% vs. 5%), h/o acute severe colitis (48% vs. 9%, $p < 0.001$) and mortality related to disease complication (16% vs. 0, $p < 0.001$) when compared with those without TE. Fifty-two per cent of UC patients with TE were on IV steroids ($p < 0.001$) and 88% on 5 ASA ($p = 0.005$) before TE onset. More CD patients with TE had A2 disease (60% vs. 57.5%), terminal ileal ± caecal involvement (55.6% vs. 27.5%), stricturing type of disease (62.5% vs. 30%), moderate to severe form of disease presentation (83.3% vs. 25%, $p = 0.004$), chronic continuous disease course (50% vs. 10%, $p = 0.003$), steroid dependent (70% vs. 27.5%, $p = 0.012$), H/o surgery (20% vs. 7.5%) and mortality related to disease complication (10% vs. 0, $p < 0.001$). Sixty per cent of CD patients with TE were on oral steroids and 10% on IV steroids before the onset of TE ($p = 0.043$).
Conclusions: Approximately 1% patients with IBD develop thromboembolism during their disease course. Thromboembolism is a marker of severe disease, and higher disease-related complications including mortality.

P148

Timing to surgery in symptomatic Crohn's disease—patients perception

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Background: Medical treatment is still the first approach on Crohn's disease (CD) in most of the cases. Patients on remission after medical and/or surgical treatment show significant improvement on their quality of life (QoL). However, there is scarce bibliography

evaluating the patients point of view regarding their surgery and the timing on performing this. The aim of this study was to evaluate how confident are patients with the timing of their surgery and how the surgery changed their QoL.
Methods: A questionnaire was sent to 274 patients operated, as a first surgery, between 1989 to 2018 due to CD at a single institution. The questionnaire included 12 questions: evaluating if they would have preferred their surgery (with or without stoma) to have been carried out sooner, later or at the same time as it was done and about their changes in quality of life. Clavien Dindo's classification was used to evaluate postoperative complications. A consent form was obtained from all patients participating on the study. The study was accepted by our Ethics Committee.
Results: In total, 98 (36%) patients complete the questionnaire. Seventy-two of 98 had a CD location type L1, 14/98 L2 and 12/98 L3. The behaviour of CD was 5 B1; 56 B2; and 37 B3. A stoma was done in 16 patients. Twenty-five patients needed a reintervention due to a relapse of the disease. Eighty of 98 reported a significant improvement in their QoL after their first surgery; 11/98 did not experience any change, and 7/98 explained a drop on it. Analysing the group of patients that needed a stoma as a treatment: 12/16 (75%) reported an improvement in their QoL; 2/16 (12%) did not experience changes and 2 more explain a worsen on it. Regarding the timing on surgery: 30/98 preferred their operation to have been done earlier (8/30 (26%) experienced some postoperative complication); and 6/98 thought it should have been done later. Ninety-three of 98 patient will accept a new surgery if the disease would reappear, and of them 33/93 (35%) had postoperative complications after surgery.
Conclusions: Surgery for CD improves patients QoL in a high proportion of patients even on those that need a stoma. One on every three patients in this series preferred their operation to have been done earlier. More studies should be done to consider if earlier surgery should be offered as an alternative to medical treatment rather than as an option when medical treatment fails.

P149

Searching for bile acid malabsorption using serum fibroblast growth factor 19 (FGF19) and faecal bile acids in patients with inflammatory bowel diseases, microscopic colitis and irritable bowel syndrome

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Background: Excessive amounts of bile acids (BA) entering the colon due to bile acid malabsorption (BAM) cause chronic bile acid diarrhoea (BAD). Fibroblast growth factor 19 (FGF19) is the ileal hormone providing feedback inhibition of BAs synthesis in the liver. Little is known about the mechanisms of BA dysregulation in patients with inflammatory bowel disease (IBD), irritable bowel syndrome (IBS-D) and microscopic colitis (MC).
Methods: The aim was to evaluate the diagnostic accuracy of serum levels of FGF19, total free faecal bile acids (TFFBA), and faecal calprotectin (FC) in patients with chronic diarrhoea. Methods: we enrolled 40 adult patients with chronic diarrhoea who underwent standard laboratory tests, colonoscopy, serum FGF19, FC, TFFBA. Patients were divided into five groups: 14 patients with active IBD, 5 patients with IBD in remission, 5 patients with IBD after surgery, 11 patients with IBS-D and 5 patients with MC. Fasting serum FGF19, TFFBA were measured by ELISA test and FC by the quantitative immunochromatographic method.
Results: Diagnosis of BAM was confirmed in 24 of 40 patients (60%) and excluded in 16 of 40 patients (40%). For IBS-D, serum FGF19 produced a ROC curve with AUC of 0.777 (p-value of 0.007 and 95% CI [0.628–0.927]). Sensitivity and specificity of FGF19 were 72.7% and 72.4%, respectively for a cut-off value of 88.22 pg/ml, which will lead to accurate prediction of BAM in 72% IBS-D patients. TFFBA shows no significant difference between all the groups.
Conclusions: BAM is very under-diagnosed and FGF19 could be used for screening for BAM in patients with chronic diarrhoea, because there is bile acid binder's treatment. Further bigger studies are needed to establish the efficacy of FGF19 and TFFBA.

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High adherence to surveillance guidelines in IBD results in low CRC and dysplasia rates, while rates of dysplasia and cancer are low before the suggested start of surveillance. Results from a tertiary IBD centre

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Background: Patients with Crohn's disease(CD) and ulcerative colitis(UC) are at increased risk for colorectal dysplasia (CRD) and cancer (CRC). Adherence to CRC surveillance guidelines is reported to be low internationally. Our aim was to evaluate surveillance practices at the tertiary IBD Center of the McGill University Health Center (MUHC) and to determine CRD/CRC incidence rates.
Methods: A representative IBD cohort with at least 8 years of disease duration (or with PSC) who visited the MUHC between 1 July and 31 December 2016 were included. Adherence to surveillance guidelines was compared with modified 2010 BSG guidelines. Incidence of CRC, high-grade dysplasia (HGD), low-grade dysplasia (LGD) and colorectal adenomas (CRA) were calculated based on pathology reports.
Results: In total, 1356 CD and UC patients (disease duration: 12 (IQR: 6–22) and 10 (IQR: 5–19) years) were identified. The surveillance cohort consisted of 689 patients (296 UC and 384 CD). 91.5% of patients had at least one surveillance colonoscopy. Adherence to surveillance guidelines was 75.6/82.1% in UC/colonic CD. Adequate number of biopsies were taken in 53.7/54.2% of UC/colonic CD patients. Incidence of CRC/HGD in UC and CD with colonic involvement was 19.5/58.5 and 25.1/37.6 per 100 000 patient-years. Incidence of dysplasia before 8 years of disease duration was low in both UC/CD (19.5 and 12.5/100 000 patient-years) with no patients developing CRC. The CRA rate was 30/38% in UC/colonic CD.
Conclusions: High adherence with surveillance guidelines and overall low CRC and dysplasia, but not CRA rates were found in the

screened population, suggesting that meeting updated, stratified, surveillance recommendations may result in low advanced neoplasia rates. CRC and dysplasia rates incidentally detected before the suggested start of the surveillance were low.

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Risk factors for first intestinal surgery in Crohn's disease

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Background: Despite improved treatment options, intestinal complications and subsequent surgeries are still frequent in Crohn's disease (CD). We aimed to investigate the likelihood of first surgery in patients with CD treated at a tertiary centre and to explore potential risk factors early in the course of disease.
Methods: This is a single-centre cohort study of 887 patients with CD (female 455; median age at diagnosis 25 years) usually referred after diagnosis. Medical characteristics were received from a validated database (IBDIS, Inflammatory Bowel Disease Information System). The primary end point was first intestinal surgery (resection, strictureplasty). Cox proportional hazard regression analysis was used to explore the impact of potential confounders on the time from diagnosis to first surgery or to last follow-up. The following variables were included in the analysis: diagnostic delay (time from symptom onset to diagnosis), immunosuppressive and/or biological treatment, location of disease, smoking habits, gender, and year of diagnosis. Hazard ratios (HR) with 95% confidence intervals (CI) are reported.
Results: 457 (52%) patients underwent intestinal surgery during a median follow-up period of 13 years. After 12 years 50% of the patients had undergone first intestinal surgery. Forty-six per cent of patients received immunosuppressives and 35% of patients received biological treatment prior to first intestinal surgery. Ileal location, no immunosuppressive and no biological treatment and smoking were found to be significant as well as strong independent risk factors for first intestinal surgery in CD (Table). Patients with late initiation (after 2 years after diagnosis) of immunosuppressives as well as biologics tended to be at lower risk for surgery compared with patients with early initiation (within 2 years after diagnosis) (HR 0.736, 95% CI 0.503–1.078 and HR 0.588, 95% CI 0.330–1.046). Diagnostic delay, gender and year of diagnosis had no significant influence on the risk of surgery.

Parameter	HR (95% CI)	*p*-Value
Location Montreal L1 vs. L2	5.933 (3.757–9.369)	<0.001
Location Montreal L3 vs. L2	3.861 (2.488–5.988)	<0.001
No immunosuppressive treatment	2.117 (1.673–2.678	<0.001
No biological treatment	3.793 (2.731–5.268)	<0.001
Smoking	1.260 (1.008–1.575)	0.042
Diagnostic delay	1.000 (0.998–1.001)	1.000
Female gender	0.878 (0.717–1.076)	0.211
Time of diagnosis: (–1999) vs. (2000–2009)	1.263 (0.983–1.621)	0.068
Time of diagnosis: (–1999) vs. (2010–2018)	1.175 (0.864–1.600)	0.305

Risk factors for first intestinal surgery in CD patients.

Conclusions: Patients with ileal location, without treatment with immunosuppressives or biologics, as well as smokers are more likely to undergo first intestinal surgery in CD. Even late initiation of immunosuppressive as well as biological treatment might avert this risk of surgery in CD patients.

P152

Fatty liver disease in IBD patients as a part of extraintestinal manifestations

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Background: Inflammatory bowel diseases (IBD) are frequently associated with pathologic findings in the liver and biliary tract, ranging from minor alterations, such as liver fatty changes, to severe conditions, like primary sclerosing cholangitis.[1] Fatty liver disease (FLD) is the most common liver complication of IBD and is often reversible, affecting people with ulcerative colitis (UC) and Crohn's disease (CD).
Methods: The aim of the study was to investigate the incidence of hepatic steatosis as a part of the extraintestinal manifestations (EIMs) in IBD patients and the related biochemical laboratory abnormalities. A total of 480 patients was studied, 160 with UC, and 160 with CD and the results were compared with those of a control group of 160 patients with irritable bowel syndrome (IBS). An abdominal ultrasound (AUS) was performed on all of them as a non-invasive method of assessing the presence and the degree of liver steatosis, in combination with the liver function tests (LFTs), lipid and glycaemic profile blood tests.
Results: Of all the studied IBD patients, hepatic steatosis based on AUS criteria was discovered in 59.4% with CD and in 51.9% with UC. In the control group steatosis was found in 38.8% of cases (⊠ = 0.001). In both groups of patients predominant are those with mild steatosis: IBD group (33.43%) and IBS group (17.50%). 15.62% of IBD patients have moderate steatosis, only 5% have severe steatosis, unlike the IBS group, where 9.37% have severe steatosis. According to the severity of the disease (CDAI), we found that in patients with CD, steatosis prevailed in those with moderate disease activity (46.30%), while in patients with UC in those with severe activity (43.40%), as measured by the Mayo Scoring System. Over three-fourth (77.70%) of IBD patients with steatosis have other concomitant EIMs (⊠ < 0.001), in CD (57.20%), and in UC (42.80%). Steatosis is frequent in the inflammatory-type behaviour of CD (51.60%) and ileocolonic localisation of CD (41.10%), and prevalent in the chronic recurrent form of UC (77.10%) and in those with pancolitis (51.80%). In patients with CD less than one-fourth (22.30%) of those with steatosis have perianal disease. There was no significant difference in steatosis grade and association between FLD and IBD behaviour and extent. In our study, we found that in IBD patients with hepatic steatosis, the presence of elevated liver enzymes, lipid and glycaemic status disorders was significantly more frequent than in the control group.
Conclusions: The incidence of hepatic steatosis is higher amongst IBD patients. We need further studies to determine the influence that the evolution of IBD has over the hepatic steatosis.

P153

Quantum blue anti-adalimumab: development and evaluation of a point of care rapid test for measuring anti-adalimumab antibodies in human serum

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Background: Patients suffering from inflammatory bowel disease (IBD) treated with adalimumab might not respond to the biologic at all, or might suffer from a secondary loss of response (SLR). A SLR is often caused by an immune response during which neutralising anti-adalimumab antibodies (ADADs) may develop. These ADADs are by nature of different isotypes and vary in their affinity and specificity towards their biologic target. The development of ADADs causes a significant decrease of the biologic's trough level. A rapid test for the detection of ADADs is therefore crucial and allows the adaptation of the treatment regime. In order to detect all varieties of ADADs it is inevitable to have an assay which is not limited to one specific antibody isotype.
Methods: A drug-sensitive sandwich lateral flow assay was developed using adalimumab coated gold nanoparticles and an adalimumab capture on the membrane, allowing the detection of drug neutralising anti-adalimumab antibodies in human serum samples. The calibration is performed with calibrators based on human serum, spiked with monoclonal human ADAD. Real patient samples were used to compare the Quantum Blue® Anti-Adalimumab rapid test with a commercially available ELISA test.
Results: The Quantum Blue® Anti-Adalimumab rapid test allows the analysis of diluted human serum samples within 15 min. A single 1:10 dilution step of the serum sample is required before sample loading onto the test cassette (volume 80 µl). The readout is performed with a Quantum Blue® Reader resulting in a preliminary measuring range of 0.5 to 12.5 µg/ml. Due to missing international standard material for ADAD and the polyclonal immune response in patients, the Quantum Blue® Anti-Adalimumab was classified as semi-quantitative. By testing patient samples a good diagnostic agreement between the Quantum Blue® Anti-Adalimumab and the commercial ELISA was achieved.
Conclusions: The Quantum Blue® Anti-Adalimumab rapid test allows a fast detection of anti-adalimumab antibodies in human serum samples. The assay can be carried out with a minimum of external equipment and may therefore support a fast adaption of the treatment regime, providing a valuable tool for pro-active therapeutic drug monitoring.

P154

Development of a novel ultrasound based score for assessing disease activity in ulcerative colitis: preliminary results

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Background: Colonoscopy based scores are the gold standard for assessing disease activity in ulcerative colitis (UC). The aim of this study was to develop a new bowel ultrasound (USG) based score for assessing disease activity in UC and to assess its correlation with Mayo endoscopic score (MES).
Methods: Patients who underwent colonoscopy for assessment of disease activity also underwent USG within 2 weeks. Endoscopic activity was graded with MES; clinical disease activity was assessed using the Total Mayo Score (TMS). All assessments were performed for the rectum, sigmoid, descending, transverse, and ascending colon and caecum. A novel score based on Colonic wall thickness (CWT), loss of bowel wall stratification, Doppler activity (D) was calculated for each segment and correlated to the MES.

USG Feature	Score
Colonic Wall thickness	
<3mm	0
3-5mm	2
>5mm	4
Wall stratification	
Present	0
Absent	4
Doppler Activity	
No vessels	0
1-2 spots	2
Stretches in wall	4
Extending beyond the wall	6
Total US Score	
Total USS correlation to MES	**Mayo Score**
<4	0/1
4-8	2
>8	3

USG based score.
Results: A total of 102 colonic segments were analysed. Median CWT was lower in patients with MES 0-1 when compared with MES 2-3 (3 mm vs. 4.1 mm, $p = 0.01$). The ultrasound score (USS) was calculated for each colonic segment and correlated to the MES for that particular segment. USS correlation to MES for each segment was as follows: caecum ($r = 0.95$, $p = 0.0001$); ascending colon ($r = 0.9$, $p = 0.001$), transverse colon ($r = 0.955$, $p = 0.0001$), descending colon ($r = 0.845$, $p = 0.001$), sigmoid colon ($r = 0.816$, $p = 0.0001$), rectum ($r = 0.761$, $p = 0.001$). The USS for sigmoid colon correlated with the overall MES ($r = 1$, $p = 0.0001$), and Total Mayo Score ($r = 0.918$, $p = 0.0001$).
Conclusions: The novel ultrasound score has excellent correlation with MES. USS assessment of the sigmoid colon correlates with overall endoscopic activity and the Total Mayo score.

P155

Adherence to quality indicators among patients with inflammatory bowel disease: an international comparative analysis

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Background: Deficiencies in quality of care have been identified in a variety of inflammatory bowel disease (IBD) care domains, such as appropriate use of steroid sparing agents and preventative health maintenance measures. Many of these differences are due to practice variations among providers. The aim of this study was to assess variations in adherence to IBD-specific quality indicators across two tertiary referral centres.
Methods: A retrospective chart review measuring inpatient and outpatient quality indicators was conducted at Mount Sinai Hospital, Toronto, Canada (MSH) and the University of Leuven, Leuven, Belgium (UZL). The data were summarised using descriptive statistics and differences in quality indicators were assessed using the Fischer's exact test. A p-value of <0.05 was considered significant.
Results: Among 450 outpatients (MSH = 225, UZL = 225), 269 (59.8%) had CD, 169 (37.7%) had UC, and 12 (2.7%) had IBD-U. All patients at UZL had undergone a post-operative colonoscopy to assess for recurrent disease within 12 months of surgery, when compared with 78% of patients at MSH ($p < 0.001$). More patients at MSH had been on a prolonged course of steroids, defined as a period of greater than 3 months (57.4% vs. 6.4%, $p < 0.001$), however no differences were seen in the use of steroid sparing therapy between the two sites. More patients at MSH underwent routine bone density screening (12.2 vs. 4.4%, $p = 0.003$). However, there were no significant difference in screening rates among patients who had been on a prolonged course of steroid (17.09 vs. 28.57%, $p = 0.287$). Dysplasia surveillance according to recommended intervals was more commonly performed at MSH (83.5 vs. 64.8%, $p < 0.010$). Flu and pneumococcal vaccinations were more often recommended at UZL (80.5 vs. 53.7% MSH, $p < 0.001$). Among 352 inpatients (MSH = 194, UZL = 158), more patients at MSH received DVT prophylaxis (86.1 vs. 31.7%, $p < 0.001$) and underwent *C. difficile* testing (70.1 vs. 57.6%, $p = 0.015$). There was no significant variation in initiation of salvage therapy after 7 days of IV steroids among inpatients with acute, severe UC (75.68 vs. 58.33%, $p = 0.170$).
Conclusions: There were important differences in adherence to many of the quality indicators across two IBD referral centres. These differences underscore the notion that practice variations exist in managing complex IBD patients, even at IBD centres of excellence. Moreover, the regional variations noted underscore the importance of adapting quality improvement initiatives to the local context.

P156

Long-term outcomes of steroid-responsive and non-responsive patients with acute severe ulcerative colitis

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Background: Up to one-third of patients with acute severe ulcerative colitis (ASUC) will fail intravenous steroid (IVS) treatment, requiring rescue therapy with cyclosporin (Cys), infliximab (IFX), or colectomy. Even with the best available therapy, over 1/3 of these patients will still require surgery. Long-term outcomes of steroid-responsive (SR) patients have seldom been studied. We hypothesise that this subgroup of patients also presents an unfavourable short- and long-term prognosis.
Methods: Retrospective multi-centre study including patients fulfilling Truelove and Witts criteria for ASUC. Response to IVS was determined by the attending physician between the third and fifth day of admission. Patients were then classified as steroid non-responders (SNR) or SR. A cohort of consecutive patients admitted with a flare of ulcerative colitis but without criteria for ASUC served as a control group (CG). Endpoints included the need for biologics, surgery or both in the 5 years following discharge.
Results: A total of 253 patients were included, 170 (67.2%) with ASUC (SNR: 47, SR: 123) and 83 controls. 53.4% were male with median age of 33 (18–80). Although SR patients presented lower surgical rates than SNR patients (13.9% vs. 53.2%, $p < 0.001$) they were substantially higher than in the CG (0%, $p < 0.001$). Of note, 70.6% of surgeries in SR patients occurred within 1 year after discharge. Furthermore, 40.6% of SR patients were subsequently readmitted with a flare of colitis requiring biologics or surgery in 44.0% and 28.0% of cases, respectively. Concerning treatment escalation, SR patients required less biologic therapy than SNR (36.7% vs. 91.5%, $p < 0.001$) but more so than patients in the CG (18.1%, $p < 0.001$). Likewise, a composite endpoint of any unfavourable outcome was more common in SR patients than in the CG (44.9% vs. 18.1%, $p < 0.001$). Time to event analysis showed that SR patients reached an unfavourable outcome sooner than the CG (log-rank test $p < 0.001$).
Conclusions: Patients with ASUC present an unfavourable prognosis, even after an adequate response to IVS. Early therapy intensification should strongly be considered in these patients as almost half develop unfavourable outcomes.

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Assessment of sexual function among perianal Crohn's disease

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Background: Sexuality is a major determinant of quality of life; especially in young patients with perianal Crohn's disease (PCD). The primary aim of our study was to assess the prevalence of sexual dysfunction in PCD and to evaluate the impact of PCD on this prevalence.
Methods: A prospective cross-sectional study including all consecutive Crohn's disease and sexually active patients followed in the gastroenterology department of Habib Thameur Hospital (Tunisia) seen from January to June 2018. Patients included were invited to fulfil a validated questionnaire on their sexual function: Female Sexual Index Function (FSIF) for women and International Index of Erectile Function (IIEF) for men. The prevalence of sexual dysfunction was compared according to the presence or absence of perianal manifestations.
Results: Thirty patients were included. Mean age was 45 years [range 18–65 years] and sex ratio was 0.875 [M/F = 14/16]. Active PCD was found in 9 patients (30% of cases). PCD presented as complex perianal

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- Improve understanding of dietary therapy among physicians and dietitians
- Support and facilitate research of diet and its role in pathogenesis and treatment of IBD
- Increase participation of IBD Dietitians in ECCO
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D-ECCO Activities

- Publications on dietary therapy
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productive fistulas in 8 cases and anal stenosis in 1 case. Seven men (50%) had an erectile dysfunction. In women, a sexual dysfunction (FSFI score >26, 55) was reported by 100% of cases. By comparing the prevalence of sexual disorders according to the presence of active anoperineal lesions, we did not find any significant difference.
Conclusions: Sexual dysfunction is common during Crohn's disease and probably under diagnosed. It affects half of the men and women in our study. However, the presence of perianal manifestations does not seem to affect the occurrence of these disorders.

P158

Comparison of three endoscopic scores for prediction of relapse risk in ulcerative colitis

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Background: Mucosal healing (MH) is a target for induction therapy in the management of ulcerative colitis (UC). MH is defined by several endoscopic examinations and correlated with long-term clinical remission. However, the relationship between endoscopic examination and prediction of relapse rate in UC management has not been fully evaluated. We compared three endoscopic scores for the usefulness of relapse prediction after 12 months of endoscopic examination in the MH and non-mucosal healing (non-MH) group in UC.
Methods: We selected 51 cases of UC who underwent endoscopy at the Tokyo Medical and Dental University hospital from September 2014 to March 2017. Clinical remission was defined as partial Mayo score (pMayo) 2 or less and all other sub-scores were 1 or less. Clinical relapse was defined as introduction of new remission induction therapy. We compared three different endoscopic scores for prediction of relapse risk in UC. MH was defined in each endoscopic scores as Mayo Endoscopy sub-score (MES) 1 or less, Rachmilewitz endoscopic index (EI) 2 or less, and ulcerative colitis Endoscopic Index of Severity (UCEIS) 2 or less, with investigation for cumulative non-relapse rate.
Results: Patient background was as follows; average age was 42.9 ± 13.2 years old, 31 males and 20 females, 31 total colitis cases, 15 left-sided colitis cases, and 5 proctitis type cases, 34 clinical remission and 17 clinical non-remission, duration of disease was 9.3 ± 6.8 years. The cumulative non-relapse rate after 12 months of endoscopic examination was not significantly different in between MH group by MES at 75%, and non-MH group by MES at 52.2% ($p = 0.071$). Similarly, EI showed no significant difference in between MH group 76% and non-MH group 53.8% ($p = 0.32$). However, UCEIS showed significant difference between MH group 81.8%, and non-MH group 33.3% ($p = 0.001$).
Conclusions: It was suggested that diagnosis of MH by UCEIS might be useful for prediction of cumulative non-relapse rate after 12 months of endoscopic examination.

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The creatinine / cystatin C ratio is a surrogate marker of low skeletal muscle mass in patients with inflammatory bowel disease

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Background: Low skeletal muscle (LSM), which is referred to as sarcopenia, has been shown to be an independent predictor of lower overall survival in various kinds of diseases. Recently, the relation between LSM and disease prognosis is also reported in patients with inflammatory bowel disease (IBD), but the awareness of the relation in Asia is unclear yet comparing with Europe. The aim of this study was to identify the incidence of LSM in IBD patients and evaluate the significance of nutritional therapy. Furthermore, we investigate serum surrogate markers to predict LSM in IBD patient without examination of computed-tomography (CT).
Methods: We evaluated the inpatients with IBD data in our hospital registered between February 2015 and March 2017. Psoas muscle mass index (PMI, cm^2/m^2) was calculated by manual trace using Image J at the lumber three level on the CT images divided by height squared. The criteria of LSM was determined by PMI for man was lower than 6.36 and PMI for woman was lower than 3.92. We extracted the occurrence of IBD patients with LSM from our database, and assessed the relation between PMI and clinical data.
Results: Of 76 IBD cases including 34 patients with ulcerative colitis (UC) and 42 patients with Crohn's disease (CD), we assessed in this study. Fifty-seven of 76 patients were men, their mean of age with standard deviation (SD) was 35.0 ± 16.3 (year), and the mean of body mass index (BMI) with SD was 19.6 ± 2.8 g/m^2. The PMI for man was 5.1 ± 1.6, and the PMI for women was 3.1 ± 0.6. In terms of the nutritional therapy in CD patients, there was no correlation between PMI and nutritional therapy for 1 year before hospitalisation ($p = 0.438$). According to our determination of LSM, 64 of 76 cases (84.2%) were IBD patients with LSM, and 31 of 40 cases (77.5%) were IBD patients with LSM even though with normal BMI (BMI range: 18.5–24.9). Moreover, we found the correlation between PMI and Cre/CysC in our data ($p < 0.001$, $r = 0.576$).
Conclusions: The most of IBD patients requiring hospitalisation were LSM regardless of their normal weight. It was suggested that the Cre/CysC ratio might be a marker of LSM in IBD patients who need hospitalisation.

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Hypercoagulability in patients undergoing abdominopelvic surgery for inflammatory bowel disease: insights from thromboelastography

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Background: Hypercoagulability in patients with inflammatory bowel disease (IBD) is a haematological extra-intestinal manifestation thought to be driven by the gut inflammatory response. However, mechanisms driving the coagulation abnormalities are poorly understood. The aim of this pilot study is to characterise coagulation profiles in IBD surgical patients using thromboelastography (TEG).
Methods: A single-surgeon retrospective study was performed after IRB approval. Consecutive patients with Crohn's disease (CD) or ulcerative colitis (UC) who underwent bowel surgery from June to September 2018 were included. All patients (100%) received

perioperative VTE chemoprophylaxis. Hypercoagulability profile based on TEG results was defined by any combination of: (1) low R-value, (2) high-degree angle, (3) high maximum amplitude (MA), (4) elevated coagulation index. Short-term (30-day) surgical outcomes were reported. Figures represent frequency (proportion) or median (range).

Results: A total of 19 IBD patients had a TEG prior to surgery. The age was 33 (23–70), more were women (63%, *n* = 12) and most patients had CD (78%, *n* = 15). Overall 11 (58%) of patients were receiving steroids and 10 (53%) had were receiving biologics, while 6 (32%) of patients were hospitalised pre-operatively. Surgery was laparoscopic in 11 (58%) with 1 conversion to laparotomy. All patients (100%) received VTE chemoprophylaxis peri-operatively. Overall, 14 (74%) patients had a hypercoagulable TEG profile with 7 of these patients (50%, or 37% overall) having more than one hypercoagulable TEG parameter. A high MA (platelet hyperfunction) in 7 (37%) patients, and 8 (42%) patients had high-degree angle (increased fibrinogen concentration/function), and 8 (42%) patient had low *R*-value (hyperfunctioning coagulation cascade). The coagulation index, indicating hypercoagulability, was abnormally high in 2 (10%) patients. One patient (5.5%) with unexplained tachycardia was diagnosed with a groin VTE 14 days post-operatively prior to discharge and required anticoagulation (TEG parameters: low *R*-value, high-degree angle, and high coagulation index. Another patient had superficial thrombophlebitis related to a midline but did not require anticoagulation; this patient had a low *R*-value. Thus any VTE occurred in 2 (14%) of those with hypercoagulable TEG profiles and in zero of those with normal TEG profiles.

Conclusions: We observed that the majority of surgical IBD patients have a hypercoagulable TEG profile, and patients with evidence of hypercoagulability on thromboelastography may be at increased risk of post-operative VTE. Our data suggest, given the multi-factorial nature of hypercoagubility in these patients, which novel VTE chemoprophylaxis approaches are needed.

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Faecal calprotectin identifies microscopic inflammation in ulcerative colitis patients with complete endoscopic healing: a post-hoc analysis of the MOMENTUM trial

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Background: Histological inflammation is associated with clinical relapse in ulcerative colitis (UC). Faecal calprotectin (FC) is a marker of mucosal inflammation. The aims were to assess (i) diagnostic accuracy of FC for histological inflammation and (ii) develop a prediction model for histological remission at 1 year.

Methods: The phase IV MOMENTUM trial (ClinicalTrials.gov Identifier: NCT01124149) evaluated the efficacy of multi-matrix mesalamine in mild-to-moderate UC. In this post-hoc analysis, endoscopic and histological outcomes were assessed at Week 8 (W8) (*N* = 604) and 52 (W52) (*N* = 355). Endoscopic healing and complete endoscopic healing were defined as endoscopy score ≤1 and 0, respectively. The Geboes histopathology index was transformed to an ordinal score (range 0–13). To evaluate the correlation between FC and histology, parameters related to chronic inflammation (Geboes < 2B.1) were scored as 0. Histological remission was defined as a Geboes score < 2B.1 (absence of neutrophils in epithelium and lamina propria) resulting in a drop in the ordinal score from >0 to 0. Receiver-operating characteristic (ROC) curves were used to determine diagnostic accuracy and optimal FC cut-off values. Multi-variable logistic regression was performed using predefined predictors.

Results: Median FC values were lower in patients achieving predefined outcomes compared with patients who did not (Figure 1). Interobserver agreement between both pathologists (GDH and JHT) was moderate (κ = 0.6, 95% CI 0.33–0.87). Area under the ROC curve (AUC) value for endoscopic healing and histological remission (HR) were 0.77 and 0.76 at W8 and 0.79 and 0.80 at W52, respectively. Optimal cut-off value for HR was 75 µg/g (sens 0.65; spec 0.77; PPV 71%; NPV 71%) at W8 and 99 µg/g (sens 0.77; spec 0.75; PPV 84%; NPV 66%) at W52. In the subpopulation with endoscopy score 0, median FC remained lower in patients with HR compared with ongoing microscopic inflammation at W8 (30 vs. 140 µg/g, AUC 0.72) and W52 (21.5 vs. 134.5 µg/g, AUC 0.71). Optimal FC cut-off value was 73 µg/g at W8 and 76 µg/g at W52. Final prediction model for W52 HR comprised endoscopic score (W8) (OR 0.52, 95% CI 0.32–0.82), FC concentration (W8) (OR 1.00, 95% CI 1.00–1.00), and histological activity at baseline (OR 0.92, 95% CI 0.86–0.98) and W8 (OR 0.89, 95% CI 0.81–0.97).

Conclusions: Even in the presence of complete endoscopic healing, FC may discriminate patients with microscopic inflammation from patients in HR. Optimal cut-off lies between 75 and 100 µg/g.

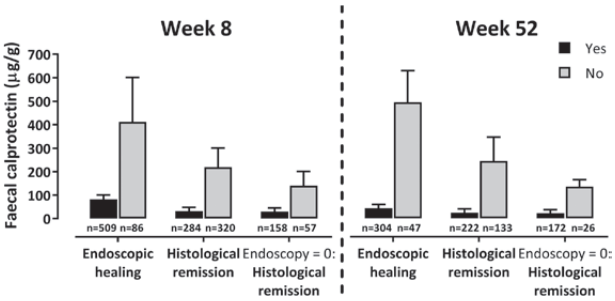

Figure 1

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RAID-Monitor: a new non-invasive method to determine endoscopic activity in inflammatory bowel diseases

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Background: Crohn's disease (CD) and ulcerative colitis (UC) are characterised by episodes of exacerbations and remissions. Monitoring disease activity based on intestinal lesion is mandatory prior to any change in the therapeutic strategy. Colonoscopy is the gold standard technique to monitor the disease activity in IBD patients, but it is usually discarded because of costs and risk issues. Inflammatory faecal biomarkers such as faecal calprotectin (FC) provide a cheaper and non-invasive alternative methodology. However, FC does not always correlate well with endoscopic indexes. RAID-Monitor is a new tool capable to correlate with endoscopic activity in IBD patients. This test is based on a bacterial signature found in faeces. The aim of this study was to evaluate the performance of RAID-Monitor in front of FC and clinical scores, as a reliable indicator for disease activity in IBD.
Methods: Two cohorts consisting of 34 patients of CD (considering endoscopy activity SES-CD ≥3, 14 active and 20 in remission) and 43 of UC (considering endoscopy activity Mayo >1, 19 active and 24 in remission) are recruited by the Gastroenterology department from four Catalan hospitals. Clinical scores, Harvey–Bradshaw Index (HBI) for CD and Mayo Partial Index (MPI), and a stool sample, to determine FC and RAID-Monitor, are collected prior to colonoscopy.
Results: RAID-Monitor differentiates the endoscopic activity with sensitivity and specificity values up to 85.7% and 95.0%, respectively, in CD patients. It obtained better results compared with the best results of FC (obtained at cut-off: 200 µg/g). FC displays the same sensitivity (85.7%) but lower specificity values (80.0%). Instead, HBI obtains the worst values of sensitivity and specificity (42.9% and 75.0%, respectively). RAID-Monitor allows a substantial increase of Positive Predictive Value (PPV) (92.3% vs. 76.9%, respectively) and Negative Predictive Value (NPV) in comparison with FC (90.5% vs. 88.9%, respectively). In UC patients, RAID-Monitor displays higher sensitivity and specificity (94.7% and 91.7%, respectively) as compared with FC using the best cut-off at 350 µg/g (73.7% and 70.8%, respectively). MPI obtains a low sensitivity (57.9%) but a similar specificity (91.7%). PPV and NPV (90.0% and 95.6%, respectively) are higher than those obtained with FC (66.7% and 77.3%, respectively).
Conclusions: RAID-Monitor is an accurate bacterial-based biomarker that correlates well with endoscopic activity in both CD and UC patients. Sensitivity and specificity obtained with our method are the highest among the techniques compared. Therefore, RAID-Monitor is a good candidate to become the non-invasive method of choice to monitor the endoscopic activity in both diseases.

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Transmural healing assessed using MRI scores is associated with better outcomes and is a potential therapeutic target in patients with Crohn's disease

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Background: The poor acceptability of repeated colonoscopies limits the use of endoscopic mucosal healing as therapeutic target in patients with Crohn's disease (CD). MRI is better accepted than endoscopy, is able to perform a concomitant assessment of ileocolonic inflammation and to detect CD complications. We aimed to evaluate whether transmural healing assessed using MRI scores was associated with decreased risk of surgery, hospitalisation and therapeutic intensification in patients with CD.
Methods: From a database including all the consecutive patients who performed an MRI to assess luminal CD between January 2012 and June 2018 in our IBD unit, we selected all the patients with CD (> 18 years-old) who underwent two MRI with: (1) objective signs of inflammation on the 1st MRI, (2) the second MRI indicated to assess therapeutic efficacy, (3) follow-up > 6 months and no surgery between the two MRI. All the patients underwent MRI assessing the small bowel and the colon using a standardised protocol (no bowel cleansing the day before and no colonic distension). Complete transmural healing was defined as normalisation of MRI. Partial transmural healing was defined as a decrease of at least 25% of Clermont score or MaRIA in each active segment. Results were expressed as Hazard Ratio (HR) and 95% confidence interval [95% CI].
Results: Overall, 443 patients undergoing 889 MRI were screened for the study. Among them 274 patients were included (mean age 33.1 ± 15.8 years, median CD duration 7.0 [2.0–13.0] years, 36.4% smokers, 31.4% prior intestinal resection, L1 = 51.5%, L2 = 5.5% and L3 = 43.1%, 25.9% perianal lesions, 35.4% stricturing CD and 31.0% fistulizing CD). At the time of the second MRI, the patients received one or several medications among: steroids (6.3%), immunosuppressants (45.2%), anti-TNF agents (65.7%) or ustekinumab (2.6%). The median interval between the 2 IRM was 9.2 months [6.0–14.1]. Overall, 53 patients had a CD-related bowel resection, 72 patients (26.3%) required CD-related hospitalisation and 163 patients (59.5%) needed therapeutic intensification (median follow-up = 14.9 mois [4.3–31.4]). In multi-variate analysis (Cox model), complete or partial transmural healing was associated with reduced risk of surgery (HR = 0.13 [0.05–0.38] ; $p < 0.001$), of subsequent hospitalisation (HR = 0.25 [0.11–0.56]; $p = 0.001$) and therapeutic intensification (HR = 0.08 [0.03–0.20]; $p < 0.001$). Complete transmural healing showed a lower risk of therapeutic intensification compared with partial transmural healing ($p < 0.05$).
Conclusions: Transmural healing assessed using MRI scores is associated with favourable outcomes in patients with CD and should be used as therapeutic target both in daily practice and clinical trials.

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Mucosal healing (MH) assessed with PICaSSO (Paddington International Virtual ChromoendoScopy ScOre) and probe Confocal Laser Endomicroscopy (pCLE) do not reflect histological normalisation using the ECAP (Extent Chronicity Activity Plus) score

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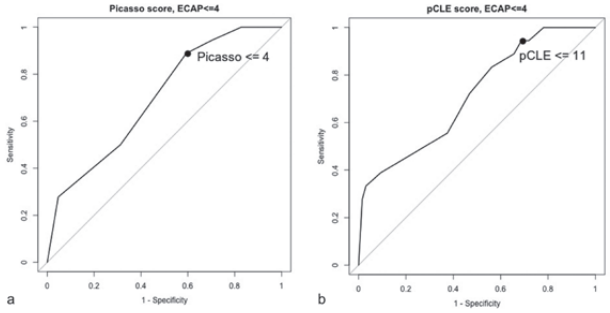
Background: Ulcerative colitis (UC) is a chronic disease that requires long-term therapy and the achievement of mucosal healing (MH) is the target of the treatment. The new histological score ECAP (Extent Chronicity Activity Plus) has been developed to detect minimal chronic changes. The electronic Virtual Chromoendoscopy Endoscopy (VCE) score PICaSSO (Paddington International Virtual ChromoendoScopy ScOre)[1] and probe Confocal Laser Endomicroscopy (pCLE) scores reflect acute histological changes (Robarts Histological Index-[RHI]) well,[2] but it is unknown whether these may reflect chronic histological changes.

Methods: This is a prospective study involving 82 UC patients at the Endoscopy Unit, Foothills Medical Center, University of Calgary, Canada. For each patient, clinical data including follow-up up to 12 months, endoscopic scores (Mayo endoscopic score, PiCasso and pCLE score) and histological ECAP score were determined. The details of ECAP score has already been published.[1] Receiver-operating characteristics (ROC) curves were plotted to estimate the cut-offs for PICaSSO and pCLE scores best predicting the MH determined by histological ECAP score.

Results: 70 patients (85.4%) were in clinical remission. We have compared the endoscopic scores (MES, PICaSSO, and pCLE) with histological healing defined by ECAP ≤ 4. Only 14 patients (28.6%) with Mayo 0 had ECAP ≤ 4. From the ROC curves, the best cut-off for PICaSSO score was 4, with sensitivity and specificity of 88.9% (95% CI 64.3%-98.6%) and 40.6% (95% CI 28.5%-53.6%), respectively with an area under ROC curve (AUROC) of 69.9% (95% CI 57.2%-82.6%). At this value, out of 54 patients with PICaSSO ≤ 4, only 16 (29.6%) have ECAP ≤ 4. The ROC curves for pCLE showed that the best cut-off point to detect MH (ECAP ≤ 4) was 11 with sensitivity of 94.4% (95% CI 72.7–99.9%) specificity of 31.3% (95% CI 20.2%-44.1%) with AUROC of 71.4% (95% CI 57.9%-84.8%). At this value of pCLE, 17 (27.9%) patient amongst 61 had ECAP ≤ 4.



ROC curve for PICaSSO in the prediction of mucosal healing (ECAP ≤ 4)

During the follow-up period, 8.06% of patients had a relapse: 80% had PICaSSO score ≤ 4, 80% had pCLE ≤ 11, and only one relapse 20% had ECAP ≤ 4.

Conclusions: According our results, the endoscopic scores (PICaSSO and pCLE) are not able to predict histological healing calculated using ECAP (both chronic and acute changes) at the value ≤ 4. An ECAP score ≤4 may however predict stable mucosal healing with few relapses over 12 months.

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A global prospective observational study in children and adolescents with paediatric-onset IBD: the PIBD-SETQuality inception cohort

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Background: The consequences of paediatric IBD (PIBD), such as growth failure, bowel resection at young age and a lifelong risk of treatment-related adverse events may hugely influence the patient's further development and quality of life. Unfortunately, we are still not able to predict which patients are at risk of developing a complicated disease course. To investigate this, large prospective international studies withlong-term follow-up are needed. In this first global cohort, we aim to evaluate which patients are at risk based on patient and disease characteristics, immune pathology and environmental factors.

Methods: In this international prospective observational study, children and adolescents diagnosed with IBD <18 years are included at disease diagnosis with the intention of up to 20 years follow-up following a visit schedule that is in line with standard PIBD care. Patient and disease characteristics, as well as results of investigations, are collected at baseline and during follow-up. In addition, environmental factors are being assessed. In specific centres with the ability to perform extensive immunological analyses, biomaterial is being collected in therapy naïve patients at baseline and during follow-up.

Results: PIBD patients data from in 14 centres in the UK (UK), The Netherlands (NL), Italy, Israel, and Malaysia are recruiting 12–13 patients per month. Ten extra centres (in 4 new countries) are preparing for their first recruitment with an estimated 19 extra patients per month. Well organised data management and responsive sites led to a completion rate of 76% of the 1700 raised queries. To date 178 PIBD patients have been recruited which equals 18% of the target number. They have a varied ethnicity (69.9% white; 13.9% South Asian; 1,7% South East Asian; 5.2% black; 0.6% hispanic/latino; 8.7% mixed race). Median length of follow-up of these patients is 8.5 months. The median PCDAI and PUCAI scores at baseline are 25 (IQR 15) and 45 (IQR 35) in CD and UC, respectively. Median baseline endoscopy scores showed a median SES-CD score of 10 (IQR 10) and UCEIS of 4 (IQR 2.5). Comparing data between countries show that the

use of maintenance therapy is equal with 62% and 61% on an immunomodulator at 6 months follow-up in UK and NL, respectively. Analysis of international and racial differences regarding presenting phenotype, performed diagnostics and induction therapies are ongoing.

Conclusions: As the first global inception cohort including data from European and Asian countries, this will reveal valuable data on standard clinical practice and immune pathology, facilitate comparisons on diagnostic and therapeutic strategies between countries and provide opportunities to compare findings with other national cohorts.

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A combined set of four serum inflammatory biomarkers reliably predicts endoscopic disease activity in inflammatory bowel disease

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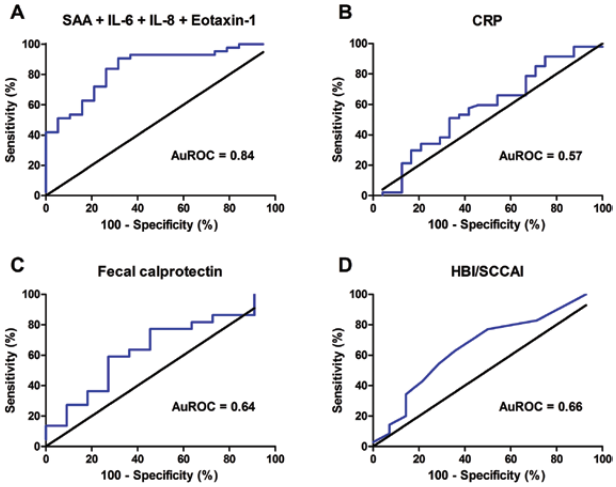
Background: Mucosal healing is the ultimate treatment goal in inflammatory bowel disease (IBD). Endoscopic examination is the gold standard to determine disease activity in IBD, as routine activity measures, such as C-reactive protein (CRP), faecal calprotectin and clinical disease indices are inconsistent in representing luminal disease activity. Therefore, there is a great need for non-invasive biomarkers to assess mucosal inflammation. The aim of this study was to build an accurate prediction model of endoscopic disease activity in patients with quiescent and active IBD, based on a combination of serum inflammatory biomarkers.

Methods: Serum concentrations of 10 inflammatory biomarkers were analysed in 118 IBD patients (64 Crohn's disease (CD), 54 ulcerative colitis (UC)) prior to biological treatment and 20 healthy controls. In 71 IBD patients, endoscopic disease activity was assessed by the Simple Endoscopic Score for CD (SES-CD) and Mayo endoscopic subscore for UC. Nonparametric ROC estimation with bootstrap inference was used to establish the best combination of inflammatory biomarkers predicting endoscopic disease activity.

Results: Six (6) inflammatory biomarkers (serum amyloid A (SAA), Eotaxin-1, IL-6, IL-8, IL-17A and TNF-α) all individually showed better prediction of IBD disease activity compared with routine measures (CRP, faecal calprotectin and HBI/SCCAI scores). The best combination of predictive inflammatory biomarkers consisted of serum SAA, IL-6, IL-8 and Eotaxin-1, showing an optimism-adjusted area under the ROC curve of 0.84 (95% CI: 0.73–0.94, $p < 0.0001$), which predicted significantly better ($p = 0.002$) than serum CRP levels with an AuROC of 0.57 (95% CI: 0.43–0.72, $p = 0.32$).



Receiver-operating characteristics (ROC) curves for (A) the best predictive combination of biomarkers (SAA, IL-6, IL-8 and Eotaxin-1), (B) serum CRP levels, (C) faecal calprotectin (FC) levels and (D) HBI or SCCAI.

The resulting combined calculated probability had a maximum sensitivity of 90.7% and specificity of 68.4% in correctly classifying IBD patients into the low and high endoscopic disease activity category (Youden's J statistic = 0.58).

Conclusions: The combination of SAA, IL-6, IL-8 and Eotaxin-1 is superior over routine measures in predicting endoscopic disease activity in IBD. Serum inflammatory biomarkers are valuable tools for monitoring intestinal inflammation and guiding therapeutic decisions.

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The variation of faecal calprotectin level within the first months after bowel resection is predictive of endoscopic postoperative recurrence in patients with Crohn's disease

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Background: Early detection of postoperative recurrence (POR) remains a major concern in patients with Crohn's disease (CD).

We aimed to assess the performances of serial faecal calprotectin (Fcal) monitoring within the three first months following ileocolonic resection to predict CD endoscopic POR at 6 months.

Methods: In this multi-centre prospective study, CD patients who underwent ileocolonic resection were consecutively enrolled. Stools samples were collected at baseline, at 1 month (M1) and M3 to

measure Fcal level. The stools samples were collected in the morning the day before the endoscopy to reduce intraindividual variation, and immediately stored at 4°C. Ileocolonoscopy was performed at M6. Endoscopic POR was defined as Rutgeerts' index ≥ i2b (central reading).

Results: Overall, 48 patients were included. The main characteristics of these patients are detailed in Table 1.

Age at inclusion, (years), mean ± SD	35.3 ± 11.5
Disease duration, (years), median [IQR]	5.0 [1.0-10.0]
Female gender, n (%)	29 (60.4%)
Active smokers, n (%)	16 (33.0%)
Prior bowel resection, n (%)	23 (47.9%)
Montreal Classification	
CD location	
L1, n (%)	21 (43.7%)
L2, n (%)	2 (4.2%)
L3, n (%)	25 (52.1%)
CD behaviour	
B1, n (%)	9 (18.8%)
B2, n (%)	22 (45.8%)
B3, n (%)	17 (35.4%)
Perianal lesions, n (%)	3 (6.3%)
Prior steroids use	48 (100.0%)
Immunosuppressants-naïve patients	18 (37.5%)
Anti-TNF-naïve patients	10 (20.8%)
Current medications	
Thiopurines, n (%)	48 (100.0%)
Small bowel resection length, median [IQR], cm	20.5 [13.3-30.0]

Among them, 18 patients (36%) presented with endoscopic POR (Rutgeerts score ≥ i2b) 6 months after surgery. We did not observe any significant difference between patients with or without early endoscopic POR (M6), respectively, regarding the level of Fcal at baseline (100 [50–190] vs. 166 [89–312] µg/g; $p = 0.15$), M1 (93 [48–104] vs. 100 [50–180] µg/g; $p = 0.44$) and M3 (100 [68–328] vs. 99 [50–100] µg/g; $p = 0.28$). Fcal kinetics during the first 3 months after surgery was significantly different between the patients with or without POR at M6 ($p = 0.021$). The relative variation (median) between the level of Fcal at baseline and M3 (ΔFcal M3-M0) was significantly higher in patients with endoscopic POR +60% [–47%–+217%] compared with those without POR –38% [–64%–0%] ($p = 0.01$). ΔFcal M3-M0 > +10% demonstrated the best performances to predict endoscopic POR at M6 (AUC = 0.73, sensitivity = 64.7% [41.1–82.7], specificity = 87.5% [68.0–96.3], negative predictive value = 77.8% [57.5–91.4] and positive predictive value = 78.6% [49.2–95.3]).

Conclusions: Fcal variation within the first months after ileocolonic resection is an accurate predictor of early endoscopic POR in CD patients.

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Adjusting serum ferritin concentrations to remove the effects of acute-phase response in patients with IBD and iron deficiency: is using C-reactive protein sufficient?

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Background: Patients with IBD have high rates of iron deficiency (ID) with adverse clinical consequences. Serum ferritin is normally a sensitive marker for iron status, but as an acute-phase reactant, ferritin becomes elevated in response to inflammation, complicating the diagnosis.[1] ECCO guidelines recommend adjusting serum ferritin concentrations by concurrently measuring C-reactive protein (CRP) to remove effects of subclinical inflammation.[2] The WHO suggests measuring α1-acid glycoprotein (AGP) as a second biomarker, since CRP and AGP reflect different—acute and chronic—stages of the acute-phase reaction.[3] We aimed to estimate inflammation-related increase in ferritin in IBD patients using two acute-phase proteins (APPs), CRP and AGP, individually and in combination, and to calculate factors to remove the influence of inflammation from ferritin levels.

Methods: Up to October 2018, 118 patients (38 with Crohn's disease [CD], 47 with ulcerative colitis [UC], 33 controls) with a mean age of 45.48 ± 15.25 years, 47.46% female, who consecutively attended the ICCC Rhein-Main, Frankfurt, Germany for routine evaluation, were included. Elevated concentrations of CRP (>5 mg/l) and/or AGP (>0.65 g/l) were used to define inflammation status to correct ferritin levels (cut-off 30 µg/ml) for inflammation.

Results: In this interim analysis of IBD patients, inflammation caused ferritin to increase by 28.78% (19/66) using CRP or 53.03% (35/66) using AGP or both ($p < 0.05$). Elevated AGP levels were relatively more common than raised CRP in UC (36.17% vs. 14.89%) than in CD (63.16 vs. 47.37%). Using CRP,[4] 8 patients were classified with ID, 18 functional ID, 1 anaemia of chronic disease (ACD), and 1 mixed anaemia (ACD/IDA). By using CRP and AGP, 25 patients were classified with functional ID and 4 with ACD. Overall, inflammation increased ferritin in 77.65% of IBD patients and was associated with a 31.04% underestimation of ID (defined according to Weiss and Goodnough[4]) using CRP as single marker.

Conclusions: Our data highlight the challenge of assessing ID and IDA using only serum ferritin as marker of iron status for patients with IBD and active inflammation. We demonstrate that correction of serum ferritin levels for inflammation using CRP alone would underestimate ID in IBD patients by ~50%, indicating the need to utilise both APPs.

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Bowel ultrasound is accurate in assessing disease extent and disease activity in ulcerative colitis

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Background: Colonoscopy is currently the standard of care for the evaluation of disease extent and activity in ulcerative colitis (UC). Bowel ultrasound (USG) is an easy, cheap, non-invasive tool and can be used to assess disease activity in UC patients.
Methods: Patients who underwent colonoscopy for assessment of disease activity also underwent USG within 2 weeks. Endoscopic activity was graded by the Mayo Endoscopic Score (MES); clinical disease activity was assessed using the Total Mayo Score (TMS). Colonic wall thickness (CWT), loss of bowel wall stratification (WS), Doppler activity (DA) were assessed. DA was evaluated semi-quantitatively by the Limberg score.
Results: Seventeen patients were included in the study, 10/17 (59%) had left-sided colitis, 41% (7/17) had pancolitis. MES of 0, 1, 2, 3 was seen in 1, 3, 8 and 5 patients, respectively. As per TMS, 8 (47%) patients had severe disease, 8 (47%) had mild-to-moderate disease and one patient(6%) was in remission. USG accurately assessed the disease extent in 16 (94%) patients. Median CWT was lower in patients with MES 0-1 when compared with MES 2-3 (3 mm vs. 4.1 mm, $p = 0.01$). CWT correlated with MES ($r = 0.763$, $p = 0.000$) and with TMS ($r = 0.748$, $p = 0.001$). DA correlated with MES ($r = 0.806$, $p = 0.001$) and TMS ($r = 0.789$, $p = 0.0001$). Loss of bowel wall stratification correlated with MES ($r = 0.551$, $p = 0.022$) and TMS ($r = 0.505$, $p = 0.039$). In patients in whom the bowel wall stratification was preserved, the MES was 1 point lower than in whom it was lost. CWT ≥ 3.2 mm had a sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 84.5%, 75%, 91.7%, 60%, 82.3%, respectively. Doppler >1 had a sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 100%, 75%, 93%, 100%, 94%, respectively.

	Sensitivity	Specificity	PPV	NPV	Accuracy
CWT ≥ 3.2 for predicting MES ≥2	84.5	75	91.7	60	82.3
Doppler >1 for predicting MES≥2	100	75	92.8	100	94.1

USG characteristics in predicting active disease.

Conclusions: USG is accurate in assessing disease extent and disease activity in UC and correlates with the Mayo score. Colonic wall thickness, loss of wall stratification and Doppler activity are useful in assessing disease activity and future USG based scores can use these parameters to assess disease activity. Colonic wall thickness ≥ 3.2 mm and Doppler >1 are accurate in predicting MES of ≥2.

P170

Diagnostic criteria for IBD subtype classification: a multi-centre validation cohort

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Background: IBD-unclassified (IBD-U) is a diagnosis on the spectrum between Crohn's disease (CD) and ulcerative colitis (UC) with very low agreement between physicians and a wide heterogeneity in the diagnosis rate of IBDU across sites. The PIBD-classes criteria were thus developed to standardise the classification of children with IBD as having CD, colonic CD, IBD-U, atypical UC and UC. We aimed to provide further validation of the PIBD-classes criteria on real-world data of paediatric IBD.
Methods: Multi-centre retrospective longitudinal study of children (2–18 years) diagnosed with IBD with at least 1 year follow-up and available gastroscopy and ileocolonoscopy. Clinical, radiologic, endoscopic and histological data were recorded as well as the 23 items required for the PIBD-classes criteria, and revised diagnosis at last follow-up.
Results: In total, 184 children were included (age at diagnosis 13 ± 3 years, 55% males) of whom 122 (66%) were diagnosed by the clinician with CD, 17 (9%) with IBD-U and 45 (25%) with UC. By the PIBD-classes criteria, 121 (66%) had CD (of whom 5 (3% of the entire cohort) had colonic CD), 22 (12%) had IBDU and 41 (22%) UC (of whom 14 (8% of the entire cohort) had atypical UC). There was high agreement between clinician-assigned and PIBD-classes-generated classification for CD (93%; 8 patients moved to IBD-U) and for UC (84%; 6 moved to IBD-U and one to CD). Of the 17 children classified as IBD-U, 9 (53%) were re-classified by the PIBD-classes criteria: 2 as atypical UC, 1 as UC, and 6 as CD. The initial clinician's diagnosis was revised at the last follow-up in 10 patients, five of whom supported the classification of the PIBD-classes (four IBD-U patients, two reclassified as CD, two reclassified as UC, 1 UC patient reclassified as IBD-U).
Conclusions: The PIBD-classes algorithm is a useful, standardised tool to facilitate accurate classification of IBD subtypes and the average rate of the disease subtypes remain as the clinicians' classification. In cases of change of IBD class during follow-up the PIBD-classes criteria accurately predicted the final allocation in half of patients. Application of the PIBD-classes algorithm should be considered to improve reliability and consistency of IBD subtype classification between physicians and centres.

P171

Augmented endoscopy for surveillance of colonic inflammatory bowel disease: systematic review with network meta-analysis

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Background: Considering the high risk of dysplasia and cancer in inflammatory bowel disease (IBD), surveillance is advocated. However, international guidelines do not reach a uniform recommendation on the way to perform surveillance. We performed a systematic review with a meta-analysis to assess the best endoscopic surveillance strategy in colonic IBD.
Methods: The systematic review was performed in PubMed/MEDLINE, EMBASE, SCOPUS and Cochrane databases to identify studies comparing white light endoscopy (WLE) and augmented endoscopy (AE) in the detection of dysplasia or neoplasia in colonic IBD. Sub-analyses between dye-spray chromoendoscopy (DCE), narrow-band imaging (NBI), I-SCAN, full-spectrum endoscopy (FUSE) and auto-fluorescence imaging (AFI), and the role of random vs. targeted biopsies were also performed. Furthermore, a meta-regression and a network meta-analysis were also performed.

Results: Twenty-seven studies (6167 IBD patients with 2024 dysplastic lesions) met the inclusion criteria. There was no publication bias. AE showed a higher likelihood of detecting dysplastic lesions than WLE (19.3% vs. 8.5%, OR = 2.036), with an incremental yield (IY) of 10.8%. DCE (OR = 2.605) and AFI (OR = 3.055) had higher likelihood of detecting adenomas than WLE; otherwise, I-SCAN (OR = 1.096), NBI (OR = 0.650) and FUSE (OR = 1.118) were not superior to WLE. Dysplasia was found in 1256/7267 targeted biopsies (17.3%) and in 363/110 040 random biopsies (0.33%) (OR = 66.559, IY = 16.9%). Meta-regression found no variable impacting the efficacy of AE techniques. Network meta-analysis identified a significant superiority of DCE on WLE in detecting dysplasia (OR = 2.12), while no other single technique was found to be superior to all others in adenoma detection.
Conclusions: AE, especially DCE, was associated with higher likelihood of discovering dysplastic lesions than WLE. Chromoendoscopy with targeted biopsies is the best endoscopic technique for IBD surveillance.

P172

Postoperative recurrence of Crohn's disease: correlation between endoscopy and bowel ultrasound

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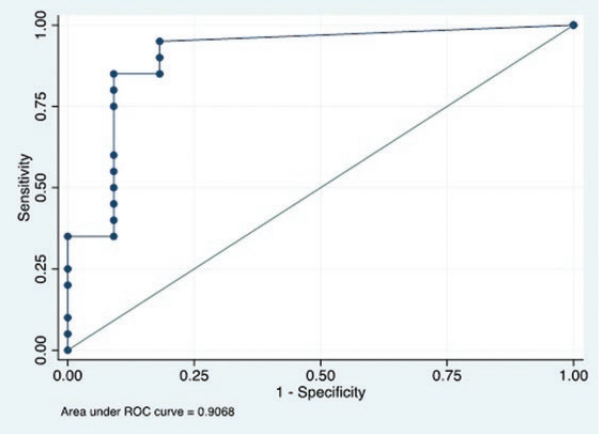
Background: Postoperative Crohn's disease recurrence (POR) is currently assessed by ileocolonoscopy. B-mode bowel sonography (US) is an alternative, non-invasive, non-ionising and well tolerated diagnostic method. Our aim was to validate US, and to establish a correlation between the different ultrasound parameters of activity and Rutgeerts endoscopic score
Methods: We selected 31 patients with Crohn's disease in follow-up at our unit, who had underwent surgical ileocolic resection, which performed ileocolonoscopy and US for the diagnosis of POR, with a difference between both tests lesser than 6 months. Recurrence was assessed by ileocolonoscopy using the Rutgeerts score, considering: i0–i1 absence of recurrence; ≥i2 endoscopic recurrence. The echographic findings were bowel wall thickness (BWT), hyperaemia, layer pattern, involvement of the mesenteric fat, presence of adenopathy and transmural complications (fistulas and abscesess).
Results: Clinical characteristics of the study population are reported in Table 1.

Female	16 (51%)
Age at diagnosis	A1 2 (6,7%); A2 22 (73.3%); A3 6 (20%)
Disease location	L1 14 (45.2%); L2 0(0%); L3 17 (54.8%)
Illness behaviour at diagnosis	B1 3 (9.7%); B2 17(54.8%); B3 11 (35.5%)
Smoke habit	Smoker 9 (29%); ex-smoker 14 (45%); non-smoker 8 (26%)
Number of surgical resection	one: 27 (87%); two: 4 (13%)
Treatment	non 6(20%); azathioprine 5 (16%); anti-TNF 8 (26,7%); combined 11 (36%)
Rutgeerts score	io–i1: 11 (35.5%); i2: 10 (32%); i3–i4: 10 (32%)
Endoscopic recurrence	≥i2: 20 (64,5%)
Faecal calprotectin	>50 ng/mg: 18 (58%)

Main demographic, clinical characteristics according to Montreal classification.

Ileoconoloscopy detected recurrence in 20 of 31 patients (64%). A statistically significant association was identified between wall thickness and recurrence ($i \geq 2$) (mean 2.5 mm non recurrence vs. 5.2 mm recurrence, $p = 0.002$). A relationship was observed between Rutgeerts endoscopic score and BWT: 2.5 mm (SD 0.39) for i0–i1; 3.68 mm (SD 0.33) for i2 and 6.79 mm (SD 0.29) for i3–i4. However, this relationship did not reach statistical significance ($p = 0.57$). To establish the relationship between each of the ultrasound variables with the endoscopic recurrence, a multi-variate analysis was performed using logistic regression. It was identified that a BWT< 3 mm is associated with the possibility of endoscopic recurrence with a relative risk reduction (RRR) of 2.03, the preservation of the layer pattern RRR = 1.05, the absence of involvement of mesenteric fat RRR = 38.15 and the absence of adenopathies RRR = 1.23 ($p = 0.003$). ROC curve analysis (image 2) shows a BWT of 2.8 mm as the best cut-off point (SE: 95% ES: 82% AUC: 90%) to discriminate patients without recurrence ($i < 2$). For BWT > 3 mm, the classic parameter, shows SE: 90% ES: 82% AUC: 87%



ROC curve analysis
Conclusions: There is a good relationship between the different echographic parameters of activity (bowel thickness, hyperaemia, wall distortion, etc.) and the presence of endoscopic recurrence, as well as the severity of the recurrence.

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The deeper, the better: Histological activity defined as Nancy Index >2 predicted bad outcomes in patients with ulcerative colitis that achieved mucosal healing

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Background: While the endoscopic remission is a well-established good prognostic factor, histological remission is a concept still to be defined, and therefore the importance of this in the evolution of patients with ulcerative colitis (UC) is still uncertain. Getting the histological remission may be the most ambitious stage. However, achieving it in patients in endoscopic remission, it probably makes the difference. The Nancy index (NI) is an index of histological activity for patients with UC. It graduates from 0 to 4; 0) without relevant histological disease, (1) chronic inflammatory infiltrate without acute inflammatory infiltrate, (2) mild acute inflammatory infiltrate, (3) moderate or severe acute inflammatory infiltrate, (4) presence of ulcers.

Methods: Our objective was to identify which patients with endoscopic mucosal healing had a higher risk of endoscopic relapse according to the degree of histological activity, by designating a useful cut-off point according to NI. For this, a retrospective cohort analysis of patients with UC in deep remission (defined as subscore endoscopic of Mayo 0) was performed in which colorectal cancer screening colonoscopies were performed by taking randomised biopsies by segments. The biopsies with greater histological damage were re-evaluated retrospectively according to the NI by expert pathologists.
Results: Of a total of 52 colonoscopies with their respective biopsies included in the analysis, 38 (73.1%) had an NI < 2, and 14 (26.9%) had an NI ≥ 2. The mean follow-up was 56.4 months (SD 25.8). Of the 14 biopsies with NI ≥ 2, six patients presented endoscopic activity in 44.5 months (SD 25.1) on average. In the 38 with NI < 2, 32 presented favourable evolution. All patients had at least one control colonoscopy at follow-up. In the univariate analysis, the presence of NI ≥ 2 predicted endoscopic relapse (RR = 2.7; IC 95%; 1.1–7).
Conclusions: NI was useful to evaluate the degree of histological remission in patients with UC who have reached mucosal healing. An NI ≥ 2 identified those patients who were going to relapse endoscopically throughout the follow-up. The NI < 2 could be a definition of histological remission useful in clinical practice, and would allow identifying those patients with greater risk of suffering a worse evolution to adjust their treatment and follow-up in an individualised manner.

P174

System delays have real consequences: Impact of timing of biologic commencement on inflammatory bowel disease patient response

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Background: The worldwide incidence and prevalence of inflammatory bowel disease (IBD) is increasing and with this the need for biologic therapy continues to rise. This inevitably strains the finite resources of public health services. We examined our cohort of IBD patients to determine whether the wait for biologic therapy impacted overall outcomes.
Methods: This was a single-centre retrospective review of adult patients with IBD who had been commenced on a biological therapy from January 2009 to October 2017. Inclusion criteria included patients with IBD who had started biologics as an outpatient. We excluded patients who had been started on biologics as an inpatient or had been admitted to hospital in the 3 months prior to starting biologics. Patients that met the inclusion criteria were divided into an early group, that is, those receiving biologics within 40 days of multidisciplinary team (MDT) approval; and a late group, that is, those patients receiving biologics over 40 days from MDT approval. Outcome measures were 1-year symptomatic, endoscopic and/or radiologic improvement (CT or MRI). Improved endoscopic appearances were classed as reduction in Mayo scores by ≥1 for ulcerative colitis (UC) or CDEIS scores of ≥2 in Crohn's disease (CD).
Results: In total, 183 patients (average age 37.5 years, range 16–75, 91 females) met the inclusion criteria. Of these, 87 (47.5%) made up the early group (average age 36.6 years, range 16–75) and 96 patients (52.5%) were included in the late group (average age 38.2 years, range 16–74). There were no significant differences between the two groups in terms of age, sex, subtype of disease, type of biological therapy and percentage on steroids and/or immunomodulators at commencement of biologic. There was a significant association between delayed administration of biologics and no improvement in endoscopic or radiological appearances at 1 year (48.6% vs. 30%, OR 2.2, 95% CI 1.1–4.4, $p = 0.03$). Delayed receipt of biologics was also associated with worsening gastrointestinal symptoms at 1 year (30.4% vs. 15.2%, OR 2.4, 95% CI 1.1–5.3, $p = 0.03$). There was no significant association between delayed biologic administration and hospital admissions over the next year, surgery in the following 3 years or primary non-response rates (OR 0.89; p = NS; OR 1.1; p = NS; OR = 1.5; p = NS, respectively).
Conclusions: In the outpatient setting, delay in biologic administration may affect improved rates of symptomatic improvement and endoscopic/radiological appearances at 1 year. Efficient mechanisms for timely biologic administration are needed to mitigate against the delay caused by increasing referrals, lack of capacity on infusion units and funding applications.

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Capsule endoscopy for small bowel Crohn's disease—should we trust in magnetic resonance enterography?

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Background: Currently, both small bowel capsule endoscopy (SBCE) and magnetic resonance enterography (MRE) can be used to assess small bowel involvement in Crohn's disease (CD). However, SBCE appears to be more sensitive in the detection of mild and proximal lesions. We aimed to compare the diagnostic yield for both techniques.
Methods: Adult patients with either confirmed or suspected Crohn's disease who were submitted to both CE and MRE were retrospectively reviewed. Only patients performing SBCE and MRE within 3 months were included and patients with changes in CD therapy during this period were excluded.
Presence of ulcers, villous oedema and stenosis were assessed in SBCE, and patients with Lewis score (LS) ≥135 were considered to have significant inflammation. SB wall thickening, hyperenhancement, oedema, comb sign or presence of ulcers were considered signs of active CD in MRE.
Results: Included 30 patients (53.3% suspected and 46.7% confirmed CD) with a median age of 31 ± 11 years, 56.7% of which were females. Comparing SBCE and MRE, SBCE had a significantly higher diagnostic yield (90.0% vs. 53.3%, $p = 0.007$), with higher detection of ileal lesions (83.3% vs. 53.3%, $p = 0.022$). Even more importantly, only SBCE identified jejunal inflammatory activity (46.7% vs. 0.0%, $p < 0.001$). Despite the fact that statistical significance was not attained, SBCE identified 2 traversable strictures that were not identified by MRE (6.7% vs. 0.0%, $p = 0.500$) and out of 14 patients with suspected Crohn's disease, SBCE identified significant inflammation in four patients with negative MRE (85.7%

vs. 57.1%, p = 0.289). MRE was more likely to detect findings when SBCE showed moderate to severe inflammatory activity (LS ≥ 790) compared with those with mild inflammatory activity (LS 135–790) (72.7% vs. 30.8%, p = 0.041).

Conclusions: In our cohort, SBCE showed a significant overall higher diagnostic yield than MRE, with higher detection of distal lesions and, more importantly, SBCE identified proximal lesions in nearly half of examination while MRE was unable to identify any case. MRE diagnostic yield was more heavily influenced by the severity of inflammatory activity, being significantly inferior to SBCE in patients with mild inflammatory activity.

P176

Real-world use of the IBD Disk tool for evaluation of patient-reported disability in the outpatient clinic

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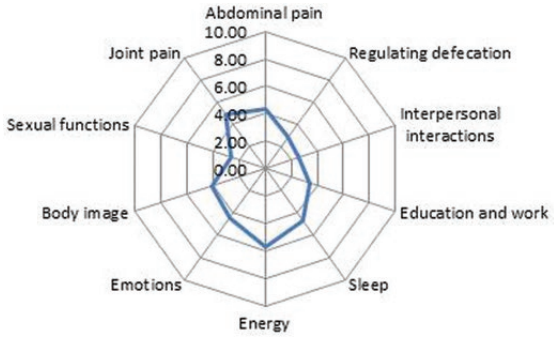
Background: The IBD disability index (IBD-DI) is a validated healthcare professional (HCP) administered tool that can assess the functional status of patients in trials. The IBD-Disk was adapted from the IBD-DI as a tool that patients can use to capture their functional status for HCPs to review. We report patient acceptability and the use of the IBD-disk in the real-world setting.

Methods: The IBD-Disk was constructed by an expert steering committee of 30 international gastroenterologists/nurses who ranked the IBD-DI items. An IBD-DI working group of 14 gastroenterologists used a modified Delphi process to agree on 10 IBD-Disk items. Inclusion criteria comprised patients aged 18 and over, of all ethnicities, with a confirmed diagnosis of CD/UC. Exclusion criteria were lack of fluency in English, not agreeable to take part or participation was deemed inappropriate. Patients were asked to rate their level of agreement for each item on the IBD Disk on a visual analogue scale of 0–10 (0 = absolutely NO, 10 = definitely YES). We included a difficulty rating of 1–10 to assess ease of completion of the questionnaire (1 = very easy; 10 = very difficult) as well as qualitative feedback.

Results: A total of 200 patients took part. The mean age of the cohort was 41 years. 113 (58%) were female. 167 were White, 6 Indian, 9 Asian, 14 Other, 4 did not specify. Fifty per cent of patients had CD, 41% had UC and 9% were unclassified. Of the domains of the IBD disk (Table 1, Figure 1), energy levels and joint pain scored highest (most impairing) with mean values of 5.71 and 4.90,, respectively, whereas interpersonal interactions and sexual functions were least affected, mean scores 2.54 and 2.62. The mean difficulty rating was 2.2. Significant correlation was found between abdominal pain and energy levels/sleep (r = 0.60 and r = 0.55; p < 0.01) and between joint pain and energy levels/sleep (both r =0.56; p < 0.01). We accounted for steroid use and noted no significant effect on sleep, energy or emotions. Clinicians highlighted that the IBD disk opened up conversations beyond GI issues and gave a good overview of well-being. Patients' feedback highlighted that they were glad they were able to express their functional status

	N	Mean (SD)
Abdominal pain	196	4.32 (3.48)
Regulating defecation	196	2.83 (3.05)
Interpersonal interactions	196	2.54 (3.18)
Education and work	196	3.44 (3.51)
Sleep	196	4.71 (3.65)
Energy	196	5.71 (3.50)
Emotions	196	4.39 (3.51)
Body image	196	4.10 (3.45)
Sexual functions	195	2.62 (3.23)
Joint pain	195	4.90 (3.69)

Mean (SD) scores for each IBD-disk item.



Visual representation of IBD disk scores demonstrating disease burden.

Conclusions: Energy levels and joint pain were the most disabling for this unselected IBD cohort. Our first experience with the IBD-Disk proved very positive.

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Small intestinal mucosal healing assessed by video capsule endoscopy in Crohn's disease patient treated with adalimumab: The SIMCHA study—interim results

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Background: Video capsule endoscopy (VCE) has been established as the most sensitive modality in evaluating small bowel (SB) Crohn's disease (CD). Endoscopic mucosal healing is recognised as a key treatment target in IBD. However, studies have generally employed ileocolonoscopy. The aim of this study was to investigate SB mucosal healing of CD after 6 months of adalimumab therapy using VCE.
Methods: Prospective single-centre study in consecutive adult CD patients (>17 years) with moderate-to-severe SB involvement, defined by a baseline VCE examination at diagnosis with a Lewis score > 790 (normal <135, mild disease 135–790) in at least one tertile. Exclusion criteria included the use of drugs known to induce SB lesions such as NSAIDs for a minimum of 1 month. Patients were also excluded if there was a history suggestive of obstructive symptoms, known strictures or a failed patency capsule examination. Patients were all treated with adalimumab monotherapy for 24 weeks prior to undertaking a second VCE. Primary endpoint was the Lewis score on repeat VCE at 24 weeks. Mucosal healing was defined as a repeat Lewis score <350, whereas partial response was defined as a >50% decrease in repeat Lewis score. Secondary outcomes included clinical index of remission (Harvey–Bradshaw Index <5) and faecal calprotectin.
Results: Interim results are available for the first 14 consenting patients (8 males, 6 females) recruited (2012–2018). Mean baseline Lewis score was 1940 (range 475–6340). Mean Lewis score on second VCE was 331 (range 112–2734; p = 0.0005 vs. baseline). Complete mucosal healing was observed in 7 (50%) cases, and partial response in 5 others. The mean decrease in Lewis score was 1632 (range 363–5189), representing a mean reduction of 80.2%. Baseline VCE demonstrated one or more ulcerated SB strictures in three cases; two had non-ulcerated strictures at Week 24 that were traversed. No capsule retention or other adverse events were observed.
The HBI was elevated (>4) in 10 cases prior to starting therapy. Repeat HBI was consistent with clinical remission (HBI < 4) in all cases at Week 24. Mean faecal calprotectin decreased from 409 (range 62–1676) to 135 (range 30–329), but the difference did not achieve significance (p = 0.1).
Conclusions: Adalimumab led to significant improvement of small intestinal mucosal Crohn's disease, with 50% achieving mucosal healing. Our preliminary data suggest that VCE is a safe and effective method to diagnose and monitor SB mucosal healing in CD.

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Role of prognostic nutritional index in predicting severity in active ulcerative colitis

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Background: A large proportion of patients with IBD shows an impairment of nutritional status. Prognostic nutritional index (PNI) has been described as predictor of colectomy and morbidity/mortality during surgery for ulcerative colitis (UC). The aim of the present study was to investigate the correlation between PNI and indices of severity in active UC and the association of PNI with the need for medical or surgical therapy.
Methods: Consecutive UC patients, referring to our IBD unit, underwent full colonoscopy to assess Mayo endoscopic subscore (MES), Montreal classification (MC) and full Mayo score (FMS). Active patients were defined as FMS >2. Blood exams including C-reactive protein (CRP), serum albumin and complete blood count were analysed. PNI was calculated according to formula: 10 × serum albumin (g/dl) + 0.005 × total lymphocyte count. Patients with previous (last 3 months) use of steroids, immunosuppressants, biological therapy or surgery, use (last 2 weeks) of topical therapy, any ongoing infectious, oncological, metabolic disease in the last 6 months were excluded. Patients were followed up for 30 days and the possible initiation of steroids, biological and immunosuppressive therapy or colectomy was assessed. Ninety-five controls were enrolled among patients referring for IBS symptoms.
Results: From 2016 to 2018, 95 active UC patients (47 females) were enrolled. UC patients displayed a median PNI (35.43, IQR 29.91–38.81) significantly lower than controls (40.62, IQR 38.11–41.51). Median PNI values discriminated patients according to disease severity (FMS mild 3–6: PNI 36.72, moderate 4–10: 35.67, severe >10: 29.48, p = 0.001; MES 1: PNI 39.12, 2: 36.44, 3: 31.74, p = 0.001; MC E1: PNI 37.81, E2: 36.21, E3: 32.77, p < 0.001). Multiple logistic regression analysis showed that lower PNI values were associated with the need for steroids/biological therapy within 30 days (OR 1.3), irrespective of age, sex, BMI, disease extent, clinical/endoscopic severity. According to ROC curves, a PNI cut-off (38.06) was identified to discriminate patients from controls (AUC 0.835, sensitivity 78%, specificity 28%) and divide patients into 2 groups.

	PNI <38.06 (n = 68)	PNI >38.06 (n = 27)	p
Mayo endoscopic subscore			
Mayo 1	5 (7.35%)	10 (37.04%)	<0.001
Mayo 2	28 (41.18%)	13 (48.15%)	
Mayo 3	35 (51.47%)	4 (14.81%)	
Montreal classification			
E1	6 (8.82%)	5 (18.52%)	0.003
E2	29 (42.65%)	18 (66.67%)	
E3	33 (48.53%)	4 (14.81%)	
Full Mayo score	9 (7–10)	7 (5–9)	0.006

At 30 day follow-up, 53 patients with PNI < 38.06 and 7 with PNI >38.06 initiated steroids/biologics; PNI values <38.06 were associated with an increased risk of steroids/biological therapy (RR = 2.06, CI 1.39–3.05).
Conclusions: PNI appears to be a novel and promising biomarker associated with disease activity. Our findings show that PNI might be considered a reliable predictor of steroids or biological therapy in active UC.

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Changes in the haemostatic system in patients with ulcerative colitis depending on the degree of activity of the disease

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Background: Patients with inflammatory bowel disease (IBD) showed more frequent development of thromboembolic complications, compared with the general population. The aim was to identify changes in the haemostatic system in patients with ulcerative colitis (UC), depending on the degree of activity of the disease.
Methods: The study included 15 patients with total lesions, who were divided into three groups, depending on the degree of activity of the disease on the Mayo scale. The first group of patients was in remission, the second group of patients with UC had moderate activity of the disease, the third group was in high activity. The state of the blood coagulation system of the patients was assessed by the method of extended coagulogram (INR, APTT, prothrombin, antithrombin III, protein S) and using the method of thromboelastography (TEG). Patients were excluded hereditary coagulopathy.
Results: In all three groups of patients with UC, according to the extended coagulogram, no changes in the indicators typical for the disorders of the blood coagulation system were revealed.
According to the TEG data in Group 1, the time from the beginning of clot formation to the achievement of a fixed level of clot strength (amplitude = 20 mm) (K) was on average 3.7 min, an increase in the angle built tangentially to the thromboelastogram from the point of clot formation (angle) to 48.9, the maximum amplitude characterising the maximum dynamic properties of the fibrin and platelets compound by GPIIb/IIIa receptors (MA) to 57.9 mm.
In the second group, the time from the beginning of clot formation to the achievement of a fixed level of clot strength (amplitude = 20 mm) (K) was on average 2.45 min, an increase in the angle built tangentially to the thromboelastogram from the point of clot formation (angle) to 58.9, the maximum amplitude characterising the maximum dynamic properties of the fibrin and platelet compounds by GPIIb/IIIa receptors (MA) to 63.05 mm. In Group 3, the time from the beginning of clot formation to the achievement of a fixed level of clot strength (amplitude = 20 mm) (K) was on average 2.92 min, an increase in the angle built tangentially to the thromboelastogram from the point of clot formation (angle) to 63.9, the maximum amplitude characterising the maximum dynamic properties of the fibrin and platelets compound by GPIIb/IIIa receptors (MA) to 71.24 mm.
Conclusions: The thromboelastography is a more sensitive method for detecting haemostatic disorders in patients with UC, compared with a standard coagulogram. According to thromboelastography in patients with ulcerative colitis there is a hypercoagulation state of the blood system, regardless of the activity of the inflammatory process. The degree of hypercoagulation increases with the activity of the disease.

P180

Cause-specific and trend of mortality analysis in patients with inflammatory bowel disease: a Taiwanese Nationwide population-based study

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Background: Our previous study reported a higher mortality rate from inflammatory bowel disease (IBD) in Taiwan than in Western countries. With advancement in diagnosis and treatment for IBD, we proposed to compare the trend of mortality change and analyse cause-specific mortality in Taiwan.
Methods: This retrospective study was conducted to analyse data for January 2001 to December 2015 from a registered database, compiled by the Taiwan's National Health Insurance.
Results: Between 2001 and 2015, a total of 3806 IBD patients [Crohn's disease (CD): 919; ulcerative colitis (UC): 2887] were registered as having catastrophic illness, and 8.2% of these patients died during follow-up. The overall mortality rates for CD and UC were 20.0 and 10.8 per 1000 person-years, respectively. The standardised mortality ratios (SMRs) of CD and UC were 3.72 (95% CI: 3.02–4.55) and 1.44 (95% CI: 1.26–1.65), respectively, from 2001 to 2015, respectively (Table 1, Figure 1).

Table 1. Mortality in IBD patients registered in Catastrophic Illness Registry between 2001 and 2015, Taiwan.

	Crohn's disease					Ulcerative colitis				
Dx year	Dx (n)	Death (n)	Person-year	Mortality rate (per 1000 person-year)	P value	Dx (n)	Death (n)	Person-year	Mortality rate (per 1000 person-year)	P value
2001-2005	205	45	2,125	21.2		886	117	10,066	11.6	
2006-2010	258	32	1,714	18.7	0.002*	1,077	79	7,572	10.4	0.020*
2011-2015	456	19	955	19.9		924	18	2,110	8.5	

*Comparison disease year of 2001–2005 and 2011–2015

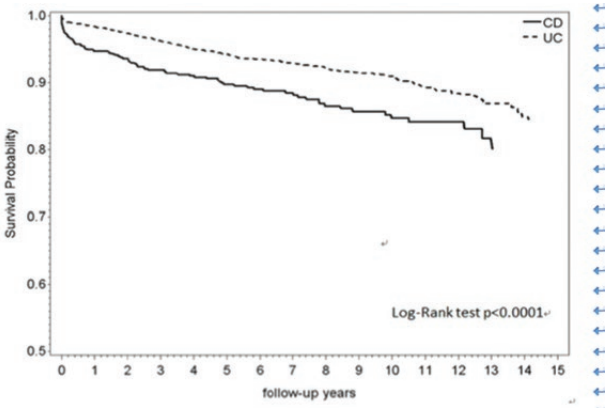

Figure 1. Survival rate of patients registered in the Catastrophic Illness Registry with IBD, Taiwan, 2001–2015.

A comparison of the periods of 2011–2015 and 2001–2005 revealed a decrease in the mortality rates from both UC and CD (Figure 2).

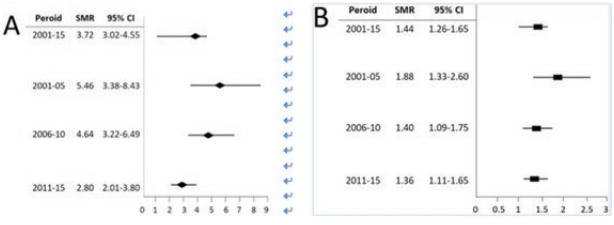

Figure 2. Standard mortality ratio of (A) Crohn's disease and (B) ulcerative colitis in different time periods.

Abstract P180 – Table 2. Age-adjusted cause-specific mortality of IBD patients registered in the Catastrophic Illness Registry, Taiwan, 2001–2015.

	IBD diagnosed/registered age								
	≤ 39			40-59			≥ 60		
	Survival	Deceased	P value	Survival	Deceased	P value	Survival	Deceased	P value
	n (%)	n (%)		n (%)	n (%)		n (%)	n (%)	
Total	1617 (100.0)	44 (100.0)		1408 (100.0)	84 (100.0)		471 (100.0)	182 (100.0)	
Gender			0.076			0.349			0.212
Male	1080 (66.8)	35 (79.6)		884 (62.8)	57 (67.9)		254 (53.9)	108 (59.3)	
Female	537 (33.2)	9 (20.5)		524 (37.2)	27 (32.1)		217 (46.1)	74 (40.7)	
Operation									
Colectomy	4 (0.3)	0 (0.0)	-	6 (0.4)	1 (1.2)	0.334	3 (0.6)	1 (0.6)	1.000
Colostomy	61 (3.8)	9 (20.5)	<0.001	56 (4.0)	13 (15.5)	<0.001	26 (5.5)	30 (16.5)	<0.001
Exploratory laparotomy	15 (0.9)	4 (9.1)	0.001	7 (0.5)	6 (7.1)	<0.001	3 (0.6)	3 (1.7)	0.356
Ileostomy	40 (2.5)	3 (6.8)	0.103	28 (2.0)	10 (11.9)	<0.001	12 (2.6)	12 (6.6)	0.014
Comorbidity									
Hypertension	70 (4.3)	3 (6.8)	0.439	356 (25.3)	25 (29.8)	0.361	283 (60.1)	103 (56.6)	0.416
Diabetes	36 (2.2)	1 (2.3)	1.000	190 (13.5)	15 (17.9)	0.259	120 (25.5)	51 (28.0)	0.507
Hyperlipidemia	95 (5.9)	2 (4.6)	1.000	369 (26.2)	18 (21.4)	0.332	194 (41.2)	42 (23.1)	<0.001
COPD	39 (2.4)	1 (2.3)	1.000	118 (8.4)	8 (9.5)	0.714	79 (16.8)	42 (23.1)	0.063
Hepatitis	90 (5.6)	2 (4.6)	1.000	152 (10.8)	11 (13.1)	0.512	45 (9.6)	13 (7.1)	0.332
EIM									
Uveitis	49 (3.0)	0 (0.0)	0.638	47 (3.3)	0 (0.0)	-	17 (3.6)	0 (0.0)	-
Psoriasis	99 (6.1)	2 (4.6)	1.000	59 (4.2)	5 (6.0)	0.403	22 (4.7)	5 (2.8)	0.268
Erythema nodosum	25 (1.6)	0 (0.0)	1.000	13 (0.9)	1 (1.2)	0.557	6 (1.3)	2 (1.1)	1.000
Arthritis	76 (4.7)	2 (4.6)	1.000	119 (8.5)	7 (8.3)	0.969	54 (11.5)	19 (10.4)	0.709
Cholangitis	14 (0.9)	2 (4.6)	0.065	12 (0.9)	6 (7.1)	<0.001	5 (1.1)	3 (1.7)	0.692
Deep vein thrombosis	7 (0.4)	1 (2.3)	0.194	17 (1.2)	3 (3.6)	0.098	14 (3.0)	6 (3.3)	0.829
Complication									
Fistula	355 (22.0)	11 (25.0)	0.631	201 (14.3)	13 (15.5)	0.760	44 (9.3)	15 (8.2)	0.660
Abdominal wall abscess	135 (8.4)	6 (13.6)	0.263	62 (4.4)	8 (9.5)	0.054	13 (2.8)	4 (2.2)	0.791
Hospitalization									
Pneumonia	49 (3.0)	13 (29.6)	<0.001	58 (4.1)	33 (39.3)	<0.001	63 (13.4)	86 (47.3)	<0.001
Urinary tract infection	88 (5.4)	6 (13.6)	0.035	90 (6.4)	17 (20.2)	<0.001	82 (17.4)	71 (39.0)	<0.001
Sepsis	126 (7.8)	26 (59.1)	<0.001	92 (6.5)	53 (63.1)	<0.001	65 (13.8)	100 (55.0)	<0.001

Regarding cause-specific mortality in IBD patients, elderly individuals; comorbidities such as hypertension, diabetes, and chronic obstructive pulmonary disease; infections; IBD-related complications; malignancies; and surgeries were the risk factors for mortality (Table 2).

Conclusions: In this nationwide population-based Taiwanese study, although SMRs of IBD patients decreased from 2001 to 2015, they were still higher than those of the general population. For further decreasing IBD-related mortality in Taiwan, we need to pay special attention towards elderly individuals, infection control, and improvement in perioperative care.

P181

Cytomegalovirus infections are rare in hospitalised patients with flares of inflammatory bowel disease—a monocentre retrospective cohort study

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Background: Cytomegalovirus (CMV) infection may complicate or mimic acute flares of inflammatory bowel disease (IBD). However, there are conflicting data regarding its prevalence and the optimal screening strategies in patients with severe IBD flares.

Methods: We performed a retrospective chart analysis of patients admitted to our department for IBD flares between 2010 and 2017. To identify potential risk factors for CMV infection, associations between clinical and laboratory parameters and proven CMV infection (as defined by positive CMV PCR from plasma or intestinal biopsies and/or significant expression of cytomegaloviral proteins as determined by immunohistochemistry) were analysed by univariable logistic regression analysis and calculated as odds ratios (OR) and 95% confidence intervals.

Results: In total, 495 hospital admissions for flaring IBD were identified. CMV testing was performed in 238 patients (43% male, 52% with ulcerative colitis [UC] and 48% with Crohn's disease [CD]). Twenty-two per cent of patients had a history of extraintestinal manifestations while 57% had previously been treated by immunomodulators or biologics. CMV infection was diagnosed in 13/238 patients (5.5%). Only 7 of these 13 patients had steroid-refractory disease. However, only 5 patients (2.1%) were considered to have clinically significant CMV infection and received antiviral therapy. Univariable regression analysis revealed that CMV infection was negatively associated with a diagnosis of CD when compared with UC (OR: 0.08 [0.01–0.6]), with increasing haemoglobin concentrations (OR: 0.47 [0.22–0.98] per increase of 3 g/dl) and serum albumin concentrations (OR: 0.25; [0.08–0.78] per increasing g/dl). Moreover, CMV infection was associated with the presence of

subfebrile temperatures (37.1–38.4°C, OR: 6.31 [1.28–31.2]) or fever on admission (≥ 38.5°C; OR: 9.85 [1.71–56.6]). We did not observe significant associations of CMV infection with severity of inflammation or ulcer depth as determined by endoscopy, age or dosage of concomitant corticosteroid therapy. 2/13 patients with proven CMV infection relapsed at later time points and the percentage of CMV-infected patients requiring proctocolectomy during follow-up was moderately, albeit not significantly elevated.

Conclusions: Based on the results of this retrospective cohort study, the prevalence of CMV infection appears to be low in patients hospitalised for IBD flares. CMV infection was associated with a diagnosis of UC, fever on admission and blood test results indicative of malnutrition or disease severity such as anaemia or albumin deficiency. CMV testing may therefore focus on (sub-)febrile UC patients with severely active disease.

P182

Prospective cohort to identify factors associated with a delay in diagnosis in patients with inflammatory bowel disease

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Background: International cohort studies have previously identified Crohn's disease (CD), ileal disease, smoking, and age (<40 years old) as factors associated with a delay in diagnosis of patients with inflammatory bowel disease (IBD). Referral from primary to secondary care has been highlighted as a significant contributor to diagnostic delay. Currently, there is a paucity of data looking at the factors influencing diagnostic delay specific to a UK population, where healthcare system is free at point-of-access. Hence, we conducted a prospective observational cohort study of patients referred to secondary care between January 2014 to December 2017.

Methods: In total, 163 patients between the age of 18 and 46 years who first presented to their general practitioner (GP) with gastrointestinal symptoms from January 2014 were included in this study. Patients above the age of 46 were excluded due to the increased risk of colorectal cancer with increasing age. This was also the upper age limit recommended for faecal calprotectin use in the investigation of suspected IBD. In addition to baseline demographic data, our main outcome measure was time to overall diagnosis including time from onset of symptoms to GP presentation (patient delay), time of GP presentation to referral (primary care delay), and time of referral to diagnosis (secondary care delay).

Results: The median time to diagnosis was 6.7 months [IQR 3.3–14.1], with no significant difference in time to diagnosis for IBD sub-types [CD, 9.8 months [IQR 5.5–18.5]; IBD-Unclassified, 7.0 months [IQR 4.5–8.5] and ulcerative colitis (UC), 5.2 months [IQR 2.9 –12.3] ($p = 0.555$)]. The median time it took patients to present to their GP was 3.0 months [IQR 1.4–6.0]; median time for GP to refer to a gastroenterologist was 0.6 months [IQR 0.2–1.7]; and the median time from GP referral to diagnosis was 1.5 months [IQR 0.8–2.5]. On multivariable analysis, rectal bleeding (OR 0.33, 95% CI 0.15–0.71, $p = 0.0046$) and abdominal pain (OR 2.49; 95% CI 1.13–5.89, $p = 0.029$) was negatively and positively associated with being in the upper quartile of patient delay. Urgent GP referrals (OR 0.14; 95% CI 0.05–0.36, $p < 0.001$) and triage by surgeons (OR 5.61; 95% CI 2.29–14.38, $p < 0.001$) had a negative and positive association with being in the upper quartile of secondary care delay, respectively. The use of faecal calprotectin or being triaged straight-to-test did not reach statistical significance.

Conclusions: Referrals triaged urgently and by a gastroenterologist were associated with a reduction in secondary care diagnostic delay. Adopting a combination of primary care faecal calprotectin testing and secondary care straight-to-test may impact diagnostic delays.

P183

Colombian real-world experience of vedolizumab use in patients with inflammatory bowel disease—EXVEDOCOL

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Background: EXVEDOCOL (EXperience of VEDOlizumab in COLombia) is a consortium of 9 inflammatory bowel disease (IBD) centres investigating the real-world (RW) clinical outcomes of vedolizumab (VDZ) in ulcerative colitis (UC) and Crohn's disease (CD) patients. RW outcomes on VDZ in Latin America are scarce. Our study aimed to assess the RW patient characteristics, effectiveness and safety of VDZ in this cohort.

Methods: A chart review was conducted in adult patients (≥18 years) with moderate to severe active IBD receiving VDZ therapy between July 2016 and October 2018. Clinical response was defined as a reduction of ≥3 points and ≥30% from baseline partial Mayo (pMayo) score in UC and a reduction of ≥3 points in the Harvey–Bradshaw index (HBI) in CD. Clinical remission was defined as Mayo score ≤2 in UC and HBI <5 in CD. Endoscopic remission was defined as a Mayo endoscopic score ≤1 in UC and Simple Endoscopic Score-CD ≤2 in CD. Deep remission was defined as achieving clinical and endoscopic remission. Descriptive statistics are reported.

Results: In total, 38 patients (31 UC, 7 CD) were included; baseline characteristics are shown in Table 1.

Abstract P183 –Table 1. Baseline characteristics of real-world vedolizumab patients from the EXVEDCOL consortium

	Ulcerative Colitis	Crohn Disease
Number of patients (n)	31	7
Age, years (SD)	37.6 (12.8)	57.0 (8.9)
Sex (female), n (%)	22 (71)	4 (57)
Disease duration (years), mean(SD)	7.4 (4.6)	12.8 (8.4)
Disease activity[§], mean (SD)	7.5 (2.9)	10.5 (1.8)
Endoscopic score[†], mean (SD)	2.5 (0.6)	6.6 (5.2)
Previous anti-TNF exposure, n (%)	18 (58)	5 (71)
Primary failure to anti-TNF, n (%)	5 (16)	0 (0)
Secondary failure to anti-TNF, n (%)	12 (39)	5 (71)
Concomitant immunomodulator, n (%)	17 (55)	3 (43)
Concomitant corticosteroid, n (%)	9 (29)	2 (28)

Note: §disease activity for UC was assessed with the partial Mayo score and for CD with the Harvey Bradshaw Index; †Endoscopic score for UC was assessed with the Mayo endoscopic score and for CD with the SES-CD score.

Thirty-one patients (25 UC, 6 CD) completed induction (doses 0, 2, and 6 week). Overall, 90% of 31 patients on VDZ achieved clinical response at Week 14 (92% [*n* = 23/25] UC, 83% [*n* = 5/6] CD); response rates in anti-tumour necrosis factor (TNF)-naïve patients was 92% (*n* = 13/14) vs. 88% (*n* = 15/17) in anti-TNF-experienced patients. Clinical response at last follow-up (median [min–max], months: 9.3 [2.1–28.2]) was seen in 81% (84% [*n* = 21/25] UC, 67% [*n* = 4/6] CD) of the 31 completers of induction (anti-TNF naïve 92% [*n* = 13/14] vs. 67% [*n* = 4/6] anti-TNF experienced). Baseline and follow-up endoscopy scores were available for 74% (*n* = 23) of patients; the endoscopic remission rate was 85% and 67% for UC and CD patients, respectively. Deep remission was achieved in 46% (*n* = 11) of patients. All patients receiving an immunomodulator (*n* = 11) were able to discontinue this therapy and only two UC patients continued corticosteroid therapy during VDZ treatment. Five adverse events (AE) were reported; one was considered severe (infusion reaction) in patients with history of allergic reaction to anti-TNF. Four patients discontinued VDZ, 2 due to an AE and 2 for unknown reasons.

Conclusions: This is the first study to show RW outcomes of VDZ in Colombian patients with IBD; high clinical and endoscopic remission rates with VDZ in IBD were observed with a favourable safety profile. Outcomes may be better in anti-TNF naïve patients. Further studies in Latin America patients are warranted.

P184

Is perianal involvement a crutch for biologic therapy on Crohn's disease?

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Background: Crohn's disease (CD) is complicated with perianal disease in 21–23% of patients. Presence of perianal disease has been associated with a disabling course of CD and dreadful impact on quality of life. We aim to identify whether perianal disease has negative implication on CD remission rates, after 1-year infliximab therapy course.

Methods: Cohort, retrospective, single-centre study, including consecutive CD patients on Infliximab perfusion. Patients were followed 1 year, since the beginning of biological therapy. Co-variables were chosen bearing in mind clinical relevance and literature evidence. We splitted our outcome variable into clinical remission; analytical remission; endoscopic remission and deep remission (including all three mentioned before). The correlation towards the outcome variable was assessed with univariate and multi-variate analysis, and a survival assessment, using SPSS—a *p*-value of <0.05 was considered statistically significant.

Results: We assessed 74 patients with CD, of whom 41 (55.4%) were female, with a mean age of 36 years old, all Caucasian. From our cohort, 36.5% of the patients presented perianal disease at diagnosis. After 1 year of treatment course, we documented 31,5% of deep remissions, 47.2% endoscopic remissions, 55.4% analytical remissions and 70.3% of clinical remissions. Sixty-six (89.2%) presented an initial response to the treatment, from whom, 20 presented disease relapses (clinical or/and analytical or/and endoscopic). Patients with perianal disease, on the first year of Infliximab therapy, have a higher probability of disease relapse, displaying statistically significant difference on Kaplan-Meyer curves (Breslow *p*-value 0.043). Several variables had statistical significance towards the outcome on the univariate analysis (age at diagnosis; disease behaviour at diagnosis; smoking; hospital admission; days of hospital stay; corticoid cycle; biological naïve patients; blood infliximab levels; calprotectin, protein c reactive, erythrocyte sedimentation rate levels before and after the year follow-up). Adjusting for confoundment, patients without perianal disease have an odd 7.6 times higher of achieving endoscopic remission ($p = 0.038$) and 26 times higher of achieving clinical remission ($p = 0.027$).

Conclusions: In CD patients on infliximab therapy, perianal disease involvement is associated with lower endoscopic, analytical and clinical remission rates, after 1-year follow-up. They are also more prone to disease relapses, on the first year of therapeutic.

P185

Correlation of patient-reported outcome measure with clinical disease activity and faecal calprotectin in patients with ulcerative colitis

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Background: Patient-reported outcome measures (PROM) have been developed to evaluate patients' perspective of disease control in inflammatory bowel disease (IBD). Measures of clinical disease activity (simple clinical colitis activity index [SCCAI]) have shown moderate correlation with faecal calprotectin (FCP), a marker of mucosal healing. However, no study has correlated FCP with PROM. Present study aimed to correlate FCP with SCCAI and PROM, and evaluate the role of PROM in predicting clinical remission and mucosal healing.

Methods: This prospective study included consecutive patients with ulcerative colitis of any disease extent/severity under follow-up at All India Institute of Medical Sciences, New Delhi India from June 2018 to July 2018. A detailed evaluation was done for demographics, disease duration, extent, and activity (SCCAI), FCP and IBD control questionnaire. IBD control-8, IBD control visual analogue scale (IBD-VAS) and SCCAI were correlated with FCP. Clinical remission was defined as SCCAI < 3, and mucosal healing was defined as FCP < 150 mg/kg of stool.

Results: Of 57 patients (mean age: 37.5 + 12.1 years, 58% males, median disease duration 5 (3–9) years, 15.8% proctitis, 45.6% left sided colitis, 38.6% pancolitis) 32 were in clinical remission and 28 had mucosal healing. There was a significant correlation between FCP and IBD control-8 (0.57, $p < 0.001$), IBD-VAS (0.46, $p < 0.001$),

and SCCAI (0.68, $p < 0.001$) and between SCCAI and IBD control-8 (0.65, $p < 0.001$) and IBD-VAS (0.64, $p < 0.001$). IBD control-8 had a moderate diagnostic accuracy to identify patients in clinical remission (area under curve: 0.82[0.69–0.84]) and mucosal healing (area under curve: 0.86[0.77–0.96]), with a score of 13 having a sensitivity and specificity of 69% and 84%, and 72% and 82% to identify patients in clinical remission and mucosal healing, respectively.
Conclusions: IBD control-8, and IBD-VAS, correlates with markers of disease activity and mucosal healing, and has a reasonable diagnostic accuracy to identify clinical remission and mucosal healing.

P186

Faecal calprotectin (FCal): a valuable non-invasive tool in the management of IBD

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Background: FCal emerged as useful tool for IBD management, but varied assay methods, cut-offs, scenarios, phenotypes and populations may influence usefulness.
Aims: Two substudies were designed: (1) To investigate the value of FCal in mucosal healing (MH) prediction (optimal cut-off, specificity, sensitivity, PPV, NPV) and thresholds for clinical activity and phenotypes and (2) to evaluate the ability of FCal monitoring in IBD in remission to predict relapse.
Methods: FCal was determined with Bühlmann® ELISA in IBD patients. from a Latin-American centre. Substudy-1 (MH prediction and activity/pattern of IBD): Included 100 IBD patients: (44 UC 56 CD), who underwent routine colonoscopy (VCC) with categorisation by IBSEN score (Frøslie KF, 2007) 'MH'(scores 0–1) and 'non-MH', colleting FCal samples within previous week. Optimal FCal cut-off for 'MH'prediction (opt-MH cut-off) was calculated (ROC analysis). Substudy-2 (Prediction of relapse): included 50 UC and 50 CD in clinical remission (≥3 months), FCal: basal, ≥biannual, VCC basal/final. Analysis: Kaplan–Meier survival analysis for FCal levels above and below opt-MH cut-off. Mean follow-up 23.0 ± 11.8 months. Global definitions of clinical activity: P.Mayo (UC), HBI (CD), Location/Extent (Montreal).
Results: Substudy-1: FCal levels (Mean ± SD) in patients. with 'MH' were significant lower vs. 'Non-MH': UC (191.3 ± 174.6 vs. 621.1 ± 368.3, $p = 0.0001$) and CD (237.0 ± 196.9 vs. 618.5 ± 319.3, $p < 0.0001$) Kruskal–Wallis. Opt-MH cut-off was 242 µg/g, AUC 0.84 (95% CI 0.753–0.906) $p = 0.0001$, sensitivity: 76.4%, specificity: 84.5%, PPV: 85.7%, NPV: 74.5%. By clinical criteria FCal was lower ($p < 0.0001$) in remission vs. activity in UC (165.7 ± 14.1 vs. 630.3 ± 349.6) and CD (276.4 ± 250.1 vs. 662.1 ± 289.9), but the cut-off was higher (284 µg/g) than opt-MH cut-off. In endoscopically active CD patients, FCal levels were higher in colonic CD (851.9 ± 232.0) vs. other locations 544.4 ± 313.3 ($p = 0.04$). Substudy-2: Cumulative probabilities of clinical relapse at 6, 12, 18, 24 months of patients with Fcal ≥ 242 µg/g ($n = 34$) were 20.6%, 38.2%, 44.7%, 51.6%, and rates with FCal under cut-off ($n = 66$) were 1.5%, 3.1%, 5.1% and 7.9%, respectively, HR: 14.22 (95% CI 6.18–32.72), $p < 0.0001$, sensitivity: 85%, specificity 82.7%, PPV: 67.7%, NPV: 93.9%. Globally, relapsed 15 (30%) of UC and 12 (24%) of CD (NS). Clinical relapses with Fcal ≥ 242 were 67.7% vs. 6.1% under cut-off, $p < 0.0000001$, endoscopic relapses (available in 91 patients) with FCal ≥ 242: 75%
Conclusions: (1) Fcal was a good predictor of MH in UC and CD according opt-MH cut-off (242 µg/g), (2) FCal values were significantly lower in remission vs. activity, in UC and CD, but in endoscopically active colonic CD, FCal was higher vs. other locations, (3) FCal showed to be an effective tool to predict relapse for levels above opt-MH cut-off.

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Clinical follow-up of patients with Crohn's disease treated with ustekinumab in our hospital

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Background: Major advances of knowledge in the immunology and pathophysiology of the intestinal inflammatory processes have helped to identify novel molecular targets for drugs and potential new therapeutic approaches fot the treatment of Inflammatory Bowel Intestinal (IBD), one of those target is Anti-Interleukin pathway. Currently, highlighting ustekinumab for moderate–severe Crohn's disease (CD) and previous anti-TNF failure. The aim of our study was to evaluate, according to clinical practice, the characteristics and evolution of CD in patients receiving Ustekinumab in our hospital.
Methods: This is an observational and prospective study about a cohort of patients with long-standing CD and failures to other biologic drugs, in treatment with Ustekinumab from November 2017 to November 2018. We assessed characteristics of the disease in each patient, based on the Montreal Classification, activity scores (CDAI and Harvey–Bradshaw) and clinical patients' evolution at 12 and 24 weeks after the beginning of Ustekinumab.
Results: We included 23 patients with CD, 43.5% (10/23) were men with an average age of 41.9 ± 11.3 years. In 65.2% (15/23) the location was ileocolic (L3), 21.7% (5/23) presented ileal involvement (L1), and 8.7% (2/23) colonic location (L2). The disease had an inflammatory behaviour (B1) in 39.1% (9/23), fistulizing (B3) in 34.8% (8/23), and the remaining 26.1% (6/23) presented a stenosing behaviour (B2) (Table 1).

Table 1. Demographic characteristics

Demographic characteristics	*n* (%)
Sex	
Men	10 (43.5)
Women	13 (56.5)
Montreal classification	
Age	A1: 1 (4.3) A2: 19 (82.6) A3: 3 (13)
Location	L1: 5 (21.7) L2: 2 (8.7) L3: 15 (65.2)
Behaviour	B1: 9 (39.1) B2: 6 (26.1) B3: 8 (34.8)
Perianal affectation	12 (52.2)
> 2 previous biologics	23 (100)

Perianal involvement was present in 52.2% (12/23) of patients and 30.4% (7/23) had extraintestinal manifestations. The most common reported were polyarthralgias, followed by dermatological involvement. In the first visit, the CDAI average score of 176 and the Harvey–Bradshaw index of 10.6. At the second visit (at 12 weeks) both showed a decrease to 88.5 points and 6 points, respectively. The third visit (at 24 weeks) was completed by 11 patients, maintaining all of them clinical remission, with a CDAI average score of 46.5 and Harvey–Bradshaw index of 4 (Table 2).

Table 2. Disease activity indices

	Visit 1 (Week 0)	Visit 2 (Week 12)	Visit 3 (Week 24)
CDAI	176	88.5	46.5
Harvey–Bradshaw	10.6	6	4

Conclusions: Treatment with ustekinumab seems to be an effective alternative in patients with advanced CD and previous anti-TNF or vedolizumab failure, warranting further evaluation with a larger cohort and a longer term follow-up.

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Validation of the modified Van Assche index for assessing response to anti-TNF therapy with MRI in perianal fistulising Crohn's disease

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Background: Magnetic resonance imaging (MRI) is used to assess perianal fistulising Crohn's disease (CD). Evaluation of treatment responses is crucial to guide clinical decisions. The original Van Assche index was modified to improve sensitivity to change, leading to the modified Van Assche index.[1] We aimed to validate the modified Van Assche index in patients with perianal CD receiving anti-TNF therapy.

Methods: An electronic search of medical records (2008–2018, Amsterdam UMC location AMC) was performed. Patients with a confirmed diagnosis of fistulising perianal CD who started or underwent intensification of anti-TNF treatment with a baseline and follow-up pelvic MRI were identified. Patients were divided in clinical responders and non-responders based on the medical notes at the time of the follow-up MRI. Items of the original and modified Van Assche index were scored in random order by two blinded, independent abdominal radiologists (JAWT and CYN), discrepant reads were reassessed by a third blinded abdominal radiologist (JS). The modified and original Van Assche index were calculated and the changes between pre and post-therapy MRI were compared in clinical responders and non-responders.

Results: Thirty cases were included (12 females, median age 27 years). Clinical responders (n = 16) had a median modified Van Assche index of 9.6 (IQR 5.8–12.7) at baseline and 5.8 (IQR 3.5–8.5) at follow-up (p = 0.008). For clinical non-responders (n = 14), corresponding scores were 7.7 (IQR 5.8–13.5) vs. 8.2 (IQR 5.8–11.5) (p = 0.624).The original Van Assche index showed a significant decrease in post-treatment scores compared with pre-treatment scores in clinical responders (13.0 vs. 9.6, p = 0.011), whereas no significant differences were observed in non-responders. Looking at individual cases, 10 out of 16 responders (62%) had a decrease in the modified Van Assche index at follow-up, and 6/16 (38%) had an unchanged or increased index (Figure 1).

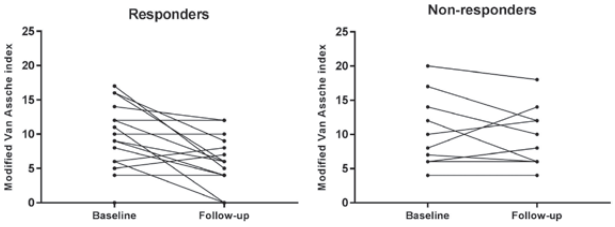

Figure 1. Modified van Assche index in clinical responders vs. non-responders.

Conclusions: This retrospective validation study showed a significant reduction in the modified Van Assche index in perianal CD patients who responded to anti-TNF treatment, whereas pre and post-treatment scores did not change in non-responders. This was, however, also true for the original Van Assche index and both indexes showed a comparable sensitivity to change. Further research is warranted to establish the modified Van Assche index' clinical value.

Reference

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P189

Role of digestive wall's ultrasound in the evaluation of post-surgical recurrence in Crohn's disease: correlation with endoscopic findings

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Background: Endoscopy remains the examination of choice in the evaluation of activity in Crohn's Disease (CD) after surgery (ADC-AS). However, digestive wall's ultrasound (US-DW) may represent a non-invasive alternative. The objective of this study was to determine the diagnostic accuracy and concordance of this modality comparatively to endoscopy.

Methods: Cross-sectional study, comprising a period of 14 months, carried out in patients with established CD and ileocaecal resection due to the disease. Performed US-DW (HI-VISION avius®, Tokyo, Japan) with linear probe B-mode/Doppler prior to ileocolonoscopy. US-DW and colonoscopy were performed on the same day by 2 specialists in gastroenterology dedicated to ultrasound and inflammatory bowel disease, in a double-blind mode. Collected demographic and clinical data [Harvey–Bradshaw index (HBI, remission: ≤4)], serological/faecal inflammatory parameters [leucocytes ($4 < N < 10 \times 10^9$ cells/l), C-reactive protein (≤0.5 mg/dl) faecal calprotectin (N <50 mg/kg), endoscopic (score Rutgeerts: remission < i2) and ultrasound [intestinal wall thickening ($N \leq 3$ mm) and digestive wall's vascularisation using the semi-quantitative score of Limberg (absent = 0, sparse = 1; moderate = 2; marked = 3)].

Results: Included 39 patients (female: 64.1%, mean age: 43.5 ± 15.3 years). Surgery performed, on average, 5.3 ± 5.3 years after diagnosis. Mean post-surgery follow-up: 9.9 ± 6.9 years. Montreal classification: L1 61.5% (n = 24), L3 38.5% (n = 15), B1 and B2 28.2% (n = 11) and B3 43.6% (n = 17). Most of patients

were in clinical remission (87.2%; n = 34) with mean HBI 2.1 ± 2.2. Twenty-two patients (56.4%) have normal inflammatory markers. US-DW (intestinal wall thickening> 3 mm and/or Limberg> 1) was abnormal in 61.5% (n = 24). Endoscopic remission (Rutgeerts <i2) in 53.8% (n = 21). Comparatively to endoscopy, the US-DW (AUROC 0.81; p = 0.001) showed a diagnostic accuracy superior to the inflammatory parameters (AUROC = 0.66; p = 0.083) and clinic (AUROC 0.64; p = 0.13). Ultrasonography showed good endoscopic concordance (Kappa 0.6, p = 0.001), higher than the inflammatory parameters (Kappa 0.33, p = 0.04) and clinic (Kappa 0.3, p = 0.01).
Conclusions: The ultrasound evaluation of the digestive wall showed a good diagnostic accuracy and a good concordance with endoscopic, superior to clinical and inflammatory parameters.

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Anaemia and iron deficiency in a tertiary IBD centre in Brazil: prevalence and significancy

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Background: Anaemia and iron deficiency anaemia (IDA) has been known to cause significant functional impairment, lower quality of life, higher morbidity and mortality. The aim of this study was to estimate the prevalence and significance of anaemia and IDA in patients with IBD in a tertiary IBD unit in Southeast Brazil
Methods: Retrospective analysis from the adult population-based IBD cohort of Clinical Hospital of Ribeirão Preto Medical School, University of São Paulo, Brazil, consisting of 579 patients, between January 2014 through July 2018. Medical records consisted of haemoglobin measurements and serum ferritin extracted from the hospital data system. We also compared the phenotype in Crohn's disease (CD) and the extension of ulcerative colitis (UC) with the anaemia prevalence. WHO criteria defined anaemia. IDA was evaluated using ferritin and C reactive protein (CRP).
Results: Of 579 patients, 529 had complete blood count available at medical records and 205 patients had IDA calculated. Means that during this 4-year median follow-up period, only 35.5% of patients with IBD (41.5% in CD and 35.2% in UC) were fully screened for anaemia. Table 1 summarises the patient's characteristics.

Table 1. Patient's characteristics (n = 529).

	Value
Female (%)	47.5
Mean age (years)	45.4
Anaemia in ulcerative colitis (UC) (%)	19.1
Anaemia in Crohn's disease (CD) (%)	29.1
Moderate to severe anaemia (UC) (%)	11.4
Moderate to severe anaemia (CD) (%)	19.8
Iron deficiency anaemia (UC) (%)	57.2
Iron deficiency anaemia (CD) (%)	53.6

CD was associated with an increased prevalence of anaemia (p = 0.008; OR = 1.76; CI 95%: 1.16–2.66) compared with ulcerative colitis. Penetrant disease phenotype in CD was associated with a lower risk of anaemia (p < 0.0001; OR = 0.25; CI 95% = 0.14–0.43). Active disease when compared with the disease in clinical remission was associated with an increased risk of anaemia (p = 0.0003; OR: 2.61; CI 95% = 1.56–4.36) in CD. Presence of anaemia was less frequent in patients with CD who underwent surgical resection compared with those who did not undergo surgery (p < 0.0001; OR = 0.24; CI 95%: 0.14–0.40). Differences were not observed in the presence of anaemia and localisation of Crohn's disease, age at diagnosis, extension of UCU, and use of biological (p > 0.05). This results are summarised in Table 2.

Variable	OR; CI 95%	p-value
CD	1.76 (1.16–2.66)	0.008
Penetrant disease phenotype (CD)	0.25 (0.14–0.43)	<0.0001
Active disease (IBD)	2.61 (1.56–4.36)	0.0003
CD who underwent surgical resection	0.24 (0.14–0.40)	<0.0001

Factors associated with higher/lower risk of anaemia. IBD = inflammatory bowel disease; CD = Crohn's disease.

Conclusions: Anaemia is a common manifestation of IBD. However, screening for anaemia and, in particular, iron deficiency, are rarely performed. CD is associated with an increased risk of anaemia, especially with active disease.[1]

References

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P191

Drug survival of biologics in Crohn's disease treatment in Norway

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Background: Real-world treatment patterns of biologics remains largely unknown. We aimed to investigate the drug survival of biologics in a national cohort of patients with Crohn's disease (CD).
Methods: Data were collected from the Norwegian Patient Registry (NPR) and the Norwegian Prescription Database. The study cohort was defined as all patients with at least two diagnosis of K50 (CD) in NPR from 2010 to 2017 with no prior IBD diagnosis in NPR (data from 2008). Treatment for patients who only received one infusion of vedolizumab or infliximab before discontinuing treatment was not included in the analysis to exclude false registrations. Vedolizumab is not given as first-line biologic treatment in Norway due to the tender process. Kaplan–Meier time-to-event analyses were performed to estimate time to treatment discontinuation. Discontinuation was defined as 3 months without a new infusion or prescription of the current drug after the predefined DDD period for the drug (i.e medication gap of >90 days). Biologic survival was compared using the log-rank test. The proportion of patients that received methotrexate or azathioprine was estimated by looking at the number of patients who received a prescription of an immunomodulator 6 months prior to or after starting biologic treatment. The chi-square test was used to compare the proportions receiving immunomodulators. Patients were followed until the outcomes of interest, death, or end of follow-up (31 December 2017), whichever occurred first.

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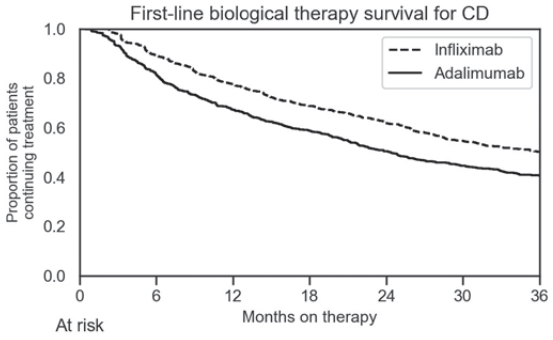
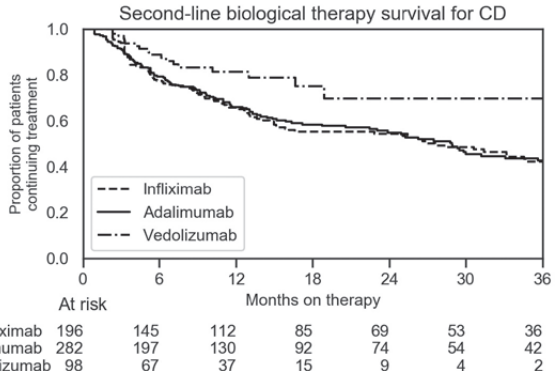
Results: In total, 2444 CD patients were included in the study. After 3 years, the survival rate of first-line biologics for CD patients was 50.3% for infliximab and 40.5% for adalimumab ($p < 0.001$).



For second-line treatment, the survival rates were 42.4% for infliximab, 42.8% for adalimumab and 69.8% for vedolizumab. Vedolizumab survival was significantly different compared with adalimumab and infliximab ($p < 0.001$).



72.4% of infliximab patients and 56.6% of adalimumab patients received an immunomodulator 6 months before or after starting treatment ($p < 0.001$).

Conclusions: In this Norwegian real-world registry study of CD patients, drug survival for biologics differed significantly in both first and second-line treatment.

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Prevalence and factors associated with impaired food-related quality of life: a cross-sectional survey of 1223 people with inflammatory bowel disease

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Background: Inflammatory bowel disease (IBD) patients often report that dietary intake and the enjoyment of food is affected by their condition. However, the prevalence of impaired food-related quality of life (FR-QoL) and associated factors have not been previously explored. This study aimed to determine the levels of FR-QoL and factors associated with it in a large, nationally representative sample of people with IBD.

Methods: A convenience sample of 1576 IBD outpatients ≥16 years old were recruited from seven UK centres. Patients consuming the majority of their intake as food completed previously validated questionnaires to capture demographic data, FRQoL-29, quality of life (IBDQ UK), IBD-distress (IBD-DS), IBD-fatigue (IBD-F), and anxiety and depression (HADS). A health professional recorded disease activity (HBI, SCCAI), disease classification (Montreal), blood results, body mass index and malnutrition risk (MUST). FR-QoL was regressed onto the explanatory variables (univariable/multivariable) using the Stata MI (20 imputed datasets) procedure.

Results: Data from 1223 patients were available (78% response, 65% CD and 51% female). FR-QoL mean score was 80.1 [SD 26.9] (minimum 29, maximum 145, higher score = better FR-QoL), considerably lower in comparison to previously measured healthy volunteers [123.0, SD 16.5]. The four items rated as the most severe (Strongly agree/Agree) were 'avoiding food and drink I know does not agree with my IBD' (71%), 'being more aware of what I am eating due to my IBD' (70%), 'certain foods have triggered symptoms of my IBD' (69%) and 'enjoyment of a particular food or drink has been affected by the knowledge that it might trigger my IBD symptoms' (67%). Twenty-six factors (demographic, clinical, drug-related, psycho-social) were significantly associated with impaired FR-QOL in univariate analysis. However, in the multi-variable regression, only lower educational level ($p < 0.001$), greater number of IBD flares in last 2 years ($p < 0.001$), more severe symptoms during last flare ($p = 0.034$), not taking immune suppressants ($p = 0.026$), greater distress ($p < 0.001$), greater fatigue impact on daily living ($p = 0.025$) and worse IBD QoL ($p < 0.001$) remained significantly associated with impaired FR-QoL.

Conclusions: In this first large study reporting FR-QoL in IBD, many factors were identified as having a significant negative effect on patients with IBD. Understanding the relationship between IBD and FR-QoL may improve communication between health professionals and patients regarding its impact.

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Prediagnostic markers in late onset inflammatory bowel disease

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Background: We aimed to determine whether patients who later develop IBD show signs of inflammatory activity in blood measured with high-sensitivity CRP, calprotectin and albumin before clinical onset of inflammatory bowel disease (IBD).

Methods: We identified 96 subjects who participated in the heath survey 'Northern Sweden Health and Disease Study' and who later developed IBD (70 UC and 26 CD). High-sensitivity CRP, calprotectin and albumin was analysed in stored blood donated from cases and sex-age-matched controls 1 to 15 years before diagnosis.

Results: We found that subjects who later developed UC had lower albumin levels and subject who later developed CD had higher levels of CRP compared with the controls. Multi-variate conditional logistic regression with albumin, calprotectin and CRP showed a lower risk for developing IBD and UC with higher albumin levels (OR 0.789; CI 0.691–0.901 respective OR 0.773; CI 0.657–0.909). Higher CRP levels were associated with increased risk of developing CD (OR 1.314; CI 1.060–1.630). Adding BMI or smoking in the logistic regression model similar results was found. Serum calprotectin levels in the prediagnostic period in patients with IBD did not differ from controls.
Conclusions: This nested case–control study show that subjects who later develop IBD have signs of low-grade systemic inflammation years before the diseases become clinical. CRP and albumin was more sensitive to detect low-grade systemic inflammation than calprotectin.

Ulcerative colitis	Case	Control	*p*-value	*N* case/ control
Median age, years	50 (40–60)	50 (40–60)	0.859	70/139
Median lag-time to diagnosis, years	5.3 (2.6–7.3)	na	na	70/na
Gender, women	61%	55%	0.766	70/139
Median BMI, kg/m^2	25 (23.2–27.5)	25.6 (23.1–27.8)	0.815	70/138
Smoking	30%	20%	0.162	65/128
Median albumin, g/l	37.8 (35.7–39.1)	38.5 (36.6–39.8)	0.025*	65/139
Median calprotectin, µg/l	671 (496–947)	693 (494–910)	0.925	65/137
Median CRP, mg/l	1.08 (0.46–2.70)	0.94 (0.49–2.52)	0.688	65/139

Basal characteristics for patients with ulcerative colitis and matched controls. Statistics: Mann–Whitney and χ^2 test.

Crohn's disease	Case	Control	*p*-value	*N* Case/ control
Median age, years	50 (40–57)	50 (40–60)	0.861	26/52
Median lag-time to diagnosis, years	4.7 (2.5–8.1)	na	na	26/na
Gender, women	46%	50%	0.936	26/52
Median BMI, kg/m^2	26.1 (23.1–30.4)	25.3 (22.9–28.4)	0.433	26/52
Smoking	35%	17%	0.176	22/42
Median albumin, g/l	37.0 (35.5–39.0)	38.0 (36.1–40.3)	0.074	26/52
Median calprotectin, µg/l	757 (520–1043)	640 (464–925)	0.369	26/52
Median CRP, mg/l	2.51 (0.34–8.71)	0.83 (0.31–2.10)	0.018*	26/52

Basal characteristics for patients with Crohn's disease and matched controls. Statistics: Mann–Whitney and χ^2 test.

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Automated real-time endoscopic scoring based on machine learning in ulcerative colitis: Red Density reliability and responsiveness study.

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Background: Endoscopic scoring in ulcerative colitis (UC) is subjective and has poor correlation with histological scoring. Histological remission predicts favourable long-term outcome in UC. Operator-independent automated digital scoring of endoscopic and histological inflammation in UC could provide an objective and predictive evaluation of remission. The aim of this study was to test the operating properties of the Red Density (RD) score (responsiveness and reliability).
Methods: The RD system uses machine learning (ML) to calculate a score based on real-time automatic extraction of pixel data from endoscopic images. This ML algorithm incorporates colour data and vascular pattern recognition. In this prospective study, consecutive patients with UC presenting at the IBD outpatient clinic with symptoms suggestive of a flare were included. At baseline and 8–14 weeks after treatment escalation we recorded endoscopic (Red Density score, Ulcerative colitis endoscopic index of severity [UCEIS], Mayo endoscopic subscore [MES]), clinical (total Mayo, PRO-2), histological data (Robarts histological index [RHI], Geboes score) and C-reactive protein. Investigators were blinded for the RD score. Correlation was tested between RD and clinical, biochemical, endoscopic, and histological scores (Spearman's rank correlation). Responsiveness was significant if standard effect size >0.8.
Results: Ten patients had two consecutive visits (M/F 4/6, median age 39 years IQR 36–48). At baseline all patients had active endoscopic disease (median (IQR) UCEIS 4.5 (2.5–5); MES 2 (1.3–2)). Nine patients had a change in their endoscopic score after treatment compared with baseline. The median delta in UCEIS and MES was 3 (IQR 2–4) (p = 0.009) and 1 (IQR 1–2) (p = 0.008), respectively. A significant number of patients achieved clinical, endoscopic and histological remission after treatment (all $p < 0.03$). Median RD score decreased significantly from baseline (166 to 58; p = 0.01) (Figure 1). RD correlated moderate with clinical outcomes (r >0.65, p = 0.001), and strong with both endoscopic ($r > 0.75$, $p < 0.0001$), and histological scores ($r > 0.75$, $p < 0.0001$). The standardised effect size for RD was 1.22.

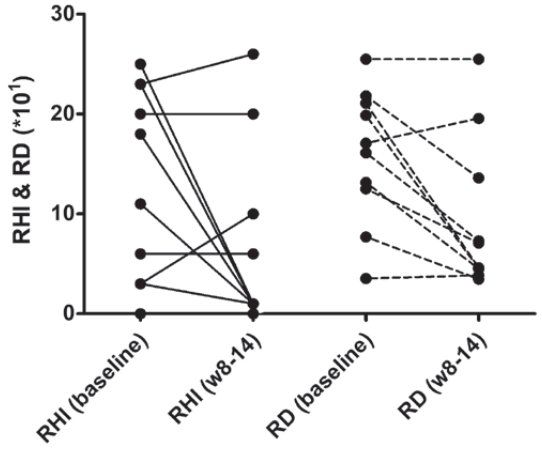

Figure 1. Evolution histological and Red Density score. RHI, Robarts histological index; RD, Red Density; w, week.

Conclusions: The automated digital endoscopic Red Density score correlates strongly with endoscopic, histological scores in UC. Red Density demonstrates an excellent sensitivity to change after treatment escalation. Red Density is an ideal operator-independent digital tool for the evaluation of endoscopic and histological disease activity in UC.

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MRI is predictive of, and anti-TNF treatment changes, the clinical course of Crohn's disease strictures

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Background: Strictures are the most common Crohn's disease (CD) complication but their natural history is unknown. There is a need to characterise inflammation and fibrosis, predict prognosis, and understand the impact of drug therapy.

Methods: Patients with a CD stricture diagnosed over a 5-year period with ≥12-month follow-up were reviewed for their clinical course, response to drug therapy, CRP, need for endoscopic dilatation, hospitalisation and surgery. Magnetic resonance enterography (MRE) scans at time of stricture diagnosis were reviewed blindly for disease extent and inflammation. Magnetic Resonance Index of Activity (MaRIA) score was calculated.

Results: Characteristics of stricture patients: 136 patients: 77 had 1 and 59 had ≥2 strictures. Median age at stricture diagnosis was 40. Thirty-four per cent had previous CD surgery. Fifty-seven per cent were *de novo* small bowel strictures, 33% anastomotic, and 10% colonic strictures. At stricture diagnosis, 28% of patients were already on anti-TNF therapy. Treatment: Median follow-up for those not requiring surgery was 41 months (IQR 26–56). Forty-six per cent of patients came to surgery for their stricture after a median of 6 months (IQR 2–11). Clinical and drug predictors of surgery: Hospitalisation due to obstruction predicted surgery (OR 2.7; p = 0.03) while anti-TNF therapy started at stricture diagnosis was associated with a reduced risk of surgery (p = 0.049). MRE predictors of outcome: On multiple logistic regression analysis MRE characteristics associated with increased risk for surgery were proximal bowel dilatation ≥30 mm diameter (OR 3.1; p = 0.005), bowel wall thickness at stricture (OR 2.5 for ≥10 mm; p = 0.01), and stricture length (OR 2.5 for >5 cm; p = 0.01). Eighty-one per cent of patients with all three adverse MRE features required surgery vs. 17% if none were present (p < 0.001; Figure 1). Accuracy for these three MRE variables combined for the prediction of future surgery was high (AUC 0.77). On univariate analysis mesenteric fat inflammation (p = 0.001), stricture bowel wall oedema (p = 0.002), MaRIA score (p < 0.001), and associated fistula (p = 0.02) were significant for surgical risk.

Conclusions: MRE findings are highly predictive of future surgery. Three simple findings (pre-stricture dilatation, bowel wall thickness, stricture length) are strongly predictive of subsequent surgery. These MRI findings predict future disease course and can identify patients who may benefit from treatment intensification. Anti-TNF therapy is associated with a reduced risk of surgery if commenced at stricture diagnosis, and appears to alter the natural history of this complication.

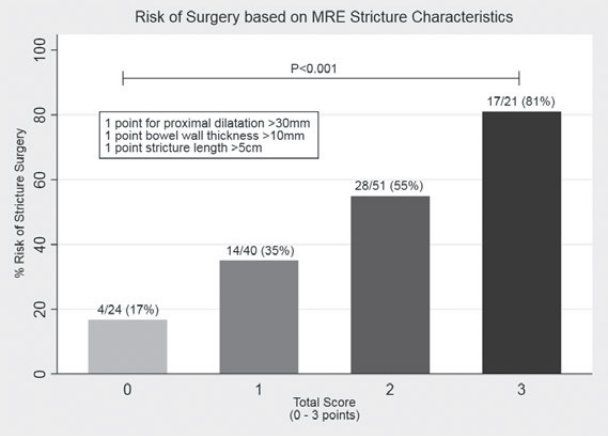

Figure 1

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Risk of venous thromboembolism according to disease activity, hospitalisation, or surgry in inflammatory bowel disease: a nationwide cohort study

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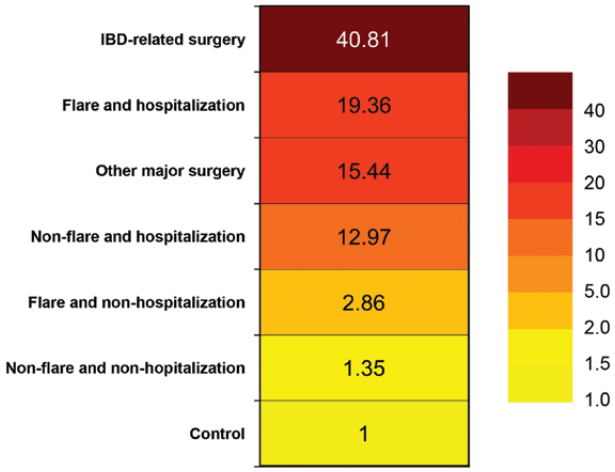
Background: The risk of venous thromboembolism (VTE) of inflammatory bowel disease (IBD) patients is higher than general population. Guidelines recommend primary prophylaxis of venous thromboembolism during their certain periods, yet little known about the magnitude of their different periods. We estimated the risk of VTE during a hospitalised flare, a non-hospitalised flare, a hospitalisation without flare, IBD-related surgery, and other major surgery.
Methods: Using the National Health Insurance claims data for the entire Korean population, we conducted cohort study, including 33 131 patients with IBD and 198 825 age- and sex-matched controls, from January 2014 until December 2016.
Results: Of 33 131 patients with IBD and 198 825 matched controls, 110 patients and 376 controls developed VTE. The overall VTE risk was higher in patients with IBD [adjusted hazard ratio (aHR) 2.10; 95% confidence interval (CI) 1.70–2.61], compared with controls. The risk of VTE during a non-hospitalised flare of IBD patients was higher compared with controls (aHR, 2.86; 95% CI, 1.70–4.80). The risks of VTE were increased much more during a hospitalisation with non-flare (aHR, 12.97; 95% CI, 8.68–19.39) and a hospitalised flare (aHR, 19.36; 95% CI, 9.59–39.07). The risk of VTE was highest at the time of IBD-related surgery (aHR, 40.81; 95% CI, 10.16–163.92). Also, the risk at the time of other major surgery was increased (aHR, 15.44; 95% CI, 7.65–31.12).



Heat map of risk of venous thromboembolism by different period of IBD patients. The colour intensity of the heat map is based on the hazard ratios for venous thromboembolic event.

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	Crude model		Model 1		Model 2	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
VTE	1.76 (1.42–2.17)	<0.001	2.00 (1.61–2.47)	<0.001	2.10 (1.70–2.61)	<0.001
DVT	2.14 (1.67–2.75)	<0.001	2.51 (1.95–3.24)	<0.001	2.64 (2.04–3.40)	<0.001
PE	1.23 (0.85–1.77)	0.267	1.33 (0.92–1.92)	0.126	1.42 (0.99–2.05)	0.06

Risk of venous thromboembolic events in patients with IBD

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	Incidence (per 1000 person-years)	Crude HR (95% CI)	*p*-value	Adjusted HR (95% CI)	*p*-value
Disease activity and hospitalisation					
Flare and hospitalisation	11.1	17.58 (8.33–37.11)	<0.001	13.54 (6.17–29.72)	<0.001
Non-flare and hospitalisation	9.85	14.34 (9.03–22.78)	<0.001	10.84 (6.76–17.37)	<0.001
Flare and non-hospitalisation	1.68	2.69 (1.51–4.79)	0.001	2.44 (1.37–4.65)	0.003
Non-flare and non-hospitalisation	0.70	1.00 (reference)		1.00 (reference)	

Risk of venous thromboembolism by disease activity and hospitalisation in IBD cohort.

Conclusions: The prophylaxis of VTE for Asian patients with IBD should be considered at the time of a hospitalised flare and IBD-related surgery. However, the prevention of VTE is not needed for non-hospitalised patients with flare.

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Crohn's disease recurrences after surgery: is there something new?

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Background: In our institution, a multi-disciplinary team consisting of endoscopists, surgeons, nutritionists, and pathologists is involved in the management of inflammatory bowel diseases. Over the last 18 years, data have been collected in a dedicated database. We retrospectively reviewed our activity to analyse whether the biological agents introduction influenced the treatment strategies in Crohn's disease (CD) patients who required a second surgery.
Methods: We retrospectively reviewed our database from 2000 to 2012 and selected patients with at least 6-year follow-up who underwent major surgery almost once in their life, including those previously treated in other centres. These patients were divided into four groups according to the medical treatment administered after surgery: patients treated with biologic agents (anti-TNFa) (Group A), with immunosuppressive drugs (azathioprine) (Group B), with immunosuppressive and biologic therapy (Group C) and with 5-aminosalicylic (5-ASA) (Group D). The difference between groups were calculated with χ^2 test.
Results: From 2000 to 2012, 206 patients with CD referred to our hospital. Among them, 137 patients underwent major surgery at least once in their life. After surgery, 23 patients were treated with biologic agents (Group A), 39 with immunosuppressive drugs (Group B), 51 with immunosuppressive and biologic therapy (Group C) and 24 with 5-ASA (Group D). Overall, 31 patients surgically recurred even though the medical therapy. Patients' surgical recurrence data are shown in Table 1 according to the pre-operative medical treatment. The reasons for re-operations are summarised in Table 2.
Conclusions: According to our data, none of the currently available drugs can significantly reduce alone the re-operation rate for CD. The combined use of immunosuppressive and biologic drugs does not seem to be the convincing strategy to delay surgical recurrence in Crohn's disease.

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Multi-alleles predict primary non-response to infliximab therapies in Crohn's disease: a simple and practicable model

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Background: Infliximab (IFX), a rather expensive medicine, is first-line treatment of Crohn's disease (CD) patients. The threptic efficacy of IFX has noticeable individual differences. Single-gene polymorphism is inadequate to predict primary non-response (PNR). In this study, we aimed at identifying genetic factors associated with PNR and predict patient primary response to IFX by develop multi-genetic prediction model.
Methods: A retrospective study was performed and patients with IFX therapy were recruited. Primary response was evaluated at 14th week according to simple endoscopic score for CD. Ninety tag single-nucleotide polymorphism (SNPs) within 27 genes were genotyped by MassARRAY Analyser system. Multi-variate prediction model was established to predict PNR. Area under the receiver-operating characteristic curve (AUROC) was applied to evaluate the performance of multi-variate model.
Results: Of 206 patients, 42 (20.4%) experienced PNR. Nine SNPs were associated with PNR ($p < 0.05$). The genetic prediction model included 5 SNPs, AUROC on representative training dataset and testing dataset is 0.794 ($p = 6.00 \times 10^{-6}$) and 0.812 ($p = 7.90 \times 10^{-5}$), respectively.

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	Total, *n* = 137	Group A, *n* = 23	Group B, *n* = 39	Group C, *n* = 51	Group D, *n* = 24	*p*-value
Number of reoperated patients, *n* (%)	31 (23)	5 (22)	9 (23)	8 (16)	9 (38)	0.30
Mean interval between surgeries (months)	86	98	79	89	77	
Number of patients treated with >2 surgeries, *n* (%)	11 (8)	3 (13)	6 (15)	2 (4)		0.07

Surgical recurrence data according to the medical treatment at the time of the re-operation.

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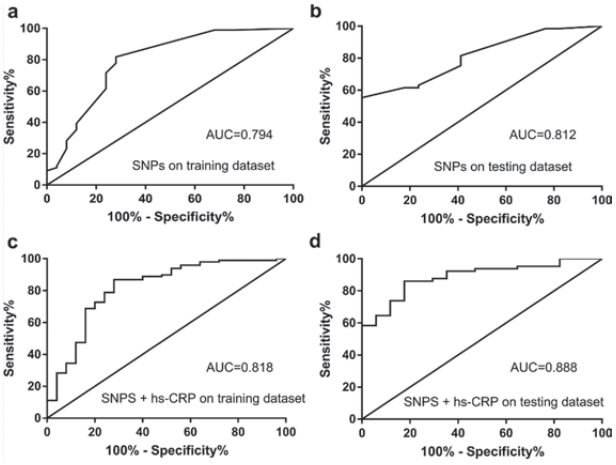
	Total, *n* = 31	Group A, *n* = 5	Group B, *n* = 9	Group C, *n* = 8	Group D, *n* = 9
Stricture or obstruction, *n* (%)	19 (61)	3 (60)	5 (55)	5 (63)	6 (67)
Intractable fistula, *n* (%)	6 (19)	1 (20)	1 (11)	2 (25)	2 (22)
Intra-abdominal abscess, *n* (%)	4 (13)	1 (20)	2 (22)		1 (11)
Perforation, *n* (%)	2 (6)		1 (11)	1 (12)	

Reasons of reoperation among medical treatment groups.



The ROC curve of SNPs on training and testing dataset.

The combined genetic-clinical prediction model, comprised 5 SNPs and one clinical indicator, is superior to genetic model, AUROC on representative training dataset and testing dataset is 0. 818 (p = 9.36×10^{-7}) and 0.888 (p = 9.52×10^{-7}), respectively.

The sensitivity and specify is 86.9% and 72.0%, respectively. On 100 training datasets and 100 testing datasets that obtained from 100 splitting process, the mean AUROC difference between them is only 0.02.

Conclusions: Genetic polymorphisms can predict PNR to IFX therapy in CD, the genetic-clinical prediction model is stable and not overfitted.

P199

Terminal ileum ileoscopy and histology in patients undergoing high-definition colonoscopy with virtual chromoendoscopy for chronic non-bloody diarrhoea: a prospective, multi-centre study

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Background: Ileocolonoscopy is the procedure of choice for chronic non-bloody diarrhoea (CNBD) of unknown origin. The histological evaluation at different colonic sites is mandatory to assess the presence of microscopic colitis. However, the value of routine ileal biopsies upon normal appearing mucosa as assessed by means of

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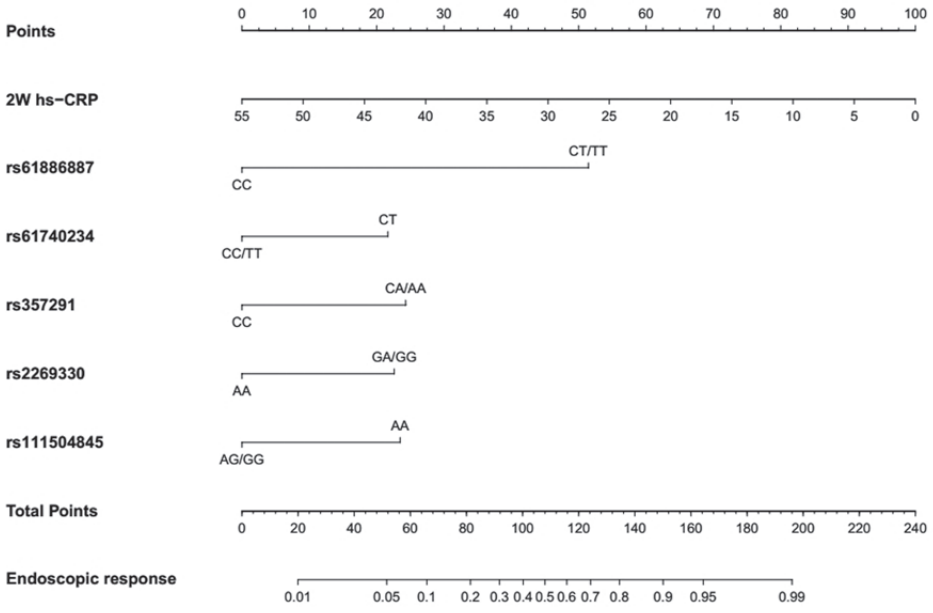

Combined predictive effect on endoscopic response in Nomography.

standard resolution white-light ileoscopy is controversial given its reported low diagnostic yield. Hence, we assessed, for the first time, the accuracy of retrograde ileoscopy using high-definition and dye-less chromoendoscopy (HD+DLC), thereby calculating the impact and cost of routine ileal biopsies in CNBD.

Methods: Patients with CNBD of unknown origin were prospectively enrolled for ileocolonoscopy with HD+DLC in five referral centres. Multiple biopsies were systematically performed in each colo-rectal segment and in the terminal ileum for histopathological analyses.

Results: Between 2014 and 2017, 546 consecutive patients were recruited. Retrograde ileoscopy success rate was 97.6%. In total, 492 patients (mean age 53 ± 18 years) fulfilled all inclusion criteria: following endoscopic and histopathological work-up,

Diagnostic definition based on ileocolorectal endoscopy and histopathology in patients with chronic non-bloody diarrhoea of unknown origin. LNH, lymphoid nodular hyperplasia; NSAIDs, non-steroidal anti-inflammatory drugs. Seven per cent had lymphoid nodular hyperplasia and 3% had isolated ileitis.

Terminal ileum endoscopic and histo-pathological assessment in patients with chronic non-bloody diarrhoea of unknown origin. LNH, lymphoid nodular hyperplasia; NSAIDs, non-steroidal anti-inflammatory drugs. Compared with the histopathology gold standard, retrograde ileoscopy with HD+DLC showed 93% sensitivity, 98% specificity, and 99.8% negative predictive value.

Test	Value
Sensitivity	0.933 (0.660 – 0.996)
Specificity	0.983 (0.966–0.992)
Positive predictive value	0.636 (0.408–0.820)
Negative predictive value	0.998 (0.986–1)
Positive likelihood ratio	55.6 (27.6–112.1)
Negative likelihood ratio	0.068 (0.010 – 0.450)

Statistical measures of the performance of retrograde ileoscopy with high-definition plus virtual chromo-endoscopy performance using histopathology as the gold standard.

In patients with normal ileocolonoscopy, ileum histology had no diagnostic gain and a $26.5 cost per patient.

Conclusions: Retrograde ileoscopy with HD+DLC predicts with excellent performance the presence of ileitis in CNBD. The

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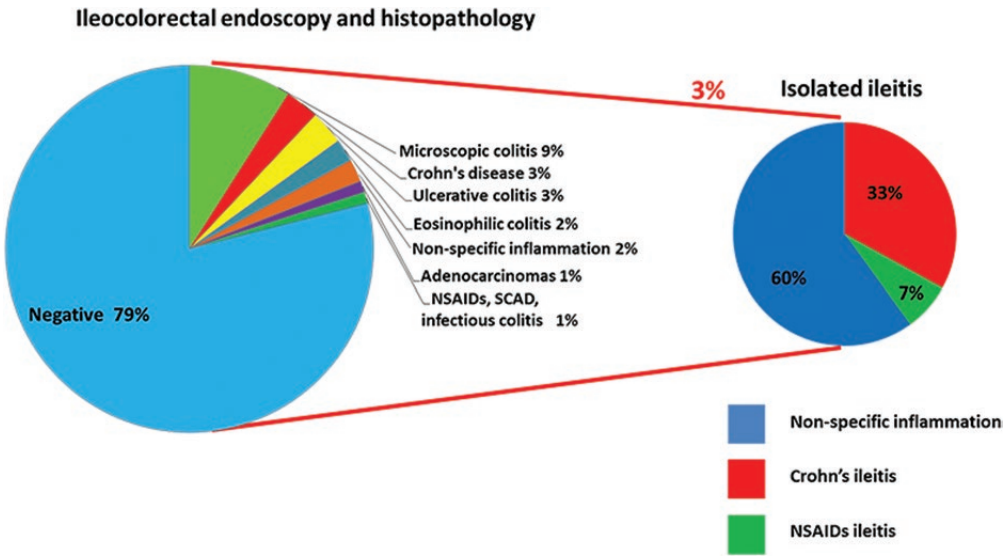

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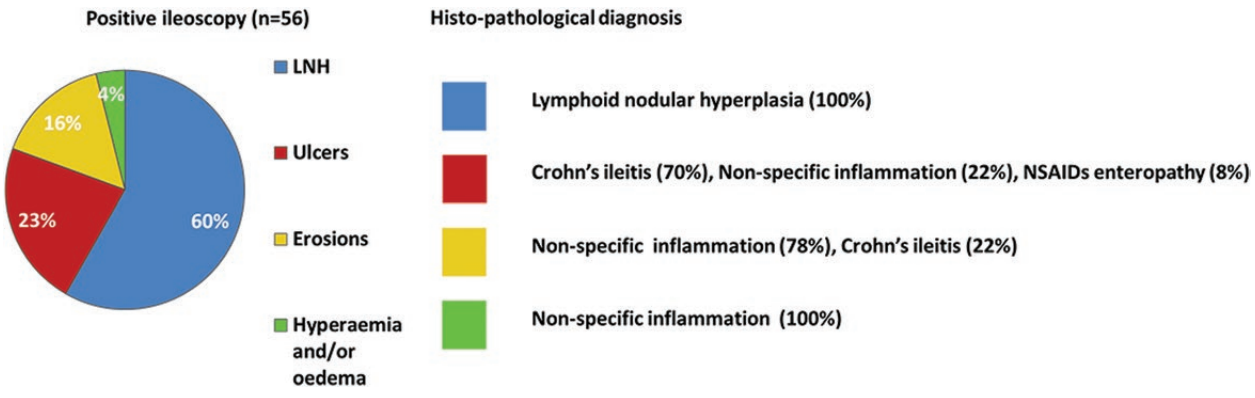

histopathological evaluation of the terminal ileum is the gold standard for the diagnostic assessment of visible lesions but has no added diagnostic value in CNBD patients with negative ileo-colonoscopy inspection using modern endoscopic imaging techniques.

P200

7α-Hydroxy-4-cholesten-3-one for diagnosis and management of bile acid malabsorption in IBD patients: 2-year clinical experience

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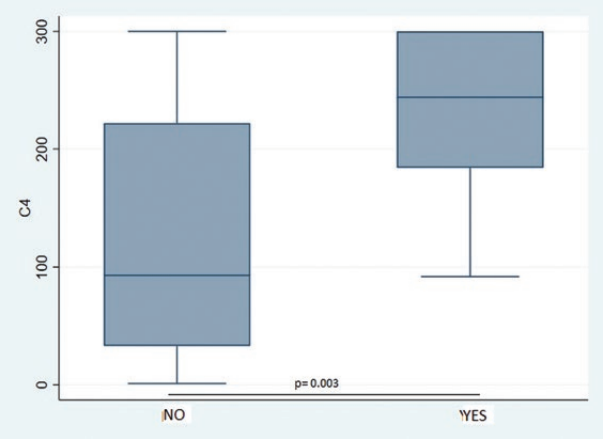
Background: 7α-Hydroxy-4-cholesten-3-one (7αC4) is a reliable method to diagnose bile acid malabsorption (BAM) which occurs frequently in inflammatory bowel diseases (IBD) patients. Since 7HCO is an intermediate metabolite in the bile acid synthesis, increased levels reflect bile acid production, which is the case in BAM.
Methods: We analysed the results of a simple and rapid (6 min), ultra-high-performance liquid chromatography–tandem mass spectrometry method[1] to measure 7αC4 on patients prospectively encountered at Bern University Hospital gastroenterology outpatient clinic with symptoms of BAM. The serum test result was correlated with clinical data such as type of disease (IBD, IBS, SIBO), symptoms (diarrhoea) and postsurgical state (eg, Ileo- caecal resection) and clinical response to bile acid sequestrants (the decision to treat with cholestyramine was at the discretion of the treating physicians).
Results: Two hundred forty-five patients were tested, among them 62 (25%) with IBD (50 Crohn's disease (CD) and 12 ulcerative colitis). The 7αC4 values of the subgroups showed a strong clinical validity with the highest values, as expected, in IBD (vs. controls, $p < 0.0001$), CD patients (vs. IBD, $p = 0.002$), after IC resection (compared with non-resected CD, $p < 0.0001$) and with response to cholestyramine ($p = 0.03$) with or without diarrhoea (p = NS).

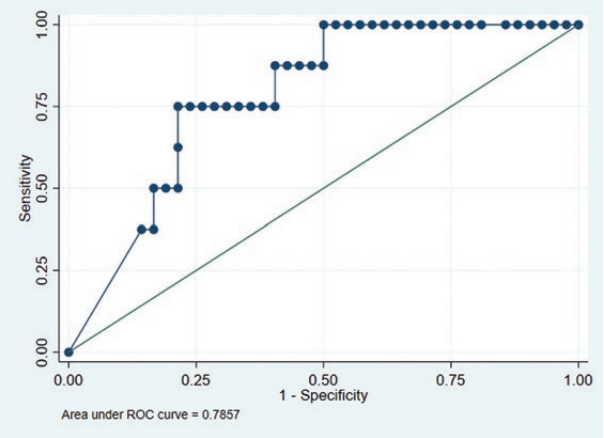
Subgroups	Number, %	Mean [ng/ml]*	±SD	*p*-value
Non-IBD patients	183	63	78	ref.
IBD patients / non	62 (25%)	65	13	< .0001
CD/ UC	50 (81%) / 12	125 / 45	13 / 31	0.002
Diarrhoea / none	44 (88%) / 6	147 /124	103/139	NS
CD IC resection / none	26 (52%) / 24	206 / 76	86 / 84	< .0001
Diarrhoea / none	23 (88%) / 3	204 / 228	82/ 124	NS
Cholest. treated / no	11 (48%) / 12	203 / 204	82/ 84	NS
Successful treatment / no	6 (54%) / 5	250 / 146	66 / 69	0.03

*Validation range 5–300 ng/ml; °*p*-value compares each line; NS = non-significant ($p > 0.05$)

A value of 7αC4 in the serum higher than 48 ng/ml had a positive predictive value of more than 80% for treatment success of the diarrhoea with bile acid sequestrants in all patients (sensitivity 74% and specificity 82%), with an AUC of 0.8514 in the ROC curve for this threshold. For the 50 CD patients with or without intestinal resection this threshold goes up to 234 ng/ml (sensitivity 67%, specificity 83%; AUC 0.7857).



7αC4 levels according to response in 50 CD patients.



ROC curve for 7αC4 50 CD patients.

Conclusions: 7αC4 levels in the serum correlate strongly with the clinical likelihood of bile acid malabsorption in IBD patients. A threshold of 234 ng/ml could be identified to predict response to cholestyramine treatment.

Reference

1. Prost J-C, Brunner F, Bovet C, *et al.* A UHPLC-MS/MS method for the quantification of 7α-hydroxy-4-cholesten-3-one to assist in diagnosis of bile acid malabsorption. *Clin Mass Spectrom* 2017;3:1–6. doi:10.1016/j.clinms.2017.02.001

P201

Faecal calprotectin in healthy children: are there factors affecting levels other than age?

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Background: Our aims were to (i) establish normal levels of faecal calprotectin (FC) in healthy children and (ii) analyse the correlation with age, gender, anthropometry, perinatal data, and the type of feeding.
Methods: Multi-centre, cross-sectional, and observational study including healthy children who attended the routine follow-up visits from the Healthy Child Program. Exclusion criteria: (i) immunodeficiency; (ii) autoimmunity; (iii) gastrointestinal disease; (iv) intake of drugs; (v) gastrointestinal symptoms; or (vi) any positive finding in the associated microbiological study. We determined FC levels (Quantum Blue® test) and performed stool cultures, parasites, rotavirus, and adenovirus detection. The statistical analysis (SPSS® software) considered a p-value of <0.05 statistically significant.
Results: We included 395 subjects (3 days to 16.9 years old); 51.6% boys (mean FC 196.8, median 86.0 µg/g) and 48.4% girls (mean FC 186.0, median 71.0 µg/g), with no significant differences (Mann–Whitney U test $p > 0.05$). FC values showed a non-normal distribution, with higher values in young participants (see table). A negative correlation trend was found between age and FC (Spearman's rho =–0.603, $p < 0.05$), as shown in the image. Weight was recorded in 389 subjects (mean 17.9 kg, 95% CI 16.4–19.6). Height was recorded in 383 children (mean 94.2 cm, 95% CI 90.4–98). BMI was calculated in 382 subjects (mean 16.4 kg/m^2, 95% CI 16.1–16.6). The multi-variate analysis with age as the control variable showed no correlation with weight or BMI but revealed an inverse correlation between height and FC. We found no significant differences between the type of birth and FC (Mann–Whitney U test $p > 0.05$) and no correlation with gestational age or birth weight (Spearman's test $p > 0.05$). Type of diet (breastfeeding, bottle feeding, or mixed feeding) in subjects under 6 months of age showed no correlation with FC (Kruskal–Wallis $p > 0.05$).
Conclusions: (i) FC values in healthy children were higher than those considered as pathological in adults. (ii) A negative correlation with age and height was observed. (iii) No correlation with gender, type of birth, gestational age, birth weight, or type of feeding in the first 6 months was found. (iv) It seems necessary to reconsider the levels of FC deemed pathological in paediatric patients by age group and further analyse the role of other factors.

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Quantum blue anti-infliximab: development and evaluation of a point of care rapid test for measuring anti-infliximab antibodies in human serum

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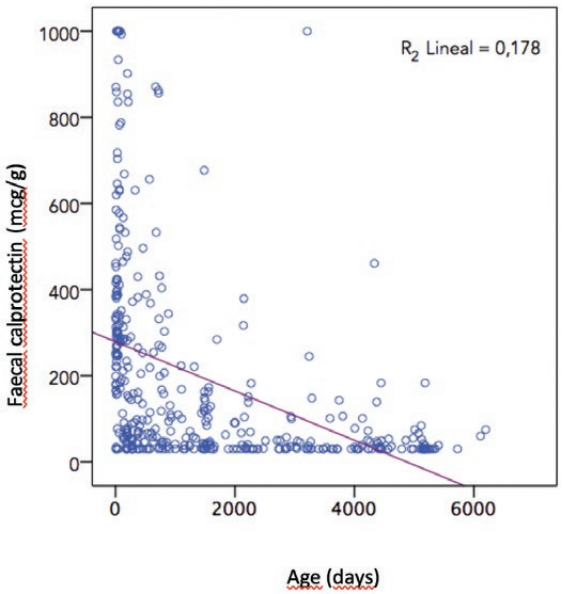
Background: The treatment of patients suffering from an inflammatory disease, like inflammatory bowel disease (IBD) may involve biologicals like infliximab. However, infliximab is a chimeric human/murine monoclonal antibody and can induce a significant immune response. Within this immune response different anti-infliximab antibodies are formed, belonging to different isotypes (eg, IgM, IgG_1, IgG_4, and IgE) with different specificities and affinities. The detection of these anti-infliximab antibodies is crucial to adjust the therapy with infliximab or to justify a switch of the used drug. For the fast and easy detection of the anti-infliximab response a lateral flow test was developed and preliminary evaluated.



Abstract P201 Figure. scatterplot showing the relationship between age and FC.

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Age group	Number of subjects	Mean FC (µg/g)	10thP (µg/g)	50thP (µg/g)	90thP (µg/g)
< 1 month	43	344.3	156	303	620
1–5 months	64	424	76	325.5	993
6–11 months	46	167.7	30	63	488
12–23 months	42	217.7	30	97	533
2–3 years	45	116.1	30	71	271
4–7 years	64	89.1	30	46	163
8–11 years	46	85.4	30	34.5	143
12–18 years	45	45.2	30	30	75
Total (0–18 years)	395	191.6	30	77	508.4

FC levels in each age group. 10thP: 10th percentile. 50thP: 50th percentile. 90thP: 90th percentile.

Methods: A drug-sensitive bridging lateral flow test was developed using infliximab-fragment coated gold nanoparticles and membrane immobilised infliximab to detect polyclonal anti-infliximab antibodies in a diluted human serum sample. Standardisation is based on a specific monoclonal anti-infliximab antibody. Using this approach limit of detection (LoD) and limit of quantification (LoQ) were determined according to CLSI EP17-A2 guideline. The influence of rheumatoid factors as well as various blood conditions was evaluated. Patient samples were used to compare the Quantum Blue® Anti-Infliximab rapid test with a commercially available ELISA test. These results were used to establish a ROC curve analysis and to identify a clinical relevant cut-off value.
Results: The current Quantum Blue® Anti-Infliximab test allows the analysis of diluted human serum samples within 15 min. The samples are diluted in chase buffer (1:10) before application on the test cassette. The readout is performed with a Quantum Blue® Reader resulting in a measuring range of 0.5 to 12 µg/ml. Due to missing international standard material and the polyclonal immune response in patients, the Quantum Blue® Anti-Infliximab was classified as semi-quantitative. The test exhibits a LoD of 0.31 µg/ml and a LoQ of 0.5 µg/ml. Rheumatoid factors as well as various blood conditions showed no interference to test results. A clinical cut-off value of 1.44 µg/ml results in a sensitivity of 0.86 and a specificity of 0.94 obtained by ROC curve analysis with 78 patient samples.
Conclusions: The here presented Quantum Blue® Anti-Infliximab test allows the fast and easy detection of anti-infliximab antibodies in human serum within 15 min. The assay can be carried out with a minimum of external equipment and may therefore support a fast adaption of the treatment regime, providing a valuable tool for proactive therapeutic drug monitoring.

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Potential, novel serum biomarkers in ulcerative colitis

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Background: Despite the advantages in the management of ulcerative colitis (UC), much less have been achieved in the field of diagnosis and monitoring of the disease, where colonoscopy remains the 'golden' method. Established serum biomarkers while commonly used, their poor correlation with the endoscopic features and poor performance as screening tools renders them as inadequate biomarkers by themselves. Therefore, the development of novel, objective, reproducible biomarkers with good correlation with disease endoscopic activity would be of great value for the diagnosis and monitoring of UC. The objective of our study was to evaluate the correlation between leucine-rich A-2 glycoprotein (LRG), high mobility group box 1 protein (HMGB1), Annexin A1 (ANXA1) and matrix metalloproteinase 3 (MMP3) with endoscopic activity and their role as potential serum biomarkers of UC.
Methods: Patients with UC, treated with 5-ASA undergoing colonoscopy, were selectively included in our study. Individuals undergoing preventive colonoscopy with no abnormal endoscopic features were also included as control group. A blood sample was obtained from each member of both groups and endoscopic Mayo subscore (Ms) was recorded for the UC patients. Serum LRG, HMGB1, ANXA1, and MMP3 levels were measured in the blood samples. Statistical analysis (Independent-samples t-test) was performed to compare the data collected and ROC curve analysis for the statistically significant differences recorded.
Results: Forty-two UC patients and fourteen controls were included. The patients' and controls' median age was 48 and 54 years old, respectively. While there were no statistically significant differences reported for HMGB1 and LRG, different results were recorded for ANXA1 and MMP3 as shown in the following table.

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ANXA1 µg/ml vs	Ms=0 N=18 Mean=2,281 SD=0,251	Ms=1 N=15 Mean=2,186 SD=0,256	Ms=2 N=6 Mean=2,248 SD=0,193	Ms=3 N=3 Mean=2,087 SD=0,863	UC N=42 Mean=2,228 SD=0,305
Control N=14 Mean=1,635 SD=0,390	P=0,00 AUC=0,913	P=0,00	P=0,00	P=0,16	P=0,00 AUC=0,881
Furthermore	Control vs Ms=0/1 P=0,000 AUC=0,898		Control vs Ms=2/3 P=0,005 AUC=0,817		

MMP3 ng/ml		
Ms=0 N=18 Mean=4,641 / SD=2,357	VS P=0,001 AUC=0.796	Ms=1 N=15 Mean=7,171 / SD=1,320
Ms=0/1 N=33 Mean=5,791 / SD=2,313	VS P=0.001 AUC=0,719	Ms=2/3 N=9 Mean=7,642 / SD=0,920

Conclusions: ANXA1 levels were significantly different between controls and UC patients implying that it could be used as a marker for diagnosis of UC. The best cut-off value was 2.043 µg/ml (88% sensitivity, 93% specificity). MMP3 was significantly lower for Ms = 0, Ms = 0/1 vs. Ms = 1, Ms = 2/3, respectively, suggesting that it could be a marker of mucosal healing and endoscopic remission. The best cut-off values were 4.743 ng/ml for Ms = 0 vs. Ms = 1 (100% sensitivity, 67% specificity) and 6.58 ng/ml for Ms = 0/1 vs. Ms = 2/3 (89% sensitivity, 61% specificity).

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The predictive value of ileocaecal resection margins for postoperative Crohn's recurrence

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Background: Surgical guidelines on Crohn's disease (CD) recommend limited resection for terminal ileitis, resecting only macroscopically affected bowel. However, recent studies suggest microscopic inflammation at resection margins as a predictive factor for postoperative recurrence. The clinical impact remains unclear, as non-uniform pathological criteria have been used. The aim of this study was to assess the predictive value of pathological characteristics at ileocolic resection margins for CD recurrence.
Methods: Both resection margins of 106 consecutive patients undergoing primary ileocaecal resection for CD between 2002 and 2009 were scored for active inflammation according to the validated Geboes score, myenteric plexitis, and granulomas. Pathological findings were correlated to recurrence, defined as recurrent disease activity demonstrated by endoscopy (Rutgeerts score ≥ i2) or imaging (preferably MRE (MaRIA score ≥ 7), requiring upscaling medical treatment.
Results: At the proximal (ileum) and distal (colon) resection margin active inflammation was found in 27% and 15% of patients, myenteric plexitis in 37% and 32%, and granulomas in 4% and 6% of patients. In total, 47 out of 106 patients developed recurrence. Only active inflammation at the distal resection margin was an independent significant predictor for recurrence (recurrence rate: 43% vs. 88% vs. 51% for active inflammation at proximal, at distal and non-involved resection margins, respectively, $p < 0.01$)
Conclusions: Active inflammation at the distal colonic resection margin after ileocaecal resection identifies a patient group at high risk for postoperative recurrence. In contrast, inflammation at the proximal ileum resection margin did not have any prognostic significance, confirming that more extensive resection is not likely to reduce recurrences. Moreover, these results suggest that patients with active inflammation at the distal colonic resection margin represent a different prognostic phenotype of CD (ileocolonic L3 disease instead of terminal ileitis L1 disease only), in which prophylactic medical therapy should be considered. Therefore, pathological evaluation of the resection specimen should be implemented in daily practice.

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The impact of the severity of microscopic inflammation at the time of diagnosis on UC-related outcomes during follow-up

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Background: Several studies have reported that the presence of histological inflammation in patients with ulcerative colitis affects prognosis and important UC-related outcomes. However, the prognostic value of histological inflammation at the time of diagnosis is not well characterised, and histology is not currently used to assess prognosis in UC patients. Our aim was to review the microscopic features at the time of UC diagnosis, and to assess its prognostic value during follow-up.
Methods: Multi-centre restrospective study. Biopsies obtained from the rectum in newly-diagnosed, treatment-naïve patients with proctitis (E1) and left-sided colitis (E2) were obtained. Pathology slides were reviewed by two independent pathologists and classified according to the Nancy score, grading from 0 (mild chronic inflammation) to 4 (ulcers). The impact of the severity of inflammation at diagnosis on a composite outcome (need for hospitalisation, steroids, and therapy escalation, acute severe UC or proximal disease extension) was evaluated using chi-square analysis. Wilcoxon test was performed to evaluate the performance of Nancy score in time to an adverse outcome.
Results: Forty patients were included (56.3% men, median age at diagnosis 47 years [17–66], median follow-up 1389 days [67–9836]). 64.6% were classified as proctitis (E1) and 35.4% as left-sided colitis (E2). Histological features found in inflamed rectal mucosa were marked chronic inflammation in 75%, moderate-to-severe basal plasmocytosis in 70.9%, moderate to severe neutrophils invasion in lamina propria in 60.5%, moderate-to-severe mucin depletion in 79.2% and ulcers in 27.1%. During the follow-up, 13/48 cases had an adverse outcome: 7/48 needed steroids, 2/48 were hospitalised, 1/48 had an acute episode of severe UC, 4/48 had proximal endoscopic extension and 9/48 escalated therapy. Moderate to severe histological features were more frequent in patients who were hospitalised (2/2), had disease extension (4/4) and needed steroids (basal plasmocytosis (6/7), neutrophils in lamina propria (5/7) and mucin depletion (6/7). In a composite endpoint no significant association was found with basal plasmocytosis ($p = 0.18$), mucin depletion ($p = 0.17$) and neutrophils invasion in lamina propria ($p = 0.60$). In the subgroup of patient developing an adverse outcome during follow-up, the median time to an adverse event was lower in Nancy scores ≥3 (781 vs. 1567 days, $p < 0.001$).

Conclusions: In our cohort of newly diagnosed patients severe histological inflammation at the time of diagnosis, as assessed by the Nancy score, was associated with a lower median time to an adverse outcome, suggesting that histological information should also be incorporated to guide prognosis assessment and therapeutic choices.

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Colectomy rate in paediatric patients with ulcerative colitis is decreasing

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Background: Paediatric-onset ulcerative colitis (UC) is often more extensive than in adults, and as disease severity is associated with disease extent, children are more prone to refractory severe episodes, sometimes requiring colectomy. Previous population-based studies in patients with UC revealed variable colectomy rates. However, a decrease in colectomy rates was observed during the last two decades. The aim of our study was to assess the colectomy rate in paediatric patients with UC and to compare the clinical features of children who had to those who did not have colectomy.
Methods: In our hospital, data on children diagnosed with inflammatory bowel disease have been prospectively collected since January 2004. Retrospectively we analysed data (including disease history, baseline characteristics, and course of disease) on all children diagnosed with UC (n = 170) from 2004 to January 2018. Four children were lost to follow-up (moved away) and were not included into analysis.
Results: Of 166 children diagnosed with UC, 12 had colectomy (7.2%). When compared with UC patients who did not have colectomy, patients with colectomy did not significantly differ in gender (girls 58% vs. 48%), age at diagnosis (12.27 vs. 12.62 years), body mass index at the time of diagnosis (median –1.2 vs. –0.22), Paediatric Ulcerative Colitis Activity Index (PUCAI) at the diagnosis (median 32.5 vs. 40), proportion of patients with extensive disease (E4) (75% vs. 57%) nor in extraintestinal manifestations. However, there was a significant difference in family history positive to IBD (25% vs. 7%, $p < 0.05$), in the highest PUCAI each patient had during the observation period (65 vs. 40, $p < 0.05$), number of patients treated with azathioprine (92% vs. 28%, $p < 0.01$) and anti-TNF therapy (58% vs. 3.9%, $p < 0.01$). We also found a significant decrease of colectomy rate (from 2004 to 2010 rate was 13.5% (7/52) vs. 4.4% (5/114) in the period from 2011 to 2018, $p < 0.05$). During the same time, the proportion of children with UC treated with anti-TNF therapy increased, although not significantly ($p > 0.05$): from 2004 to 2010, two children (3.8%) were treated with anti-TNF therapy, and both required colectomy, while in later period, 11 children (9.7%) received biologics, and 5 of them underwent colectomy.
Conclusions: Our paediatric patients presented with extensive form of the ulcerative colitis in nearly 60% of patients, requiring colectomy in overall 7.2% of patients. However, the colectomy rate decreased significantly during the observed period.

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67-Gallium citrate oral Scintigraphy evaluation in inflammatory activity in Crohn´s disease: a new highlighter?

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Background: There is not gold-standard diagnostic form to identify inflammatory activity in Crohn's disease (CD). The aim was to analyse the accuracy of oral 67-gallium scintigraphy to measure inflammatory activity in CD under treatment.
Methods: The study population was derived from eligible subjects who were known to have CD. Eligible patients were at least 18 years of age were known to have CD or were suspected of having CD. Exclusion criteria included pregnancy, intestinal surgery, and corticosteroid user. Twenty-four patients were enrolled in a prospective consecutive cross-sectional study from January 2018 to June 2018. The gold-standard test was the histopathological analyses. The patients were underwent a digestive transit studies with 67-gallium citrate (300 μCi) after oral ingestion with 10 ml of water. The radionuclide protocols were performed in 3, 6, 12, 24, 48, and 72 h after oral ingestion of radiotracer. We used statics pictures with 300 000 count each in anterior abdomen projection using a γ camera with large field of vision, medium-energy collimator, and 20% window centred in 92–300 keV photopeaks. Then, patients underwent a colonoscopy, until terminal ileum. Simple endoscopic score for CD (SES-CD) classified patients under suspect or proven for CD. In this case, each segment was subjected to two biopsies. Mucosal biopsies were taken from terminal ileum to rectum, targeting the interest area with haematoxylin–eosin. A single specialised gastrointestinal histopathologist scored affected areas using the Global Histological Activity Score (GHAS). Pairwise comparisons of areas under the ROC curves were subsequently performed.
Results: The clinical characteristics of 24 patients with CD undergoing assessment have been revealed in Table 1.

Characteristic- Crohn´s Disease	Baseline n=24
Age (years, mean and SD)	36,1 ± 10
Male (%)	31%
Female (%)	69%
Body Composition (BMI Kg/m^2)	24,4 ± 3
Ethnicity % White Latin American: Admixed: Black Americans:	 44% 50% 6%
Illness Time (years, mean and SD)	6,9± 5
CDAI (Crohn´s Disease Activity Index) Active disease (>220)	46%
Montreal Phenotype Classification L1 (Terminal Ileum) L2 (Cólon) L3 (Ileocolonic)	 4% 36% 60%
Anti-TNFs Treatment	57%

Clinical characteristics of patients with CD.

Endoscopic activity disease was present in 52% and histological activity in 77% of the sample. There is not difference between endoscopic (p = 0.88) and histology (p = 0.43) results in groups with or without clinical activity disease. The Spearman correlation between histological activity and 67-gallium scintigraphy was 0.69 with p = 0.004. When was used correlation with colonoscopy, the Spearman was 0.81 with p = 0.0001. The ROC curve showed in the Scintigraphy 0.96 area under curve with confidence interval (0.8–1) and standard error 0.05. The specificity of scintigraphy was estimated in 75%.

Conclusions: The identification of inflammatory activity in CD through 67-gallium scintigraphy have good accuracy, superior to clinical activity index and similar to colonoscopy.

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Impact of Pillcam Crohn's capsule on diagnostic yield and clinical management: results of the first multi-centre, observational study

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Background: A capsule endoscopy (CE) system tailored for Crohn's disease (CD) patients has been recently developed. This new device features two advanced optics allowing a 344°-view between both capsule heads and a prolonged operative time, to provide the direct visualisation of the entire digestive tract. The present study has evaluated, for the first time, the performance of the PillCam™ Crohn's System in a multi-centre real-life setting.

Methods: Consecutive patients with suspected or established CD were included between June 2017 and June 2018. Technical and clinical data, including the Lewis score and capsule impact on clinical management, were collected, thereby evaluating the added value of the 344° panoramic-view over the standard 172°-view.

Results: Among 41 patients (16 men; aged 43 ± 20 years), 73% underwent CE for suspected CD and 27% for established CD, with a mean time lapse of 12 years from diagnosis. The rate of complete enteroscopy was 90%. No technical failure or retention occurred. CE detected relevant lesions in 56.1% of patients, a Lewis score ≥135 in 51.4%, and had an impact on clinical management for 48.8% of patients. Compared with the standard 172° view, the panoramic 344°-view revealed a greater number of patients with a relevant lesion (56.1% vs. 39.0%; p = 0.023), resulting in higher Lewis score (222.8 vs. 185.7; p = 0.031), and improved clinical management (48.8% vs. 31.7%, p = 0.023).

Conclusions: The panoramic 344°-view improves both CE accuracy and the resulting clinical management of CD. This system should be regarded as a new standard for both small- bowel diagnosis and inflammatory bowel diseases monitoring.

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Rates of wound healing in patients with Crohn's disease undergoing proctectomy

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Background: The purpose of this study was to determine factors which may be associated with poor wound healing in patients with perianal Crohn's disease (pCD) who had undergone proctectomy in the biologics era.

Methods: Case record review was carried out of 79 patients with pCD who underwent proctectomy at St Mark's Hospital, Harrow between 2005 and 2017. Healing rates at 6 and 12 months post proctectomy were considered and univariate regression analysis was performed.

Results: Complete data regarding healing were available for 97.5% (77/79) at 6 months and 100% at 12 months. 45/77 (43.7%) patients had failure of wound healing at 6 months and 34/79 (33%) at 12 months. A younger age at diagnosis of Crohn's disease was significantly associated with failure of healing at 12 months (median age 21 ± 9.7 unhealed; median age 27 ± 13.6 healed; p = 0.03). 76.7% (61/79) patients received biologic treatments prior to proctectomy; however, exposure to biologics was not a significant factor in predicting failure of wound healing (Infliximab p = 0.74; Adalimumab p = 0.57; Vedolizumab p = 0.21). Current smoking status was not associated with poor wound healing (p = 0.18). Other parameters which were not associated with failure of wound healing in our cohort included gender, corticosteroid exposure in the previous 1 month, thiopurine exposure in previous 3 months, number of biologics exposed to, perianal sepsis on MRI within the last 12 months, Montreal Classification, duration of Crohn's disease prior to proctectomy, albumin, and CRP.

Conclusions: A third of patients have unhealed wounds after 1-year follow-up after protectomy. A younger age at diagnosis of Crohn's disease was the only factor associated with an unhealed perineal wound. This is conducive with more severe disease progression witnessed in patients diagnosed at a younger age. Larger scale studies are required to more accurately determine if other parameters such as exposure to biologics may also play a role in predicting rates of wound healing.

Abstract P209 – Table 1. Univariate analysis of parameters at 12 months post proctectomy.

	Not healed	Healed	p value
Sex (male)	19 (55.9)	19 (42.2)	0.26
Corticosteroids in last month	6 (19.4)	10 (24.4)	0.77
Thiopurines last 3 months	14 (45.2)	22 (53.7)	0.63
Number of biologics			
0	4 (13.8)	10 (28.6)	
1	16 (55.2)	9 (25.7)	
2	9 (31)	15 (42.9)	
3	0	1 (2.9)	
Infliximab	5 (16.7)	5 (12.8)	0.74
Adalimumab	8 (26.7)	10 (25.6)	0.57
Vedolizumab	0	2 (5)	0.21
Sepsis on MRI	6 (46.2)	6 (40)	0.74
Montreal Classification			
A			
1	11 (40.7)	7 (17.9)	
2	15 (55.6)	27 (69.2)	
3	1 (3.7)	5 (12.8)	0.08
B			
1	4 (44.4)	7 (38.9)	
2	1 (11.1)	4 (22.2)	
3	4 (44.4)	7 (38.9)	0.78
L			
1	1 (7.1)	0	
2	7 (50)	14 (48.3)	
3	6 (42.9)	15 (51.7)	0.33
4	1 (2.9)	1 (2.2)	
Smoking status			
Ex	1 (11.1)	1 (10)	
No	2 (22.2)	5 (50)	
current	6 (66.7)	4 (40)	0.18
Age at diagnosis	21 +- 9.7	27.6 +- 13.6	0.03
Length of CD to proctectomy	15.8 +-9.6	14.3 +- 10.9	0.57
ALB	39.2 +- 8.4	40.7 +- 7.2	0.53
CRP	53.5 +- 77.24	32.8 +- 51.91	0.3

P210

Depression and anxiety disorders impact in the quality of life of patients with inflammatory bowel disease

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Background: The relationship among anxiety, depression and quality of life (QoL) in inflammatory bowel disease (IBD) patients can be influenced by multiple factors, for instance, social isolation, difficult economic state and maladaptive coping strategies can be associated with IBD relapses and the need of surgical treatment of life. The aim of the study was to determinate the levels of sensitivity and specificity of the Anxiety and Hospital Depression Scale (HADS), and explore the quality of life in patients with inflammatory bowel disease (IBD) with depression and anxiety.

Methods: This is a case–control study of 104 adult patients with diagnosis of IBD between the period of August 2017 to February 2018. All patients answered a self-administered questionnaire (HADs) that includes 14 interleaved items, 7 of which assess for anxiety symptoms and the other 7 depression symptoms. Each patient received psychiatric intervention with Structured Clinical Interview for DSM (SCID-I) instrument as a gold standard to stablish the cut-off points of HADS. Quality of life was evaluated with IBDQ-32. The statistical analysis was performed in SPSS V. 21.0.

Results: According to the SCID-I, 24.0% of the patients had a depressive disorder characterised by major depressive disorder (84.0%) and dystymia (16%). A similar proportion of patients (20.2%) were diagnosed from an anxiety disorder such as generalised anxiety disorder in 76.2% and panic disorder in 38.1%. Using the already validated HADS Mexican version for patients with IBD, the total score for the depression dimension was 4.1 + 3.6 while for the anxiety dimension the total scoring was 5.4 + 3.8. With these scores and the SCID-I, the ROC curves for both psychiatric entities showed an adequate discriminative capacity of the HADS-Anxiety dimension (AUC = 0.84, 95% CI = 0.76–0.92) with a limited discriminability of the HADS-Depression dimension (AUC = 0.58, 95% CI = 0.46–0.70) using the proposed scoring of 8 as a cut-off point. From the four dimensions assessed in the IBDQ-32, the dimension of systemic symptoms had a high percentage of moderate and high affectation (34.6%) while less than 30% reported these levels of affectation in the dimensions of bowel symptoms (25.0%), emotional (29.8%) and social functioning (18.3%).

Conclusions: Anxiety and depression impacts negatively in the quality of life in Mexican patients with IBD. The Mexican version of HADS had good internal consistency and external validity, with favourable sensitivity and specificity for identifying cases of anxiety and depression in patients with IBD.

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Relationship between the concentrations of free sulphates and 5-hydroxyindoleacetic acid (5-HIAA) in urine for IBD patients

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Background: Sulphates are sparingly soluble salts of sulfuric acid, the increase of which may indicate the presence in patients inflammatory bowel disease (IBD). Recent findings demonstrate a possible role of sulphated compounds in the aetiology of IBD, where the latter is characterised by specific changes in 5-hydroxytryptamine metabolism. The aim of our study was to assess the level of sulphate in the urine in patients with IBD and to study relationship between the sulphate and 5-hydroxytryptamine metabolisms.
Methods: The study included 40 patients with IBD. Urine samples from patients with ulcerative colitis (UC) and Crohn's disease (CD) taken twice in the morning and afternoon, were used for the analysis of free sulphates and 5-hydroxyindoleacetic acid (5-HIAA) with specific detection strips and ELISA, respectively.
Results: Among 40 patients, UC was detected in 26 (65%) (10 male and 16 female), CD – in 14 (35%) (7 males and 7 females). The average age was 37.2 years. The clinical characteristics of the patients were analysed. According to the severity of disease: mild, 8 patients (20%); moderate, 17 (42.5%); severe, 15 (37.5%). Among UC patients, total colitis was observed in 15 (58%) patients, left-sided colitis in 7 (27%), proctitis in 4 (15%). Among patients with CD, colitis was observed in 6 (43%), ileocolitis in 5 (36%), terminal ileitis in 3 (21%) patients. Extraintestinal manifestations of IBD were detected in 21 (52.5%) cases, of which arthropathy in 13 (61.9%), aphthous stomatitis in 5 (23.9%), spondylitis/sacroiliitis 3 (14.2%). Complications (intestine perforation, bleeding, strictures, toxic dilatation) were identified in 7 (17.5%) patients. The average level of sulphates in patients with IBD was 746.3 ± 45.0 mg/l, while in patients with UC 690.4 ± 57.0 mg/l and in patients with CD 850.0 ± 66.9 mg/l. There were no differences between the level of sulphates in the urine of patients with UC and BK (p = 0.09). However, compared with the level of sulphate in the urine of a healthy population (<400), an increase in the sulphate content was found in both patients with UC and patients with CD. We found clear correlations (R > 0.72, p < 0.01) between the concentrations of free sulphates from the 'morning' urine and 5-HIAA from the 'afternoon' urine. CD patients demonstrated stronger (R > 0.77 vs. R > 0.72) correlation compare to UC patients in both sets of experiments.
Conclusions: Patients with IBD have a higher urine sulphate level than healthy populations, which can be useful as an indirect sign of inflammation. Our data suggest a close relationship between sulphate and 5-hydroxytryptamine metabolism.

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Diagnostic approach to monogenic inflammatory bowel disease in clinical practice: a 10-year multicentric experience

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Background: Up to 15% inflammatory bowel diseases (IBD) rising before the age of 6 years, defined as very-early-onset IBD (VEO-IBD), may have a monogenic disease. More rarely monogenic defects are found in later onset IBD. Monogenic IBD are associated with high morbidity and mortality and timely genetic diagnosis is essential for adequate treatment. Due to the wide phenotypic and genetic heterogeneity of these conditions, it is often difficult to reach a genetic diagnosis and the best diagnostic approach is still debated. Next-generation sequencing (NGS) techniques have been proposed as a screening tool especially in patients with poorly defined phenotypes. In a cohort study that included patients with VEO-IBD and early-onset IBD with severe/atypical phenotypes (EO-IBD s/a) we aimed to describe the genetic diagnoses and their therapeutic implications, define the clinical characteristics associated with monogenicity, and suggest a diagnostic approach to monogenic IBD.
Methods: Clinical information of patients with VEO-IBD and EO-IBD s/a referred to 2 Italian Centers (IRCCS Burlo Garofolo and Ospedale Bambino Gesù) for a genetic work-up over 10 years (2008–2017) were collected. From 2015 newly diagnosed patients and patients without a previous genetic diagnosis were screened using NGS, except patients with disease-specific features in whom candidate gene analysis was chosen.
Results: In total, 93 patients were collected and 14 (15%) reached a genetic diagnosis. Selective sequencing was performed in 46 patients (49%), NGS in 84 patients (90%). Causative defects were revealed by NGS in 5 patients (NOD2, TTC37, DKC1, XIAP, FERMT3) and candidate sequencing in 9 patients (3WAS, CYBA, CYBB, FOXP3, 2CD40L, XIAP). In 8 of 9 patients diagnosed with candidate sequencing, the analysis was guided by the presence of disease-specific features. One patient, with unspecific presentation, underwent sequential sequencing of multiple genes over 15 months before reaching the diagnosis (XIAP). NGS identified a new NOD2 mutation previously missed with single-gene approach. Genetic diagnosis impacted patient management in 9 patients (64%): 8 underwent bone marrow transplant (2XIAP, 3WAS, 2CD40L, FOXP3) and 1 patient introduced danazole (DKC1). Patients with monogenic IBD more frequently had thrombocytopenia (21% vs. 3%; p = 0.003),

hemophagocytosis (21% vs. 3%; $p = 0.02$), extraintestinal symptoms (100% vs. 32%; $p < 0.001$) and disease onset ≤ 1 month of life (36% vs. 1%; $p < 0.001$) when compared with the non-monogenic group.

Conclusions: We suggest using NGS in all patients presenting with non-specific clinical profiles and selective gene sequencing when clinical characteristics suggestive of specific monogenic conditions are present.

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Raised faecal calprotectin in inflammatory bowel disease (IBD) patients: 100% accurate or potential red herring?

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Background: Faecal biomarkers of gastrointestinal inflammation have appeared in the past decade, of which calprotectin, a neutrophil cytosolic protein, has been studied the most. Faecal calprotectin (FC) is increasingly being used in clinical practice as surrogate marker for intestinal inflammation. A meta-analysis of prospective studies using suspected IBD patients found the pooled FC sensitivity and specificity to be 93% and 96%, respectively. Previous studies showed that several medications, dietary supplements, sampling time, pregnancy, and body mass index have been mentioned as confounding variables affecting results. Single FC measurement may not be sufficiently accurate to evaluate gastrointestinal symptoms, and different biomarkers such as albumin and C-reactive protein, disease activity indices such as Harvey–Bradshaw index and Mayo score with or without endoscopic investigation should be used to interpret the full clinical context. The primary study aim is to assess the prevalence of this subgroup cohort and assess sensitivity and specificity of FC in our department. This subgroup identification may have clinical impact on provision of colonoscopy service if statistically significant.

Methods: This retrospective analysis study involved obtaining results of FC samples taken and correlate with colonoscopic and histological findings. The FC samples in our institution were processed in two external labs (Biomnis, Ireland, and Birmingham, UK).

Results: Our study cohort involved 80 patients (43 females, 37 males). The median age was 44. There were 38 patients with Crohn's disease, 35 with ulcerative colitis, 5 indeterminate, and 2 newly diagnosed IBD. The FC range in our external lab (Biomnis) are subdivided into 3-negative for level <50 µg/g, between 50 and 200 grey zone, and >200 is positive whilst the laboratory in Birmingham used the cut-off FC level < 60 µg/g as negative. There were 64 patients (80%) who had raised FC results. Of these, 55 (86%) had findings of colitis on histology and 9 (14%) showed negative histology ($p = 0.01$, CI 95%). There were 13 (16.3%) patients who had normal FC and had colonoscopy performed which showed colitis findings and confirmed histologically. There were 3 patients (3.7%) who had normal FC with no colitis evident endoscopically and histologically.

Conclusions: Faecal calprotectin is utilised in IBD centres as surrogate markers and initial non-invasive screening for intestinal inflammation. The FC specificity and sensitivity is variable and the possibility of confounding variables and patients' factors should be taken into account when interpreting results.

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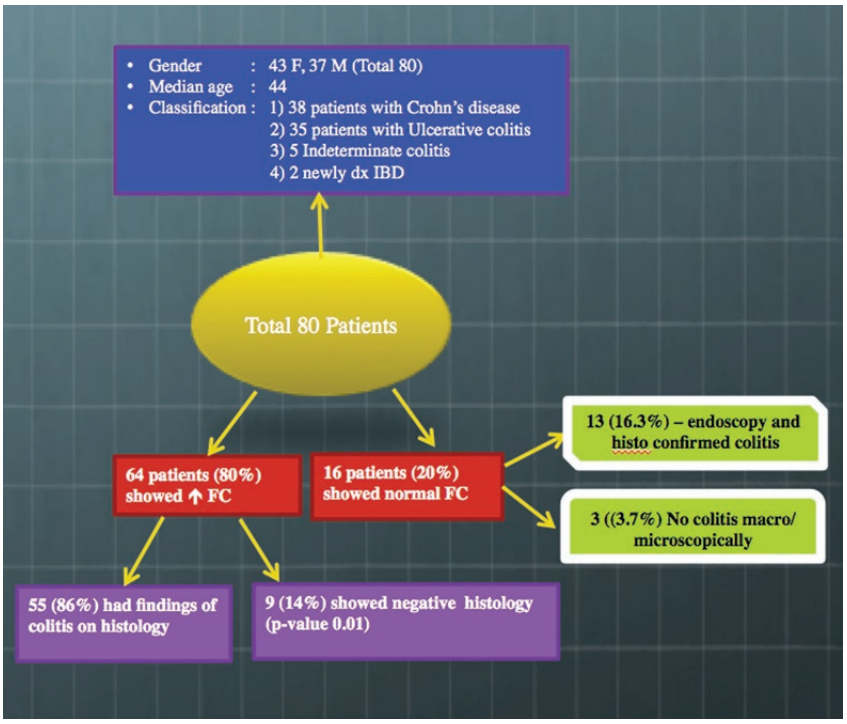

Faecal calprotectin results breakdown.

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How to incorporate patients preference into ulcerative colitis current clinical management: initial document from a Spanish multidisciplinary steering committee

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Background: To provide a patient-centred care in ulcerative colitis (UC), it is essential to address and to incorporate patient's opinions, preferences, etc. Our aim was to define and integrate UC patient's preferences in the management of the disease in clinical practice.

Methods: Qualitative study. A review of the literature was carried out in Medline and in the Clinical Queries of PubMed. We performed primary searches with Mesh terms and free text to identify preferences of patients with UC as well as clinical scenarios that may determine specific preferences. We selected articles that included: patients with UC, adults, who analysed their preferences. Likewise, only the following designs were included: meta-analysis, systematic reviews, clinical trials, studies, observations, and qualitative studies. The quality of the studies was evaluated with the Oxford scale. The results of the literature review were presented and discussed in a nominal group meeting, composed by a multidisciplinary steering committee of 6 gastroenterologists, 1 primary care physician, 1 nurse, and 1 patient. After that, a series of clinical relevant scenarios were identified and related patient preferences were proposed for them. This was the base to the generation of a set of general recommendations. The level of agreement among the multidisciplinary steering committee with the recommendations was established in a Delphi process in which the members of the committee voted from 0 = totally disagree to 10 = totally agree. Agreement was defined if at least 70% of the participants voted ≥7.

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1	The opinion and preferences of patients with ulcerative colitis should be taken into account in routine clinical practice	Level of agreement, 100%
2	There are key clinical scenarios such as the diagnosis, follow-up, surgery or specific patients profiles like children, adolescents, women or the elderly, in which we must have a special sensitivity with their opinion and preferences	Level of agreement, 100%
3	Regarding to the diagnosis, it is recommended to provide and discuss the information about the disease and its impact through different visits, focussing this information on patients concerns and needs, adapting it to patients and disease features, in order	Level of agreement, 87.5%
4	At the time of the diagnosis, regarding the disease (pharmacological and non-pharmacological) treatment, it is recommended to make informed and shared decisions with the patients, that includes the definition of therapeutic objectives	Level of agreement, 100%
5	Regarding to the diagnosis, the relationship between patients and health professionals should be honest, trustworthy, empathetic, and it should also focussed on patient's needs and concerns	Level of agreement, 87.5%
6	During the follow-up, it is recommended to follow the same recommendations described for the diagnosis	Level of agreement 87.5%
7	During the follow-up, continuity of care is recommended, as well as a coordinated and efficient multidisciplinary care when needed	Level of agreement, 87.5%
8	During the follow-up, medical visits schedule should be adapted to patients characteristics and needs, allowing urgent or on-demand consultation (face-to-face, tele-medicine, etc.)	Level of agreement, 100%
9	During the follow-up, it is recommended to address other issues that have not been covered in the diagnosis and/or that appear during the follow-up, such as intimate relationships or work problems	Level of agreement, 87.5%
10	During the follow-up it is recommended to evaluate that the patient follows the treatment as agreed and with confidence	Level of agreement, 100%

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Results: The review of the literature included 69 articles, most of them qualitative studies of moderate quality. UC patient's preferences were classified according to different topics including information, treatment (pharmacological and non-pharmacological), disease follow-up, relations with health professionals, health system and with the administration. In the nominal group meeting several key clinical scenarios were identified: the diagnosis, follow-up, surgery and special clinical scenarios/patients profiles (children, teenagers, elderly, women, pregnancy and lactation, family, and socio-work environment). A total of 11 recommendations about the incorporation of UC patients into daily practice across the key clinical scenarios are were generated (see table). All of them reached the level of agreement established

Conclusions: UC patients preferences should always be taken into account in the management of the disease.

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The mean platelet volume compared with other serum biomarkers: is it predictive of activity of Crohn's disease?

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Background: During Crohn's disease (CD), several serum markers are non-invasive means of assessing the activity of the disease. Recently several studies have suggested that mean platelet volume (MPV) varies during CD potentially constituting a marker of disease activity. The aim was to study the variation of MPV in patients with remission and those having an active disease and the correlation with other indices of disease activity.

Methods: We retrospectively collected consecutive patients hospitalised for MC from 2008 to 2018. Crohn's Disease Activity Index (CDAI), MPV, neutrophils, lymphocytes, albumin, and CRP levels were recorded. We calculated neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and platelet/albumin ratio (PAR). PAR = (platelets/albumin) 100.

Results: Seventy-four patients were collected. There were 33 men (45%) and 41 women (55%) The sex ratio was 0.8. The mean age was 41 years ± 14.1 [14–79]. The location was ileal, colonic, and ileocolic in, respectively, 22%, 22%, and 56%. Upper location was found in 7% of patients. Anoperineal lesions were detected in 40% of cases. The CD had inflammatory, stricturing, and penetrating behaviour in, respectively, 39%, 22%, and 23%. The disease was both stricturing and penetrating in 16%. Sixty-six per cent of patients were treated. The treatment was salicylates, azathioprine, anti-TNF-α, and combination therapy in, respectively, 15%, 32%, 6%, and 14%. These patients were divided into two groups according to the activity of the disease. There was no significant difference between these groups in age and sex. Fifty-two per cent of the patients were in remission with a mean CDAI of 79.2 [28–142], the mean CRP was 4.5 mg/l. Mean platelet, lymphocyte, and neutrophil counts were, respectively, 287 605, 1803, and 3962. The mean value of the MPV was 10.07 FL [6.7–11.4]. Forty-four per cent of the patients had active disease. The activity was minimal, moderate, and severe at, respectively, 17%, 23%, and 4%. Mean CDAI was 247 (range 152–523), mean CRP was 73.6 mg/l, mean platelet, lymphocyte, and neutrophil levels were, respectively, 404 000/mm^3; 1698/mm^3 and 5756/mm^3. The mean value of the MPV was 9.68 FL [7–12.7]. MPV was not significantly associated with CD activity. CRP and platelets were associated with activity with respective p of 0.0001 and 0.004. The NLR, the PLR, and the PAR were associated with active CD with respective p of 0.004, 0.014, and 0.0001. The predictive value of CRP and platelet accounts activity were, respectively, 65.4 mg/l and 366 582/mm^3. Predictive NLR, PRL, and PAR rates of the activity were, respectively, 1.57, 329.6, and 57.6.

Conclusions: The MPV was not predictive of activity of CD. Other biomarkers such as NLR, PLR and PAR had significant correlation with it.

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Impact of disease knowledge on quality of life of inflammatory bowel disease patients

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Background: Inflammatory bowel disease (IBD) impairs patients' quality of life (QoL). Several factors are involved in the impact of QoL, being the most important the activity of the disease. Subjective aspects can also be involved in QoL. One factor that has been scarcely studied is the impact of knowledge of the disease on Qol. Patients who are more knowledgeable could have an easier and more active participation in the management of their disease and on the decision-making process thus improving their QoL. We analysed the relationship between patients' objective and subjective disease knowledge and their QoL.

Methods: Prospective observational study in IBD patients (regardless of type, activity, treatment, surgery, etc.). Patients signed an informed consent, and completed different questionnaires: QUECOMIICAT questionnaire for objective knowledge; a visual analogue scale of self-perceived knowledge of IBD for subjective knowledge; IBDQ-9 for QoL measurement. We considered that patients had an objective high-level of knowledge if QUECOMIICAT score was >75 and a low-level of knowledge with a QUECOMIICAT score <25.

Results: One hundred and forty-four patients were included (83 UC and 61 Crohn's disease). Sixty-nine per cent were in remission at time of inclusion. IBDQ-9 score did not correlate with the level of objective knowledge of the disease by QUECOMIICAT (r = 0.1, p = ns), in both UC and Crohn's disease patients. IBDQ-9 was also not statistically different between patients with a high level vs. a low level of knowledge (median IBDQ9 of 69 vs. 68 points, p = ns). When only IBD patients in remission were analysed, correlation between QUECOMIICAT score and QoL was also not significant. Spearman test showed that QoL was inversely correlated with disease activity (r = –0.6, p < 0.001) and positively correlated with self-perceived knowledge (r = 0.24, p < 0.01). In the multi-variate analysis we found that having an active disease and being female were the only variables independently associated with a worse QoL (p < 0.01).

Conclusions: Quality of life was not influenced with the objective measure of patients' knowledge of IBD. However, higher subjective self-perceived knowledge was associated with a better QoL.

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Serological biomarkers of type VI collagen remodelling reflect endoscopically and clinically active Crohn's disease

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Background: The relapsing and transmural inflammation of Crohn's disease (CD) may cause intestinal tissue damage that eventually may result in surgery. Disease activity in CD patients is assessed by clinical symptoms and macroscopic findings of intestinal inflammation at endoscopy. Type VI collagen reside in the interface of the intestinal interstitial matrix and basement membrane. It affects epithelial cell-fibronectin interaction that is important for cell proliferation, adhesion, and migration. Collagens hold signalling potential, and endotrophin that is released from type VI collagen can stimulate fibroblasts to produce more ECM. Thus, type VI collagen is more than just a structural protein and we investigated if serum biomarkers of its remodelling could serve as surrogate of disease activity in CD patients.

Methods: Serum from 17 CD patients with active (n = 10) and inactive (n = 7) disease based on the simple endoscopic score for CD (SES-CD) were included in this study. Two competitive ELISAs were used to estimate serum levels of degradation and formation of type VI collagen, respectively. One for a neo-epitope of MMP-9-mediated degradation of type VI collagen α3 chain (C6Ma3) and one for endotrophin; C-terminus of released C5 domain of type VI collagen α3 chain (PRO-C6).

Results: Serum C6Ma3 was elevated in CD patients with a SES-CD above 2 compared with patients with a SES-CD of 0–2 (Figure 1A–C). A receiver-operating characteristic (ROC) analysis showed an area under the curve of 1 for C6Ma3 with specificity and sensitivity both at 100% (Figure 1D). The area under the ROC curve for CRP and Fcal were 0.87 and 0.81, respectively (Figure 1E and F). Serum PRO-C6 was lower in CD patients with active disease compared with patients in remission based on the Harvey–Bradshaw Index (HBI) (Figure 1G) and serum PRO-C6 showed an inverse correlation to HBI (Figure 1H).

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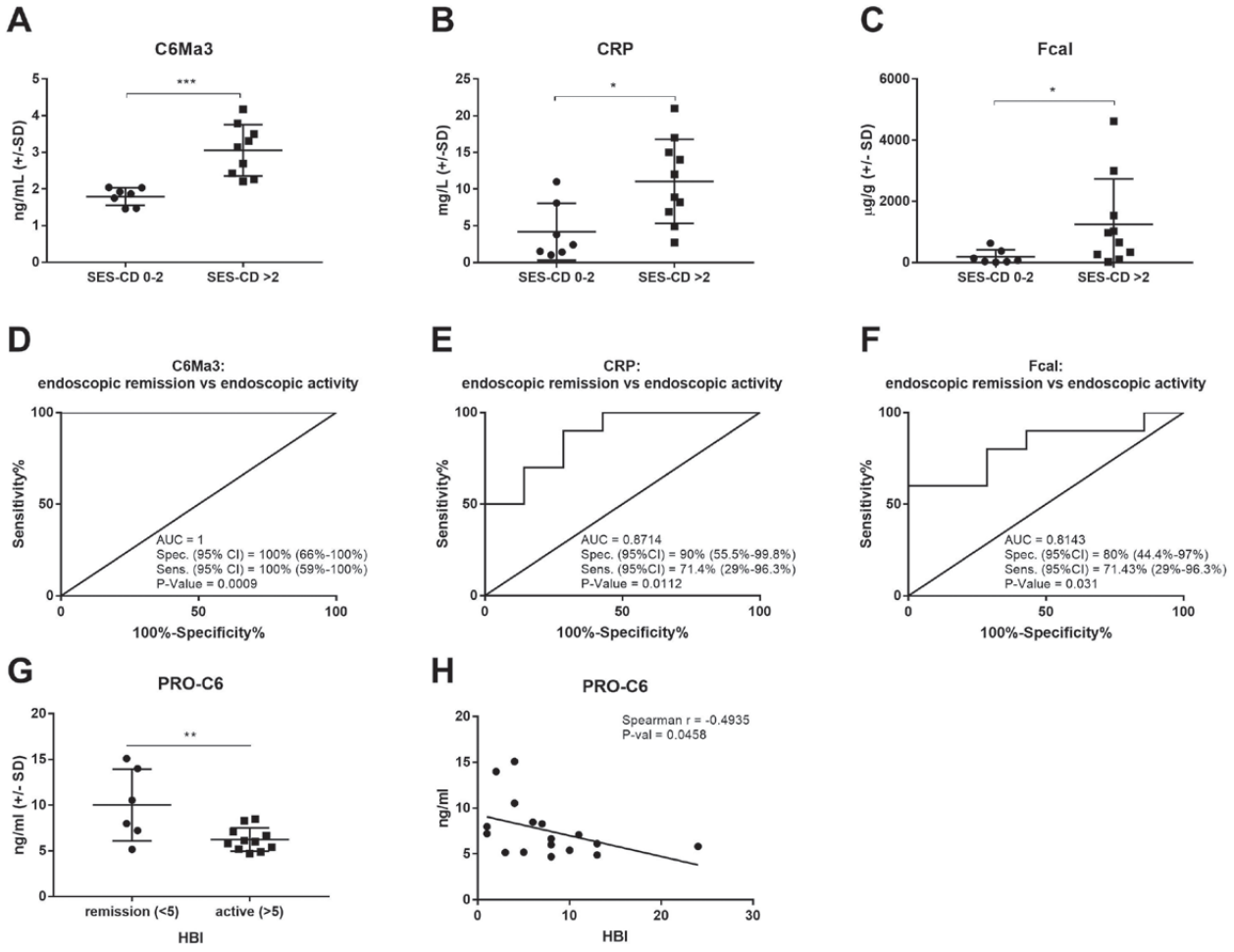

Figure 1. Serum levels of C6Ma3 (A), CRP (B), and Fcal (C) in patients with endoscopically inactive (SES-CD = 0–2) and active (SES-CD >2) CD. Reciever-operating characteristic curves of C6Ma3 (D), CRP (E), Fcal (F), and their ability to distinguish endoscopically active (SES-CD >2) CD from endoscopically inactive (SES-CD = 0–2) CD. Serum levels of PRO-CO (G) in CD patients with inactive (H81 < 5) and active (HBI > 5) CD. Unpaired t-test, area under the ROC curve, and Spearman correlation r were applied. *$p \leq 0.05$, **$p \leq 0.01$, and ***$p \leq 0.001$.

Conclusions: Our data show that biomarkers of tissue remodelling reflect endoscopically and clinically active CD. MMP mediated destruction of type VI collagen (C6Ma3) was associated with endoscopically active CD and could separate endoscopically active and inactive patients with 100% sensitivity and specificity. Decreased levels of endotrophin (PRO-C6) was associated with clinically active CD and showed an inverse relationship with HBI. This indicates that remodelling of type VI collagen measured by C6Ma3 and PRO-C6 can be used as surrogate markers of endoscopically and clinically active CD, and that fragments and signalling molecules released from type VI collagen are associated with pathological features of CD.

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The cost-effectiveness of biological therapy cycles in the management of Crohn's disease

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Background: The objective of this study was to compare the cost-effectiveness of two de-escalation therapies with continued combination therapy using infliximab and an immunomodulator in patients with Crohn's disease in clinical remission. The cost-effectiveness of different withdrawal strategies in which treatment is de-escalated in periods of remission is largely unknown. Published studies of related treatment strategies suggest that the cost-effectiveness is determined by the exact content of the treatment strategies compared and pharmaceutical prices. Thus, our objective was to examine the cost-effectiveness of continued treatment for patients with moderate–severe Crohn's disease (in clinical remission) with a combination of anti-TNFα (infliximab) and immunomodulator therapy, compared with two different withdrawal strategies (1) withdrawal of the anti-TNFα therapy and (2) withdrawal of the immunomodulator therapy, respectively, and to examine the significance of pharmaceutical prices for the estimated cost effectiveness.
Methods: A decision-tree simulation model (Markov type) was constructed mimicking three treatment arms: (1) continued combination therapy with infliximab and immunomodulator, (2) withdrawal of infliximab, or (3) withdrawal of the immunomodulator. Relapses in each arm are managed with treatment intensification. State dependent relapse risks, remission probabilities and quality of life weights were collected from previous published studies.
Results: Combination therapy was less costly and more efficient (produced better health outcomes) than the withdrawal of the immunomodulator, and more costly and more efficient than withdrawal of infliximab. The incremental cost-effectiveness ratio for the combination therapy compared with withdrawal of infliximab was estimated at SEK 755 449 per additional QALY. This is well above the informal willingness-to-pay threshold in Sweden (500 000 SEK/QALY). The estimated cost-effectiveness of the combination therapy was found highly sensitive to the unit cost of infliximab; at a 36% lower unit cost of infliximab, the combination treatment would become cost-effective. The qualitative content of these results were quite robust to changes in the clinical effectiveness and the quality-of-life figures adopted in the calculations.
Conclusions: Combination therapy using a combination of anti-TNF (infliximab) and immunomodulator is cost effective in the treatment of Crohn's disease compared with treatment cycles in which the immunomodulator is withdrawn. Combination treatment is not cost effective compared with treatment cycles in which infliximab is withdrawn, at current pharmaceutical prices. This conclusion is likely to be altered as the price of infliximab continues to decrease.

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Retrospective investigation of tacrolimus combined with an anti-TNFα antibody as remission induction therapy for refractory ulcerative colitis: efficacy, safety, and relapse rate

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Background: Combined therapy with tacrolimus (TAC) and an anti-TNFα antibody is used to induce remission in ulcerative colitis (UC) who have not responded to monotherapy with either drug. We evaluated the efficacy and safety of combined therapy, as well as the relapse rate.
Methods: The combined therapy was performed to induce remission in UC showing an inadequate response to monotherapy with TAC or an anti-TNFα antibody. The following items were assessed retrospectively: (1) clinical characteristics, (2) the remission induction rate, (3) the relapse rate, and (4) adverse events.
Results: Combined therapy induced remission in seven of the 12 patients (58.3%). There were no significant differences in clinical characteristics between the patients with and without the successful induction of remission. However, female patients tended to be more frequent in the remission group than in the non-remission group. The remission group also showed trends of a lower clinical activity index (CAI) on admission, and before combined therapy, and a lower total dose of prednisolone during hospitalisation. The 1-year relapse rate was 33.3%. Adverse events due to combined therapy included renal impairment (n = 2), tremor (n = 2), influenza (n = 1), and a positive cytomegalovirus antibody test (n = 3). None of these events were serious.
Conclusions: The combined therapy was effective in more than half of the patients with refractory UC who had not responded to mono therapy. Our findings suggest that combination therapy may be an option as a new third treatment for refractory UC.

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IBIS-Q (IBd Identification of Spondyloarthrytis Questionnaire): a new tool to detect spondyloarthritis in inflammatory bowel diseases

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Background: Extraintestinal manifestations (EIM) are frequent in IBD and spondyloarthritis (SpA) are the commonest EIM (4%–23%). However, the reported delay to diagnosis ranges from 8 to 11 years. Early detection of SpA is clinically relevant to drive the therapeutic management. The aim of this study was to develop a questionnaire able to identify SpA in a cohort of IBD patients.
Methods: During a preliminary meeting a group of experts in SpA-IBD (6 rheumatologists and 4 gastroenterologists) generated a list of 42 items able to cover all of possible manifestations of SpA, exploring spinal, articular and entheseal involvement. The questionnaire was tested on 20 patients with different levels of education with consequent elimination of 4 unclear items. Consecutive patients referring to our IBD Unit were enrolled from January to May 2018 without excluding patients affected by EIM. Patients affected by other rheumatic disease were excluded. The questionnaire was somministrated before the routine clinical assessment of the IBD Clinic. Rheumatologic assessment was performed in the same day by a rheumatologist blinded to the medical story and to the questionnaire results to (collect data about joint cunt of 66 SJ and 68 TJ, MASEI, LEI, presence of ASAS criteria for axial and pheripheral SpA, presence of diagnostic criteria for FM and NSLB pain mainly due to OA). If the patient presented a tender/swollen entheses an US examination completed the clinical examination. The patient completed BASDAI and BANSFI questionnaires in the same day. Factorial analysis to identify the main factors; ROC curves for sensibility/specificity; Youden index for cut-off were performed.
Results: A final 38-items questionnaire was tested in 210 patients (excluding 17 patients for the presence of other rheumatic diseases and 12 for incomplete evaluation). The psychometric analysis of the questionnaire was done on data of 181 patients. Fifty-eight patients of the enrolled patients presented the ASAS criteria for the diagnosis of SpA (13 axial, 5 both axial and peripheral 40 peripheral). SpA prevalence in our cohort was 32% with 10 new cases detected by the questionnaire (5.5%: 7 peripheral and 3 axial). Psoriasis prevalence in our cohort of SpA: 36%. Through the psychometric and factorial analysis we selected 14-items to include in the final questionnaire (named IBIS-q) having a sensitivity 84.4% and specificity 80% to detect SpA (AUC 0.8803 with CI 95% 0.8305- 0.9301); we proposed as cut-off to identify SpA patients the presence of 4 positive questions of IBIS-q
Conclusions: IBIS-q seems to be a useful and simple tool to use in our IBD clinic for the early referral of SpA , with a good statistical performance. Further studies are needed to validate this questionnaire.

P221

Drug survival of biologics in ulcerative colitis treatment in Norway

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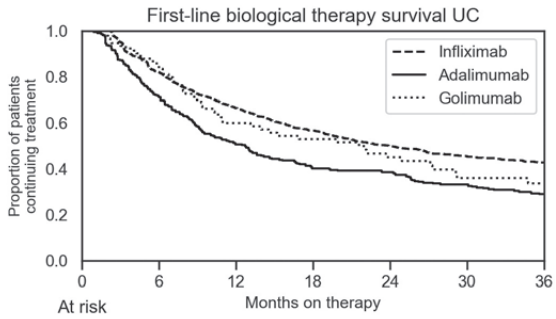
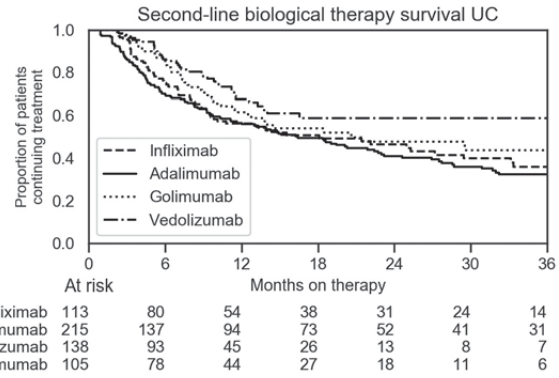
Background: Real-world treatment patterns of biologics remains largely unknown. We aimed to investigate the drug survival of biologics in a national cohort of patients with ulcerative colitis (UC).
Methods: Data were collected from the Norwegian Patient Registry (NPR) and the Norwegian Prescription Database. The study cohort was defined as all patients with at least two diagnosis of K51 (UC) in NPR from 2010 to 2017 with no prior IBD diagnosis in NPR (data from 2008). Treatment for patients who only received one infusion of VDZ or IFX before discontinuing treatment was not included in the analysis to exclude false registrations. VDZ is not given as first-line biologic treatment in Norway due to the tender process. Kaplan–Meier time-to-event analyses were performed to estimate time to treatment discontinuation. Discontinuation was defined as 3 months without a new infusion or prescription of the current drug after the predefined DDD period for the drug (ie, medication gap of >90 days). Biologic survival was compared using the log-rank test. The proportion of patients that received methotrexate or azathioprine was estimated by looking at the number of patients who received a prescription 6 months prior to or after starting biologic treatment. The χ^2 test was used to compare the proportions receiving immunomodulators. Patients were followed until the outcomes of interest, death, or end of follow-up (31 December 2017), whichever occurred first.
Results: In total, 2113 UC patients were included in the study. After 3 years, the survival rate of first-line biologics for UC patients was 42.7% for IFX, 28.7% for ADA and 33.7% for GOL. GOL and IFX survival was significantly different from ADA ($p < 0.001$).



First-line biological therapy survival UC.

For second-line treatment, the survival rates were 35.9% for IFX, 32.3% for ADA, 43.7% for GOL and 58.8% for VDZ. GOL and VDZ survival was significantly different from ADA ($p < 0.01$ and $p < 0.001$). VDZ survival was also significantly different from IFX ($p < 0.001$).



Second-line biological therapy survival UC.

Six months before or after starting treatment 65.1% (IFX), 57.4% (ADA) and 49.5% (GOL) received an immunomodulator (GOL vs. IFX $p < 0.001$, and $p > 0.05$ for the other comparisons).
Conclusions: In this Norwegian real-world registry study of UC patients, drug survival for biologics differed significantly in both first- and second-line treatment.

P222

Purely fibrostenotic Crohn's disease without chronic inflammation is uncommon – a histopathologic study of resected intestine

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Background: Crohn's disease (CD) is a chronic inflammatory condition with multiple phenotypes of which the fibrostenotic type (B2) carries significant morbidity and risk of surgery. We have shown previously that stenotic segments are characterised by expansion of multiple layers of the intestine which can be quantitated by a novel scoring system.
We characterised histological changes in resected ileal specimens using this scoring system.
Methods: We identified all patients undergoing surgery for symptomatic stricturing CD unresponsive to anti-inflammatory therapy using the histopathology database at Queen Elizabeth Hospital in Birmingham, UK, between 2012 and 2017. Phenotypic data were recorded; most representative haematoxylin and eosin-stained section of specimens reviewed and evaluated for histological features of active and chronic inflammation, fibrosis, smooth muscle hyperplasia, neuronal hypertrophy, and adipocyte proliferation for each layer of bowel wall. Two independent pathologists applied the semi-quantitative scoring system. The percentage [%] of the possible maximum total score [PMTS] calculated: adjusted score [%] = [actual total score/PMTS] × 100. The correlations between different contributions to intestinal layers were calculated using Pearson's correlation coefficient.
Results: Among 48 patients (M = 25; median age 45 years, range 21–72 years), median duration of disease was 7 years (range 3 months–39 years); 32 (66%) patients ileo-colonic disease (L3); 16 patients were on thiopurines, 19 on steroids and 4 on biologics.
The histological grading in each layer of the intestine are shown in Table 1. In the mucosa, chronic inflammation was more prominent whereas fibrosis was predominant in the submucosa; chronic inflammation and muscular hyperplasia (MPH) were consistently prominent features across all layers of strictured bowel and had statistically significant correlation with fibrosis (Pearson correlation coefficient $r = 0.339$, $p = 0.018$ and $r = 0.648$, $p < 0.001$, respectively)
Conclusions: Our results suggest that pure fibrostenotic disease is uncommon and chronic inflammation is a prominent feature of this phenotype. In addition to fibrosis, muscle hyperplasia is an important component. Other components such as volume expansion, neuronal hypertrophy and adipose hyperplasia are likely to be important in specific layers of the bowel. This suggests that inflammation driven tissue remodelling leading to stricture formation is a complex process resulting in a multitude of changes and not simply characterised by excess deposition of fibrotic tissue.

P223

Efficacy and safety of tacrolimus in Crohn's disease: a nationwide, multi-centric study from GETECCU

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Abstract P222 – Table 1. Histology scores.

	Active Inflammation		Chronic inflammation		Fibrosis		Muscular hyperplasia		Neuronal hypertrophy		Adipocyte proliferation		Space volume expansion	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Mucosa	22.92	2.37	52.95	2.56	40.28	5.15	46.88	3.32	-	-	-	-	24.31	3.81
Submucosa	12.50	2.60	48.38	2.86	70.83	4.40	45.14	3.99	31.94	5.87	33.33	4.09	39.58	4.05
Muscularis propria	6.02	2.04	28.24	2.96	31.25	3.77	30.90	2.86	22.92	4.46	4.86	1.72	38.89	3.34
Subserosa	4.02	1.19	38.06	2.94	53.19	5.13	21.99	4.09	26.24	5.06	-	-	36.88	4.45

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Background: Crohn's disease (CD) is chronic inflammatory disease of the gastrointestinal tract. Tacrolimus (TCR) is a calcineurin inhibitor drug commonly used for prophylaxis of rejection in renal and liver transplantation. There is some evidence on the short- and medium-term efficacy and safety of TCR in CD, but data are still scarce. The primary aim of our study was to evaluate the efficacy and safety of TCR in CD in clinical practice in Spain.

Methods: We performed a retrospective, multi-centric study in 22 inflammatory bowel disease Units in Spain. We included all adult patients with an established diagnosis of CD in whom oral TCR was prescribed for this condition. Clinical response was assessed by Harvey–Bradshaw index (H-B) and physician global assessment after 3 months. Perianal disease was evaluated by fistula drainage assessment (FDA) at the same time point. Follow-up period was considered until the last visit during therapy or 12 months after stopping the drug. Descriptive statistics and non-parametric tests were used in the statistical analysis.

Results: Between January 2000 and November 2017 a total of 85 patients received TCR (mean age 36 years; 55% female; 69% perianal disease; mean CRP 14 mg/l). The most common indications for TCR were refractory luminal disease (57%) and perianal disease (32%). Most patients (81%) had previously received at least one anti-TNF agent and 61% ≥2. Blood drug levels were 5–10 ng/ml during induction (34%) and maintenance (47%). In 25% of cases, TCR was started concomitantly with systemic steroids, in 11% with an anti-TNF agent and in 6% with vedolizumab. The drug was maintained for a median time of 6 months (2.7–18) and the median follow–up was 28 months (15–56). We found statistically significant differences in H-B after 3 months (median 7.4 (SD 4.4), $p = 0.014$). FDA showed a complete response in 8%, while 34% had partial response. In the univariate analysis, concomitant thiopurines were significantly associated with short-term clinical response (OR 5.53 95% CI 1.36–22.5, $p = 0.017$). We observed statistically significant differences in CRP levels 1, 3, 6, and 12 months when compared with baseline ($p < 0.03$). The drug was stopped in 86% of patients after a median time of 6 months (2–17): 62% requiring a new immunomodulator, 44% hospitalisation and 42% surgery. A total of 34% patients suffered adverse events related to the drug (45% tremor, 28% acute kidney injury), and in 37% they led to the discontinuation of the drug.

Conclusions: Tacrolimus shows a clinical benefit in CD in the short-term, but its lower long-term effectiveness and frequent adverse events remain relevant issues in clinical practice.

P224

Responder definitions for the ulcerative colitis Patient-Reported Outcomes Signs and Symptoms (UC-PRO/SS) tool using patients with ulcerative colitis treated with etrolizumab

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Background: Patient-reported outcomes (PROs) are important for evaluating treatment efficacy; there is a need to define what is a clinically meaningful change in PROs. The UC-PRO/SS is the first PRO to undergo a rigorous development process outlined by health authorities, with input from patients and clinical experts.[1] Responder definitions for the UC-PRO/SS may allow for it to be a valuable tool for use in clinical trials and practice. We propose responder definitions for the UC-PRO/SS using patients treated with etrolizumab from the Phase 3 open-label induction cohorts of HICKORY (NCT02100696) and LAUREL (NCT02165215).

Methods: Analysis included patients with moderate to severe ulcerative colitis (UC) who were treated with etrolizumab 105 mg every 4 weeks during a 10- or 14-week induction period. The UC-PRO/SS consists of 2 separately scored scales: a 3-item functional symptoms domain and 6-item bowel signs and symptoms domain (Table 1). The domain score is equal to the sum of the items (0–12 for functional and 0–27 for bowel; no combined total score). Item scores were calculated as an average of 4–7 days during a 9-day window before follow-up. Minimum clinically meaningful differences were calculated using distributional- and anchor-based methods. Responder definitions were triangulated from the anchor-based thresholds based on a reduction of ≥ 16 points in the inflammatory bowel disease Questionnaire and > 3 points in the full Mayo Clinic Score at Week 10 or 14.

Table 1. The UC-PRO/SS. BM, bowel movement; UC-PRO/SS, ulcerative colitis Patient-Reported Outcomes Signs and Symptoms.

Bowel (0-27)	Item 1: # of BMs	0-7
	Item 2: Liquid BM	0 (never) - 4 (always)
	Item 3: Blood in BM	0 (no) - 4 (always)
	Item 4: Mucus in BM	0 (no) - 4 (always)
	Item 5: Stool/blood/liquid leakage	0 (no) - 4 (always)
	Item 7: BM right away	0 (no) - 4 (very severe)
Functional (0-12)	Item 6: Pass gas	0 (no) - 4 (very often)
	Item 8: Pain in belly	0 (no) - 4 (very severe)
	Item 9: Bloating in belly	0 (no) - 4 (very severe)

Results: As of May 2018, 218 patients (38% aTNF-experienced) provided a baseline UC-PRO/SS response (Table 2). The anchor methodology provided a range for the minimum clinically meaningful change of 1.48–2.07 for the functional domain and a range of 4.85–6.31 for the bowel domain. From these ranges, responder definitions of a reduction ≥ 1.5 points in the functional domain and ≥5 points in the bowel domain were determined through triangulation. Using these cut-offs, 56% of patients were responders according to the functional domain and 62% according to the bowel domain.

Table 2. Baseline, Week 10/14 and Change from Baseline in UC-PRO/SS Scores by Domain. UC-PRO/SS, ulcerative colitis Patient-Reported Outcomes Signs and Symptoms.

	Functional	Bowel
Baseline		
n	218	218
Mean	4.93	12.97
Median	5.00	13.15
Range	0, 10.28	3.14, 23.43
Week 10/14		
n	152	152
Mean	2.90	6.22
Median	2.50	4.93
Range	0, 8.7	0.8, 20.7
Change from baseline at week 10/14		
n	152	152
Mean	−2.02	−6.81
Median	−1.86	−6.13
Range	−10.28, 3.28	−17.7, 9.16

Conclusions: Preliminary definitions for response to treatment using the UC-PRO/SS are a reduction of ≥ 1.5 points in the functional domain or ≥5 points in the bowel domain. These cut-offs will be confirmed in the ongoing Phase 3 UC placebo-controlled studies.

References

1 Higgins PDR, Harding G, Revicki DA, et al., (2017), Development and validation of the ulcerative colitis patient-reported outcomes signs and symptoms (UC-pro/SS) diary, J Patient Rep Outcomes, 26

P225
Day of admission results predict failure of first-line treatment in acute ulcerative colitis

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Background: Intravenous (IV) steroids remain the standard first-line treatment for patients admitted with acute ulcerative colitis (UC). However, 30% of patients fail to respond and require second-line therapies and/or surgery. The purpose of this study was to determine whether Day 1 parameters could identify a group at high risk of failing first-line therapies.

Methods: All admissions for acute UC (ICD-10 K51) to hospitals in NHS Lothian (4 sites) and St Mark's Hospital, Harrow from 1/11/11 to 31/10/16 were obtained from the regional coding departments. Case record review was performed. Response to IV steroids was defined as discharge from hospital with no further acute medical or surgical treatment. Non-response was defined as need to escalate to ciclosporin, infliximab, other acute therapy, or to have surgery. The following parameters were recorded for the first 10 days post admission: haemoglobin (Hb), platelet count, CRP, albumin, stool frequency and faecal calprotectin. Each patient was later attributed a score based on CRP (≤50 mg/dl = 0; >50 mg/dl = 1), albumin (≥30 g/l = 0; < 30 g/l = 1) and platelets (≤400 × 10^9/l = 0; >400 × 10^9/l = 1).

Results: In total, 592 admissions with acute UC were identified; 391/592 (66%) responded to steroids, 201/592 (34%) patients were non-responders. 44 (22%) non-responders received infliximab as second-line therapy, 108 (54%) cyclosporine, and 4 (2%) other. Eighty-three (41%) non-responders required surgery; 7 (8%) had infliximab prior to surgery; 35 (42%) cyclosporine; 12 (14%) went straight to surgery. Insufficient data were available regarding 33 patients.

On univariate analysis, albumin (p = <0.001), platelet count (p = 0.004) and CRP (p = <0.001) were significantly different between responders and non-responders. On multi-variate analysis platelets were not significant. No difference was seen for Hb or stool frequency. 64.3% of patients with concurrent hypoalbuminaemia, high CRP and high platelets (score = 3) were non-responders.

Table 1. Day one results.

	Platelets (x10^9/L)		CRP (mg/dL)		Albumin (g/L)	
	Responders (n=372)	Non-responders (n=187)	Responders (n=359)	Non-responders (n=179)	Responders (n=340)	Non-responders (n=180)
Median	343	381	26	56	36	31
p value	0.004		<0.001		<0.001	

Table 2. Patient scoring.

Score	No. of patients	Responders (%)	Non-responders (%)
0	190	149 (78.4)	41 (21.6)
1	176	124 (70.5)	52 (29.5)
2	82	40 (48.8)	42 (51.2)
3	56	20 (35.7)	36 (64.3)

Conclusions: A third of patients failed to respond to IV steroids. Day of admission albumin, CRP and platelets significantly predicted failure of first-line therapy. 64.3% of patients with a score of 3 failed first-line medical therapy. The combination of these readily available parameters identifies a high-risk population who may benefit from earlier second-line medical or surgical intervention.

P226
Systematic review with meta-analysis of individual data: impact of cut-off values on the performance of faecal calprotectin to detect endoscopic recurrence after intestinal resection in patients with Crohn's disease

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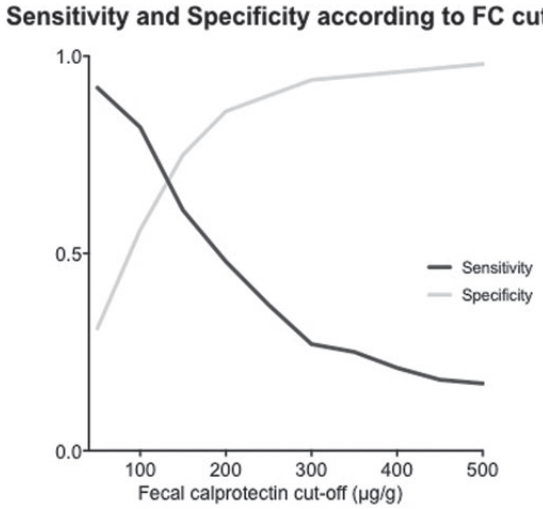
Background: Endoscopic assessment of post-operative recurrence (ePOR) is recommended within 1 year after ileocaecal resection (ICR) for Crohn's disease (CD) as it accurately predicts clinical course and guides medical management. However, endoscopy is an invasive procedure and a frequent endoscopic monitoring is not feasible in routine care. Although faecal calprotectin (FC) has been studied and validated as a useful tool in CD in several settings, it is still not well defined how thresholds impact the performance of FC to detect ePOR. In this meta-analysis including cohort studies of CD patients who underwent intestinal resection, we aimed to determine how cut-off values influence the performance of the FC to detect ePOR.

Methods: A systematic search using PubMed and EMBASE databases was performed independently by two authors. The search strategy used the following terms: calprotectin, Crohn's, Ileocaecal, postop*, intestinal resection. Studies performed in adult patients with CD who underwent intestinal resection, in which FC (expressed in µg/g) was evaluated as a surrogated marker of ePOR (defined as a Rutgeers score ≥ i2 or i2b) were included. The extracted data were pooled using a hierarchical summary receiver-operating curve model. We assessed the sensitivity, specificity and positive and negative likelihood ratios for FC cut-offs ranging from 10 µg/g to 500 µg/g.

Results: A total of 158 titles and abstracts were identified. After selection, 11 studies remained for further analysis. A total of 892 patients were included, among whom 421 (47.2%) developed ePOR. Eight studies were designed as cross-sectional studies with

either a retrospective or a prospective selection of patients. Two studies were a sub analysis of randomised control trials (POCER and TOPPIC). For FC cut-offs set at 50 µg/g and below, the sensitivity to detect ePOR was at least of 0.92. Specifically for 50 µg/g, it was estimated at 0.92 (95% confidence interval (95CI) [0.85–0.96]). On the other hand, a cut-off at 250 µg/g or more provided a specificity of at least 0.90 to detect ePOR (0.90 95CI[0.79–0.96] for 250 µg/g).



Sensitivity and specificity of FC to detect ePOR according to cut-off.

Conclusions: After ICR for CD, FC outside a 50–250 µg/g range could avoid unnecessary colonoscopies, as it allows the detection with a high probability of endoscopic remission (< 50 µg/g) or ePOR (>250 µg/g).

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Association between pouchitis and faecal calprotectin following restorative proctocolectomy in patients with ulcerative colitis

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Background: Recently, faecal calprotectin has been shown to be a useful assessment tool for confirmation of disease activity in ulcerative colitis. On the other hand, few reports have suggested its usefulness for prediction and assessment of pouchitis. There is lack of sufficient evidence whether the faecal calprotectin is more useful for diagnosis of pouchitis or not than ordinal clinical, endoscopic, and histological diagnostic procedures.

We prospectively examined faecal calprotectin during pouchoscopy and analysed the association with pouchitis.

Methods: Patients who underwent a pouchoscopy following a total proctocolectomy and ileal pouch-anal anastomosis for ulcerative colitis were analysed regardless of symptoms suspicious of pouchitis. Faecal samples were collected for measurement of calprotectin during the pouchoscopy. Pouchitis was determined when the modified-pouchitis disease activity index (m-PDAI) score was ≥5. The associations of development of pouchitis with m-PDAI score, faecal calprotectin, and serum markers, including C-related protein (CRP), erythrocyte sedimentation rate (ESR), albumin (Alb), and white blood cell (WBC) count, were examined.

Results: A total of 24 patients were enrolled, of whom 14 were diagnosed with pouchitis, with a median m-PDAI score of 7.5 (range 5–11). The median value for faecal calprotectin was 1395 µg/g (44.9–7730 µg/g) in patients with and 98.1 µg/g (12.2–1580 µg/g) in those without pouchitis ($p < 0.01$). The correlation coefficient between calprotectin and m-PDAI score showed a significant association ($r = 0.565$, $p = 0.004$). The cut-off value for faecal calprotectin level in ROC analysis was 494 µg/g [area under the curve (AUC) 0.84, sensitivity 78.6%, specificity 90.0%], and the correlation coefficient between ESR and m-PDAI score also indicated a significant association ($r = 0.514$, $p = 0.01$). The cut-off-value for faecal calprotectin in ROC analysis was 494 (AUC 0.821, sensitivity 71.43%, specificity 90.0%), while no significant association was found for the other examined markers (CRP: $r = 0.284$, $p = 0.17$; WBC: $r = 0.333$, $p = 0.11$; Alb: $r = 0.257$, $p = 0.225$). The cut-off values for those other markers were 0.32 mg/dl (AUC 0.7785, sensitivity 85.7%, specificity 70%), 7100 (AUC 0.557, sensitivity 57.14%, specificity 70%), and 3.8 g/dl (AUC0. 6857, sensitivity 50%, specificity 90%), respectively.

Conclusions: Elevated faecal calprotectin appears to have a significant correlation with development of pouchitis. We need to clarify the alterations of the concentration of faecal calprotectin during treatment in the further study.

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Preliminary Evaluation of a new immunofluorescence mosaic assay for inflammatory bowel disease diagnosis: a pilot study in Udine

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Background: Inflammatory bowel disease (IBD) is characterised by a broad spectrum of clinical phenotypes with different outcomes. To improve disease management, we need specific biomarkers, either to help differential diagnosis and to identify early patients with worse prognosis. Several new IBD-associated autoantibodies have been recently proposed, in particular anti-pancreatic glycoproteins (PAB) antibodies appear highly promising as diagnostic and prognostic tool in Crohn's disease (CD).[1] In this pilot study, we aimed to test the analytical performances of a combined panel of new and classical antibodies associated with chronic inflammatory bowel diseases (IBD) in a well selected series of patients diagnosed as CD or ulcerative colitis (UC).

Methods: We enrolled 80 patients with IBD (40% females; mean age 43 ± 15 years), comprising 57 CD and 23 UC. Sera were collected and stored at –20°C until analysis. As controls, we enrolled 20 age- and sex-matched blood donors (BDs). All sera were tested for: anti-PAB antibodies (anti-GP2 and anti-CUZD1), anti-goblet cells antibodies, anti-saccharomyces cerevisiae antibodies (ASCA)

and lactoferrin-specific P-ANCA, using indirect immunofluorescence (IIF) according to manufacturer's instructions (Euroimmun CIBD profile, Germany). The slides contained a biochip mosaic consisting of PAB-transfected HEK293 cells (a mixture expressing recombinant CUZD1 or GP2), mock-transfected control cells, goblet cells, ethanol fixed human granulocytes, lactoferrin-specific (LFS) human granulocytes and, in a separate incubation field, a smear of saccharomyces cerevisiae. Both IgG and IgA antibodies were evaluated at proper dilutions.

Results: Overall, positive anti-PAB IgG and/or IgA antibodies were found in 16/57 (28.1%) CD patients vs. 0/23 UC (OR 18.7, 95% CI 1.1–326; $p = 0.004$) and 0/20 BDs (specificity 100%). The combined presence of anti-CUZD1 and anti-GP2 antibodies were recorded only in 3 samples; in the others, only one of the anti-PABs was present. Of note, 5/16 (31%) aPAB+ patients were ASCA negative and all presented colonic or ileocolonic localisation: in these cases aPAB would be highly useful to make differential diagnosis with UC. ASCA resulted positive in 40/57 (70.1%) CD patients vs. 2/23 (8.7%) UC and 2/20 (10%) BDs. A positive IIF reactivity in LFS-granulocytes was observed in 14/57 (24.6%) CD patients vs. 14/23 (60.9%) UC and 0/20 (0%) BDs. Anti-goblet cells resulted always negative.

Conclusions: The combined assessment of several markers of IBD by this new mosaic IIF assay appeared highly promising to improve the characterisation of CD and UC patients, both for diagnosis and prognosis.

Reference

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The relationship between computed tomography enterography findings and levels of faecal biomarkers in patients with small bowel Crohn's disease: A prospective study

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Background: The value of faecal biomarkers for evaluating small bowel inflammation in patients with Crohn's disease (CD) remains to be elucidated. This prospective study was designed to assess the relationship between computed tomography enterography (CTE) findings and levels of faecal biomarkers in patients with small bowel Crohn's disease.

Methods: One hundred twenty-two consecutive patients with a diagnosis of CD in the small intestine were screened for eligibility. CTE was undertaken to evaluate small bowel inflammation followed by colonoscopy to confirm no large bowel involvement. Seventy eligible patients with inflammation confined to the small intestine were included. Faecal samples were collected for assaying calprotectin, lactoferrin and haemoglobin. For assessing the degree of small bowel inflammation, a semi-quantitative scoring system (CTE0, normal; CTE1, mild; CTE2, moderate; CTE3, severe) was applied. The relationship between findings of CTE (the number and locations of lesions, mucosal irregularity and hyperdensity, stenosis, prestenotic dilatation, fistula, target sign, comb sign, and CTE score) and levels of faecal biomarkers.

Results: There was a significant relationship between the levels of faecal biomarkers and almost all of the examined parameters including the number and locations of lesions, mucosal irregularity and hyperdensity, stenosis, prestenotic dilatation, and comb sign. Target sign and fistula were not included in this analysis because only a few patients ($n = 2$) had positive findings. The median calprotectin, lactoferrin and haemoglobin levels were significantly higher in 42 patients with small bowel inflammation (CTE scores 1–3) than in 28 patients without small bowel inflammation (CTE score 0): Calprotectin, 330 vs. 40 ng/ml, $p < 0.0001$; lactoferrin, 14 vs. 3 ng/ml, $p < 0.0001$; haemoglobin, 29.5 vs. 6.5 ng/ml, $p = 0.005$. There was a significant and positive relationship between the faecal biomarkers and the CTE scores (calprotectin, $p < 0.0001$; lactoferrin, $p < 0.0001$; haemoglobin, $p = 0.0004$).

Conclusions: Faecal calprotectin, lactoferrin and haemoglobin are relevant biomarkers for evaluating small bowel inflammation in CD patients without large bowel involvement.

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Prediction of loss of response to anti-TNF therapy using SES-CD in patients with Crohn's disease

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Background: Biological therapies enable to set treatment target as mucosal healing in Crohn's disease (CD) patients. When mucosal healing could be achieved, it has been indicated that loss of response (LOR) rate is significantly decreased. However, the definition of mucosal healing varies widely because of the complexity of previously reported endoscopic scoring systems. Among them, simple endoscopic score for Crohn's disease (SES-CD) seems applicable in daily clinical practice for the assessment of mucosal healing. We thus evaluated clinical usefulness of SES-CD for predicting LOR to anti-TNF therapy in CD patients.

Methods: We retrospectively investigated clinical data of 99 CD patients with ileocolitis or colitis type, who were treated by either infliximab (IFX) or adalimumab (ADA) from January 2003 to September 2018. We excluded 61 patients based on the exclusion criteria, including insufficient clinical data, history of intestinal surgery, primary non-response to IFX /ADA, and intolerance to IFX/ADA. We thus included remaining 38 patients with induction of clinical remission whose clinical course could be followed up for more than a year after ileocolonoscopy. We then analysed possible risk factors associated with subsequent LOR to IFX/ADA. As for mucosal healing, two types of definition were set in the present study; one to be ≤10 based on SES-CD, and the other to be the absence of ulceration ≤ 5 mm in size. The cumulative risk of LOR was calculated by Kaplan–Meier method. Risk factors associated with LOR were examined by univariate and multi-variate analyses using Cox proportional hazard model.

Results: Median duration from IFX/ADA initiation to endoscopic evaluation was 13 months (range: 1–105 months). A significantly higher rate of LOR was observed in patients with SES-CD of >10 than in those with SES-CD of ≤10 (p = 0.0032). However, no difference was observed between patients with ulceration (>5 mm) and those without ulceration with respect to LOR rate (p = 0.50). Under multi-variate analysis, duration from IFX/ADA initiation to endoscopic evaluation <5 month (p = 0.0016), serum albumin < 4.2 g/dl (p = 0.0074), and SES-CD >10 (p = 0.014) were the factors associated with the risk of LOR to IFX/ADA.
Conclusions: Although further prospective studies with a larger number of cases are necessary, SES-CD can be useful for predicting LOR to anti-TNF therapy.

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CECDAIic: a new score for panenteric evaluation in Crohn's disease patients

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Background: Crohn's disease (CD) is a chronic and progressive disease characterised by inflammation affecting all the gastrointestinal tract. Panenteric capsule endoscopy has been used to assess both the small and large bowel in a single examination. The Capsule Endoscopy Crohn's Disease Activity Index (CECDAI or Niv score) was initially devised to measure mucosal disease activity in small bowel, although in 2018 it was extended to the colon for standardisation of inflammatory activity (CECDAIic). The aim of this study was to apply the CECDAIic in a cohort of CD patients that underwent panenteric capsule to evaluate the inter-observer agreement among three observers and the correlation between this score and inflammatory parameters.
Methods: CECDAIic was calculated after dividing the bowel in 4 segments (1=proximal small bowel, 2 = distal small bowel, 3 = right colon, 4 = left colon) and according to the formula defined by the authors (A1 xB1+C1)+(A2xB2+C2)+(A3xB3+C3)+(A4xB4+C4), where A indicates inflammation; B extent of disease, and C presence of strictures. The videos were read and scored by the three independent and experienced operators, blinded to the results of the standard workup. Statistical analysis was performed with SPSS®, using Kendall's coefficient to evaluate the interobserver agreement. Spearman correlation (r's) was used to access the correlation between the score and inflammatory biomarkers.
Results: Included 22 patients, 59.1% (n = 13) male gender with median age 28.0 (17–54) years. In 3 patients (13.6%) the capsule was not exteriorised within the battery time. The median CECDAIic score was 9.17 (0–37). The overall CECDAIic score Kendall coefficient was 0.94, demonstrating a statistically significant (p < 0.001) excellent agreement between the three observers. In addition, we verified a high concordance between the observers for all the parameters of CECDAIic score analysed with Kendall's coefficient of concordance (A1=0.91; B1=0.95; C1=1; A2=0.91; B2=0.91; C2 = 0.87; A3 = 0.84; B3 = 0.80; C3 = 1; A4 = 0.94; B4 = 0.88; C4 = 1; p < 0.001). We found a very good correlation between CECDAIic and Calprotectin (r's = 0.82; p = 0.012) and a moderate correlation with C-reactive Protein (r's = 0.50; p = 0.019).
Conclusions: CECDAIic is a new score with excellent inter-observer agreement and with a strong correlation with calprotectin. These characteristics, associated with its ease of application, may enable CECDAIic to become the tool of choice when reviewing panenteric capsule endoscopy, to more accurately and objectively assess CD inflammatory activity.

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Oesophageal Crohn's disease: diagnosis and outcome of an ECCO-CONFER case series

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Background: Crohn's disease (CD) can involve any part of the gastrointestinal tract. We aimed to characterise clinical, endoscopic, histological features and treatment outcomes of CD patients with oesophageal involvement.
Methods: This was a European Crohn's and Colitis Organization (ECCO) retrospective observational study performed as part of CONFER [COllaborative Network For Exceptionally Rare case reports] project. A call was made to all ECCO members to report CD patients with oesophageal involvement. Clinical data were recorded in a standardised case report form.
Results: Forty patients were reported [24 males, mean age at oesophageal CD diagnosis: 22 years (10–46) and mean time of follow-up: 61 (3–240) months]. Oesophageal involvement was established at CD diagnosis in 25 patients (62.5%) and during follow-up in 15. CD was exclusively located in the oesophagus in 2 patients while in the rest, small bowel involvement was present in 81.5%, colonic in 73.6% and gastric in 50%. Twenty-three patients (57.5%) presented with non-stricturing, non-penetrating behaviour, 18 (45%) had perianal disease, and 12 (30%) extra intestinal manifestations. Nine patients (22.5%) were asymptomatic at oesophageal disease diagnosis. Distal oesophagus was the most common site of involvement (62.5%). Oesophageal strictures were present in six patients

and fistulising oesophageal disease in one. Eight patients exhibited granulomas on biopsies. Medical treatment: proton-pump inhibitors (PPIs, 87.5%), steroids (52.5%), thiopurines (52.5%), anti-TNFs (52.5%) and exclusive enteral nutrition (20%). Three patients underwent endoscopic dilation for symptomatic strictures and none oesophageal surgery. Oesophageal disease diagnosed during follow-up for CD (15/40) resulted in treatment modifications in 9 patents. Remission or improvement of oesophageal disease was seen in 38/40 (95%) patients after a mean time of 7 (1–18) months while in overall CD these outcomes were reported in 29/38 patients (76.3%). Follow-up endoscopy was performed in 30/40 patients and 27/30 (90%) achieved mucosal healing.

Conclusions: Oesophageal CD involvement can be detected either at CD diagnosis or during follow-up, manifesting as the only site of CD location in rare cases. Phenotypic characteristics are similar to those of other sites of involvement and diagnosis can be done even during overall CD remission. Optimal treatment is conservative but not consensual depending also on extra oesophageal sites of involvement, with PPIs administered in the majority of patients and treatment modifications occurring infrequently when diagnosed at a later phase. These results should be interpreted with caution due to the small sample size and the design of this project.

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Do you see what I see? Teaching Gastroenterology trainees how to report endoscopic findings

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Background: The skills in endoscopy go beyond technical competence. Trainees should be able to accurately describing findings, as this can significantly affect management. We aimed to determine whether a web-based (WB) module can teach trainees how to accurately describe lesions in inflammatory bowel disease (IBD).

Methods: In this pilot study, we designed an interactive WB module that provided education on IBD lesions. First, trainees were taught the descriptors used to explain the presence of inflammation. Thereafter, they were taught how to use the Mayo Endoscopic score (MES) for ulcerative colitis and the simple endoscopic score for Crohn's disease (SES-CD). They completed a 6 question image-based pre-test (asking them to describe a lesion, score it using the MES or SES-CD, and rate its severity as healed, mild, moderate, or severe). After completing the module, they completed a different six question image-based post-test and a satisfaction questionnaire. Both pre-test and post-test included images with varying severity of disease (that had been previously validated by three IBD experts). We assessed inter-rater agreement among the trainees, as well as improvement in test scores before and after the intervention (for describing lesions and disease severity). The IBD expert answers were used as the correct answers (for comparison purpose). Furthermore, we compared post-test results to a historic cohort of trainees who had not received the module.

Results: In total, 23 trainees completed the pre-test, compared with 30 trainees who completed the post-test and 32 trainees in the historic cohort. The pre-module and post-module total test score were unchanged at 7/12 (58.3%, pre-module IQR 5.5–8, post-module IQR 5–8, $p = 0.83$). Similarly, there was no difference between the pre-module and post-module subscore for MES (66.7% IQR 33.3–66.7%, $p = 0.89$). While not reaching significance ($p = 0.07$), there was an increase in the subscore for SES-CD from pre to post-module (33.3 IQR 33.3–66.7 to 66.7% IQR 33.3–66.7%), with the post-module subscore also correlating with the historic cohort. The accuracy in lesion description improved significantly from pre-module (54.5%, IQR 45.5–63.6%) to post-module (68.8% IQR 62.5–75%) assessments ($p < 0.001$). For lesion description, the post module score was again comparable to the historic cohort (68.8% IQR 50.0–75.0, $p = 0.78$).

Conclusions: In this pilot study, our WB interactive module led to improvement of trainees' ability to describe IBD lesions on colonoscopy. However, it did not lead to improvement in the use of IBD scoring systems. Further research with a larger cohort is needed to determine why there was a gap in knowledge and how to modify this teaching tool accordingly.

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Longitudinal course of inflammatory bowel diseases: a model of microbial, immune, and neuropsychological integration

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Background: While there is a literature suggesting associations between gut microbiota, physiological factors, psychological state, immune modulation and IBD, there has been little attempt to integrate these factors over time and assess their interdependence with IBD disease activity. This study pursued longitudinal monitoring in IBD, examining integrated data to explain how major factors associate and interact, leading to exacerbation of symptoms and disease activity.

Methods: 59 participants (24 UC, 26 CD, 9 IBS) were followed up for 12 months. Complete longitudinal datasets including demography, disease status (CDAI, Mayo score), monthly stool and blood samples for immune biomarkers, monthly validated scores of psychological state and sleep measures, assessment of physiological state and autonomic nervous system (ANS) function during cognitive tasks, were collected for analysis of association. Microbiome analysis was performed using V4 16S rRNA for identification of microbial phylogenetic relationships, scores were assigned for microbial diversity and richness.

Results: Baseline analysis of contributing factors was performed in IBD participants in clinical remission, at study entry. This revealed a significant association between quality of life and health related QoL ($r = 0.45$, $p < 0.001$), with the latter also significantly and negatively associated with sleep quality ($r = -0.40$, $p = 0.002$). A significant negative relationship between psychological scores and health-related QoL ($p < 0.001$) was identified. There was a significant relationship between sleep quality and stress in the study cohort. There was no association between serum and stool immune biomarkers with sleep scores, psychological state, autonomic function or microbiome profile. Assessment of ANS function showed major bidirectional impact between baseline heart rate and heart rate during cognitive tasks (task 1; $r = 0.925$, $p < 0.001$ and task 2; $r = 0.941$, $p < 0.001$). There was no significant relationship between autonomic function and psychological states, or between ANS function and microbial

diversity and richness. Similar microbial abundance at phylum level was identified in CD, UC and IBS, with the expected reduction in bacterial diversity in CD compared with IBS.
Conclusions: We showed baseline differences in microbiome, psychological state and sleep quality between CD, UC, and IBS. Assessing the interplay between all contributing factors revealed some significant associations suggesting underlying interaction between biological and psychological factors which were plausible and consistent with current literature. It will be important to examine the interplay between biopsychosocial factors in longitudinal analyses, in persistent remission and in relapse.

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How useful are blood tests in the diagnosis of paediatric inflammatory bowel disease?

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Background: Paediatric inflammatory bowel disease (PIBD) often presents following a significant diagnostic delay, with symptoms being attributed to other causes. Blood tests are a routine part of the work-up in children with chronic abdominal symptoms (pain, diarrhoea etc.). Normal tests cannot exclude PIBD, however normal results are often seen as reassuring to the clinician, sometimes incorrectly. We analysed blood results at diagnosis of PIBD over a 5-year period.
Methods: Patients diagnosed from 2013 to 2017 were identified from the Southampton-PIBD database. Blood results were obtained up to 100 days prior to diagnostic endoscopy. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), albumin, haemoglobin, platelets, packed cell volume (PCV), white cell count (WCC) and alanine transferase (ALT) were analysed. Statistical analysis was performed using Fisher exact test. Hierarchical clustering was performed following normalisation of data.
Results: In total, 256 patients were included, 151 had Crohn's disease (CD), 95 had ulcerative colitis (UC), and 10 had IBD-unclassified. Median age at diagnosis 13.48 years, 36.7% (n = 94) female. The mean number of tests per patients was 7.5 (range 2–8). In PIBD, 9% presented with all normal bloods, 21.9% presented with normal CRP and ESR. Abnormal results were seen in all tests: ESR (56.4% of patients), CRP (53.4%), albumin (28%), haemoglobin (61.9%), platelets (55.6%), PCV (64.6%), WCC (22.7%), and ALT (7.2%). Abnormal inflammatory markers were more common in CD compared with UC (UC = 34% normal, CD = 15.6%, p = 0.0035). UC presented with all normal results more frequently than CD (UC = 14.4% normal, CD = 5.3%, p = 0.02). CRP, ESR, and platelets were significantly higher in CD compared with UC, albumin and haemoglobin were significantly lower (Table 1).
Hierarchical clustering of patients based on normalised results revealed novel groupings enriched for CD and UC (Figure 1).
Conclusions: Most cases of PIBD present with more than one abnormal blood result, although 1/11 patients will present with all normal bloods and 1/5 will present with normal inflammatory markers. Diagnosis of PIBD cannot be excluded with normal blood results. Children with red flag symptoms may benefit from faecal calprotectin testing and prompt referral to specialist care regardless of blood results.

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	CRP (mg/l)	ESR (mm/H)	WCC (10^9/l)	Haemoglobin (g/dl)	Platelets (10^9/l)	ALT (U/l)	PCV (%)	Albumin (g/dl)
All PIBD	13	21	9.2	115	424	13	0.359	35
Crohn's disease	24.5	27	9.2	115	445	12	0.36	32
Ulcerative colitis	4	12	9.0	117	381.5	16	0.353	38
p-Value CD vs. UC	0.00001	0.0001	0.168	0.596	0.0001	0.00001	0.502	0.00001

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Inflammatory bowel disease epidemiology a tertiary centre in Brazil

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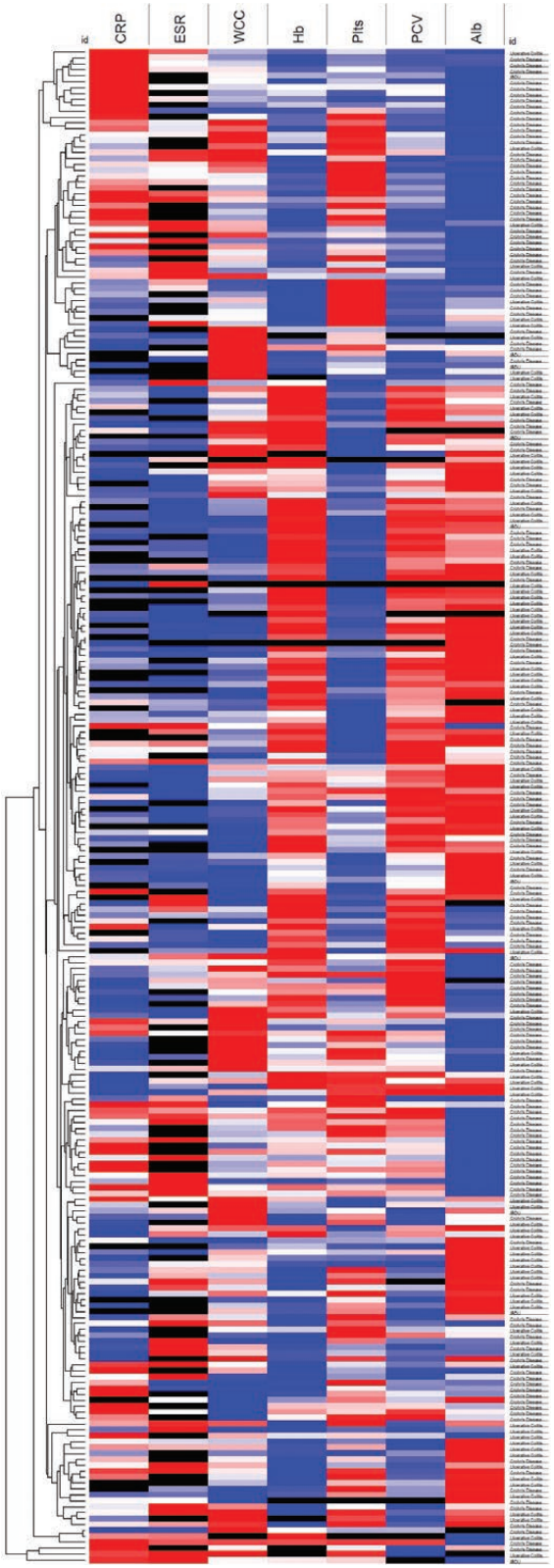
Background: Data regarding the prevalence of inflammatory bowel disease (IBD) are scarce in Brazil. The aim of this study was to determine the prevalence of IBD and to analyse the demographical, clinical phenotipes of these cases in a tertiary IBD Unity in Southeast Brazil.
Methods: Retrospective analysis from the adult population-based IBD cohort of Clinical Hospital of Ribeirão Preto Medical School, University of São Paulo, Brazil, between 2014 and 2018. Medical records consisted in age, gender, occupation, disease (Crohn's disease [CD]; ulcerative colitis [UC]), disease location, moderate-to-severe feature, previous surgeries, treatments, and biological therapy.
Results: Of 579 patients, 325 had CD and 254 had UC. Fifty-three (53%) were females. Mean age at diagnosis was 32.4 years. Eighty-two per cent of patients were moderate to severe. The mean time of disease was 159 months (13.25 years). Two hundred and two patients (n = 272) are in the use of biological therapy. The distribution of CD cases in relation to location was: L3 (54.8%), L1 (29.1%), L2 (15.2%), and L4 (0.9%) and the behaviour was; B1 (26.3%), B2 (12.7%), B3 (20.1%), B3P (31.9%), B2 / B3 (4.6%) and B2 / B3P (4.3%).In the UC the distribution of the cases in relation to the location was; E3 (53.1%), E2 (26%) and E1 (20.9%). Table 1 summarises the results in UC and CD. Female was more frequently in UC (60.6% vs. 47.4%, p = 0.0019; OR = 0.5848; CI 95%: 0.419–0.815). Biological therapy was more frequently in CD (64.3% vs. 26.0%,



Abstract P235 – Heatmap showing normalised data . Data were normalised by mean value and standard deviation. Red indicates a higher value, blue indicates a lower value, and white indicates a value of 0 (mean value). Black represents missing data.

$p < 0.0001$; OR = 5.064; C1 95%: 3.531–7.262). Previous surgeries (59.1% vs. 19.7%, $p < 0.0001$; OR = 5.89; C1 95%: 4.027–8.615) and deaths (2.8% vs. 0%) were more common in CD.

Variable	CD (n = 325)	UC (n = 254)
Female	154 (47.4%)	154 (60.6%)*
Age at diagnosis (years)	30.4	34.81
Disease duration (months)	166.5	149.7
Biological therapy	208 (64%)*	66 (26%)
Previous surgeries	192 (59.1%)*	50 (19.7%)
Cancer	5 (1.54%)	2 (0.79%)
Cholangitis	7 (2.2%)	11 (4.3%)
Deaths	9 (2.8%)	0 (0%)
Employed	195 (47.4%)	129 (50.8%)

Clinical features in UC and CD. *Statistical significantly.

Conclusions: There was a predominance of patients with CD in our IBD Unit. Most of UC patients were female. CD was associated with higher risk of surgery, biological therapy and death.[1,2]

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P237

Regional IBD surveillance endoscopy north west (RISE NoW): an audit of surveillance colonoscopy practice in inflammatory bowel disease in north-west England

Gastroenterology Trainee Research and Improvement Network North West (GasTRIN NoW)

Background: Interval surveillance colonoscopy plays a crucial role in identifying and managing colitis-related dysplasia to reduce the risk of colorectal cancer. Dye based or image enhanced chromoendoscopy have been endorsed by multiple organisations as the preferred means of detecting dysplasia since 2015. We aimed to assess the methods of surveillance utilised within the north-west of England using the established trainee research network, GasTRIN NoW.

Methods: GasTRIN NoW investigators prospectively collected data from 10 hospitals in North West England to assess surveillance practice between June and October 2018. All IBD interval surveillance colonoscopies were included. SCENIC consensus guidelines were used as the standard for adequate surveillance while BSG standards were used for the interval surveillance standard.[1,2]

Results: In total, 226 patients underwent IBD surveillance endoscopy (143 UC, 66 CD, 17 IBDU) with a median disease duration of 12 years (IQR 9–20). There were 122 males and the median age was 54 years (range 20–86). A total of 46 (20%) procedures did not adhere to and 21 (46%) of which were delayed (>6 months). Dye spray was used in 22%(n = 49) of the procedures while the remaining had random colonic biopsies. Image enhanced chromoendoscopy was no used in our cohort. There was more visible dysplasia identified in the dye spray cohort (13 dye spray vs. 8 non-dye spray, χ^2 $p = 7 \times 10^{-6}$). Adenocarcinoma was confirmed in the dye spray group

while no cancers were identified in the non-dye spray group. There were no differences in histological dysplasia between these groups (5 vs. 6, respectively, $p = 0.11$). Where withdrawal time was recorded ($n = 139$), median times were significantly different between both groups (dye spray 16 min (IQR: 12–25) vs. no-dye spray 10 min (8–14); χ^2 $p = 3.7 \times 10^{-4}$).

Conclusions: Our data demonstrate that there are delays to elective IBD surveillance in clinical practice. Dye spray colonoscopy is not widely practised across north-west England. Dye spray colonoscopy identified more visible dysplasia and was associated with longer withdrawal time, a recognised surrogate marker for colonoscopy quality. Our data will inform future work in optimising IBD surveillance in England.

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P238

Female gender increases the risk of anxiety and depression in patients with inflammatory bowel disease under anti-TNFα therapy

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Background: Depression and anxiety are significant predictors of worst health-related qualify of life in inflammatory bowel disease (IBD) patients. Nevertheless, the role of anxiety and depression in IBD patients under treatment with anti-TNFα has been poorly investigated. The aim of the study was to evaluate the frequency of anxiety and depression symptoms in IBD patients under anti-TNFα therapy, and the potential factors influencing the development of these symptoms.

Methods: A prospective observational cohort study was designed. All IBD patients older than or with 18 years under treatment with anti-TNFα were consecutively included. Prevalence of anxiety and depression was assessed in IBD outpatients using the Hospital Anxiety and Depression scale (HAD). When using this scale we considered scores of 8 or higher to be abnormal. Relapse was defined in Crohn's disease (CD) as a Harvey and Bradshaw index higher than 4, and in ulcerative colitis (UC) as a Partial Mayo index higher than 2. Patient demographics and disease characteristics were also collected: age, sex, marital status, smoking habit, type of IBD, phenotype included in Montreal classification, extra-intestinal manifestations, clinical activity, prior surgery, perianal disease and steroid or immunosuppresant use. Results are shown as OR and 95% CI, and analysed by logistic regression.

Results: One hundred and nineteen patients were included (50 male, mean age 40 years, range from 20 to 83). Seventy-seven patients (64%) had CD and 42 (36%) UC; 90 of them (75%) were under maintenance treatment with infliximab and 25% with adalimumab. Anxiety and depression symptoms were presented in 38.9% and 25.2% patients, respectively. Females were more likely to have anxiety (OR = 6.13; 95% CI: 2.47–14.63; $p = 0.001$) and depression (OR = 3.32; 95% CI: 1.26–8.73; $p = 0.015$). Patients with active disease were no more likely to have anxiety (OR = 1.001; 95% CI: 0.973–1.029; $p = 0.972$) or depression (OR = 1.013; 95% CI: 0.984–1.042; $p = 0.389$). None of the other socio-demographic and clinical parameters were significantly associated with the development of anxiety or depression.

Conclusions: An important number of IBD patients under anti-TNFα present anxiety or depressive symptoms. Female gender is associated with more anxiety and depression in this group of patients. However, disease activity was not associated with neither anxiety nor depression.

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Real-life clinical and quality of life outcomes collected remotely from patients with moderate to severe active ulcerative colitis during induction treatment with golimumab in GO OBSERVE

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Background: Limited data are available concerning real-life experience with remotely collected patient-reported outcomes (PROs) in ulcerative colitis (UC).

Methods: GO OBSERVE is an ongoing international multi-centre observational trial with golimumab (GLM) in moderate to severe active UC patients naïve to or previously exposed to one other biological therapy. Patients receive standard subcutaneous GLM induction followed by maintenance with 100 mg or 50 mg every 4 weeks (q4wk). Mayo or partial Mayo score is collected at baseline and end of induction visit at either wk6, wk10, or wk14. Patients are asked to self-report their stool frequency score (SFS; 0–3) and rectal bleeding score (RBS; 0–3) q4wk into an electronic data capture system (EDC). Quality of life (QoL) scores are spontaneously reported by Short Health Scale (SHS) at baseline and end of induction. Partial Mayo response is defined as a decrease from baseline with ≥30% and ≥3 points and either a decrease from baseline in the rectal bleeding sub-score ≥1 or a rectal bleeding sub-score of 0 or 1. The use of concomitant UC medications is allowed per investigator's decision. This pre-specified interim analysis reports the results at the end of induction.

Results: In total, 102 patients were included; 88 patients have end-of-induction data for this interim analysis, including 18 patients who discontinued before wk14 due to lack of effect ($n = 12$), adverse event ($n = 3$) or withdrawal of consent ($n = 3$). Clinical response was achieved at either wk6, 10 or 14 in 32/88 (36.4%) patients; in 27/69 (39.1%) and 5/19 (26.3%) bio-naïve and anti-TNF exposed patients, respectively. Baseline and end of induction CRP (mg/l) was 5.20 ($n = 67$) and 2.20 ($n = 36$), respectively ($p = 0.038$). Baseline and end of induction median PRO2 was 4 ($n = 101$) and 2 ($n = 68$), respectively ($p < 0.001$) with a median change from baseline of -1 for both SFS and RBS. SHS scores were self-reported by 39 patients, with only 17 reporting SHS at both baseline and end of induction.

Per cent improvement of SHS domains was: symptom burden (13%; $p = 0.008$), social function (20%; $p = 0.015$), disease-related worry (10%; $p = 0.030$), and sense of general well-being (10%; $p = 0.167$). Adverse events were reported in 20/102 patients (19.6%), including infections ($n = 4$), lack of efficacy ($n = 9$), and UC ($n = 3$). Serious adverse events were reported in 7 patients (6.9%) including 2 cases of severe UC.

Conclusions: These results from real-life practice confirm the effectiveness of GLM in active UC and show low compliance with self-reporting of PROs in UC, particularly for QoL. There is a gap between current consensus on the role of PROs in IBD and their true adoption for UC monitoring in real-life practice.

P240

Surgical resection in a tertiary IBD centre in Southeastern Brazil: clinical aspects and associated factors

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Background: Despite the numerous advances in medical treatment, it is estimated that a significant percentage of patients with IBD requires bowel resection at least once. The aim of this study was to evaluate patient characteristics and factors associated to surgical resection in patients with IBD in a tertiary IBD unit in Southeastern Brazil.

Methods: Retrospective analysis of data from 446 patients with IBD in follow-up at the University Hospital, Ribeirão Preto Medical School, from January 2000 up to December 2016. Medical records data comprised age, gender, disease type (Crohn's disease [CD] or ulcerative colitis [UC]), disease location, disease behaviour, disease duration and smoking. Patients were divided into two groups: presence or absence of surgical resection.

Results: Out of the 446 patients, 143 (111 CD and 32 UC) underwent surgical resection (53.2% female, 82.9% Caucasians, mean age: 45.49 ± 13.30 years). Main indications for surgery were: stenosis (10.3%), clinical intractability (6.5%) and massive haemorrhage (2.7%). Smoking ($p = 0.0109$, OR = 2.244; 95% CI: 1.237 to 4.056), stenotic phenotype ($p < 0.0001$, OR = 5.294; 95% CI: 3.073 to 9.1212), ileo-colonic location ($p < 0.0001$, OR = 3.447; 95% CI: 2.061 to 5.698) and longer disease duration (15.17 ± 9.19 vs. 7.94 ± 5.96 years) [$p < 0.0001$] were significantly associated with operations for CD. Longer duration (21.15 ± 21.58 vs. 9.79 ± 7.08 years) [$p < 0.0001$] and pancolitis ($p = 0.0014$; OR = 3.823; 95% CI: 1.698–8.605) were associated with surgical resection in UC. This results are summarised in Tables 1 and 2.

Variable	OR (95% CI)	*p*-Value
Smoking	2.244 (1.237–4.056)	0.0109
Stenotic phenotype	5.294 (3.073–9.1212)	<0.0001
Ileo-colonic location	3.447 (2.061–5.698)	<0.0001
Longer disease duration (mean)	15.17 ± 9.19 years	<0.0001

Clinical factors associated with higher risk of surgery in Crohn's disease

Variable	OR (95% CI)	*p*-Value
Longer disease duration (mean)	21.15 ± 21.58 years	< 0.0001
Pancolitis	3.823 (1.698–8.605)	0.0014

Clinical factors associated with higher risk of surgery in ulcerative colitis.

No significant differences were observed in relation to gender, race, age at diagnosis, and previous use of corticosteroids.

Conclusions: Need for surgical treatment is still frequent in patients with IBD. Smoking (current or past), longer disease time, stenotic phenotype, and ileo-colonic localisation in CD and more extensive disease in UC (pancolitis) were associated with a higher risk of surgery in our IBD Unit. Awareness about factors associated with unfavourable outcome allows these patients to be treated more appropriately.[1]

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P241

Focussing on the future: reducing barriers and improving access to IBD specialty care

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Background: inflammatory bowel disease (IBD) is a chronic, immune-mediated disease that affects approximately two million North Americans. Canada has the highest age-adjusted incidence and prevalence rates of IBD globally. Given its cumulative prevalence, the IBD clinical burden in North America continues to grow. Limitations in accessing specialty healthcare services is not a new issue facing patients and healthcare providers. Despite this persistent problem, no research elucidating the patient perspective using qualitative approaches to compare and contrast the patient experience across diverse geographic regions has been conducted.

Methods: IBD patients (≥18 years of age) were recruited from gastroenterology clinics and communities through IBD specialists and Crohn's and Colitis Canada. Patients were recruited from both urban and rural locales to ensure adequate representation from geographically diverse regions. Focus groups provided a powerful and more naturalistic tool through which a focussed understanding of the patient experience was derived. Co-facilitated by a researcher and a patient research partner, the focus groups were held in Nova

Scotia, New Brunswick, Quebec, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia. Patient demographics were collected to contextualise observed themes. Themes were distilled through qualitative thematic analysis using Atlas.ti software to ascertain congruence or discordance of patient experiences. Eastern Canadian focus groups have been completed, with recruitment underway for the Western Canadian focus groups.

Results: A total of 20 participants were recruited as of October 2018. The majority of participants were male (11/20, 55%) and were from urban/suburban regions (10/20, 50%). The mean age of participants was 44 years of age (SD = 12 years, range = 24–67 years). Preliminary analyses show that the main patient-identified barriers to accessing IBD care fall into the following categories: (1) Lack of multidisciplinary care (including psycho-social support), (2) Diagnostic delay, and (3) Inability to effectively receive and provide communication with healthcare providers. Solutions identified by patients included: (1) Integration of more holistic care into the clinical practice, (2) Readily accessible psychiatric and nutritional support, (3) Increased patient advocacy, and (4) Continuity and liaison through provision of a healthcare navigator resource.

Conclusions: Healthcare access for IBD patients is complex. It is important to not only have a robust understanding of the healthcare system structure and processes but also the significant impact these factors have on patients. Access improvement research can be best tackled through patient-centred exploration of themes related to access to care.

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Accuracy of Doppler transabdominal ultrasound in assessing disease severity and extent in IBD

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Background: A paradigm shift in the treatment of inflammatory bowel disease (IBD) has emerged with recent medical advancements. Beyond clinical remission, endoscopic mucosal healing has become a major therapeutic goal of IBD and is associated with better long-term prognosis. Therefore, endoscopic evaluation is considered indispensable, however, frequent ileocolonoscopy (CS) may not be feasible due to its invasiveness. Transabdominal ultrasonography (TAUS) is a non-invasive imaging technique which enables to frequently monitor the disease and its utility has been previously reported. This study examined the usefulness of Doppler TAUS in assessing disease severity of IBD comparing with CS for each ileocolonic segment.

Methods: A retrospective chart review of 60 patients with IBD (ulcerative colitis (UC) 35, Crohn's disease (CD) 25) who were examined both CS and Doppler TAUS from May 2017 to November 2018 within the interval of 1 month was conducted. The Mayo Endoscopic Subscore (MES) or the Simple Endoscopic Score for Crohn's disease (SES-CD) were used for CS and Limberg score was graded from Grade 0 to 4 for Doppler TAUS [2] . Endoscopic scoring indices (MES, SES-CD) and Limberg score were compared per-segment (ileum, ascending, transverse, descending, sigmoid and rectum) and per-patient. The sum of each score was calculated. Finally, the association of Limberg score with endoscopic indices was assessed by non-parametric Spearman rank correlation (r_s) and receiver-operating characteristic analysis.

Results: Limberg score was significantly associated with MES (r_s = 0.68, $p < 0.01$) or SES-CD in per-patients analysis (r_s = 0.53, $p < 0.01$). The sum of Limberg scores of five segments also well-correlated with the sum of MES (r_s = 0.84, $p < 0.01$) and SES-CD (r_s = 0.76, $p < 0.01$). Per-segment analysis (UC: 208 segments, CD: 149 segments) demonstrated a significant correlation between Limberg score and MES/SES-CD (r_s = 0.84 and 0.67, respectively). Association was significant in ileum, ascending, transverse, descending, and sigmoid colon, whereas not significant in rectum (Table 1). Limberg score ≤1 had a sensitivity of 1.00 and a specificity of 0.75 for mucosal healing defined by MES ≤ 1 or SES-CD (ulcer score) = 0 with area under the receiver-operating characteristic curve values of 0.91.

Table 1. Correlation (r_s, Spearman rank test) between ultrasonographic (Limberg score) and endoscopic score (MES/SES-CD) in per-ileocolonic segment analysis. *$p < 0.01$.

		Total	Ileum	$A_{scending}$	$T_{ransverse}$	$D_{escending}$	S_{igmoid}	Rectum
UC	r_s	0.84*	0.56*	0.88*	0.87*	0.81*	0.70*	0.30
CD	r_s	0.67*	0.69*	0.59*	0.42*	0.52*	0.52*	0.32

Conclusions: Doppler TAUS is a useful monitoring tool alternative to CS, however, is less accurate in the assessment of rectum.

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P243

The different role of histology in ulcerative colitis and Crohn's disease: a retrospective study in a single referral centre

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Background: In addition to endoscopic evaluation, a consistent set of studies has demonstrated an important role for histology in ulcerative colitis (UC) patients, both for diagnosis and in follow-up, while in Crohn's disease (CD) evidence are scantier. The aim of the study was to investigate the different role of histological evaluation in CD and UC patients, in a single referral centre.

Methods: Data of 86 IBD patients in follow-up at IBD Outpatient Clinic in San Giovanni-Addolorata Hospital in Rome (2016–2017) were retrospectively evaluated. We included only patients (n = 30 UC and 30 CD) who had a visit and a colonoscopy within 1 month, and who had a 1-year follow-up visit. Active symptoms, endoscopic

activity, histological inflammatory activity and specificity, and flare occurrence at 1 year of follow-up, were considered as dichotomous variables (0–1). In the histological report, neutrophilic infiltrate, criptitis and criptic abscesses were considered features of active inflammation, and basal plasmocytosis, mucin depletion, structural disarray and granulomata were considered specific features for IBD. Moreover, in patients with established diagnosis of IBD (12 CD and 14 UC), the presence of specific histological features at the first colonoscopy was evaluated, to investigate the role of histology for the initial diagnosis in those patients.

Results: In patients in follow-up, a significant higher rate of UC patients showed full concordance (specificity and activity) between histological and endoscopic evaluation comparing with CD patients [26/30(87%) vs. 12/30(40%), $p < 0.005$]. In IBD patients in follow-up, 72% of UC and 57% of CD patients showed specific histological IBD features. Eighty-four per cent of UC and 58% of CD patients displayed concordance between endoscopic and histological inflammatory activity. In UC, but not in CD, both endoscopic and histological inflammatory activity correlated with the presence of active symptoms of disease ($p < 0.001$ and $p < 0.05$, respectively). No significant different rate of flare at 1 year was observed in patients with endoscopic/histological features or symptoms of active vs. inactive disease, both in UC and CD. In the first colonoscopy performed for suspected IBD, specific diagnostic features were found in 86% of UC and 67% of CD patients.

Conclusions: in UC patients, histological evaluation consistently correlated with endoscopic and clinical features of active disease, and showed an elevated specificity both for the diagnosis and in the follow-up. In CD patients, correlation with histology and endoscopic/clinical features was less impressive. In a referral centre histological evaluation has a potential relevant role in IBD diagnosis and follow-up.

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Use of complementary and alternative medicine in patients with inflammatory bowel disease in Germany

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Background: Many patients ask to combine complementary and alternative medicine (CAM) with guideline-based state of the art medicine in inflammatory bowel disease (IBD). In line with this, the new German S3 Therapy Guideline for Ulcerative Colitis (UC) was published in 2018, with an update of how to use CAM in IBD. In our study, we asked our patients about their use of CAM to better understand their intentions and desires around CAMs.

Methods: 298 IBD patients in 3 specialised IBD outpatient clinics in Germany (Ulm, Blaubeuren, Biberach) filled in an anonymous questionnaire including 88 questions on the underlying IBD itself, on CAM, socio-economic parameters and 6 psychological tests (HADS, STAI-S, STAI-T, F-Sozu, Neo-FFI, BL-R).

Results: In total, 139 (47.3%) male and 155 (52.7%) female patients, 185 (63.4%) with Crohn's disease (CD) and 107 (36.6%) with UC completed the questionnaire. HBI in CD was 5.4 (± 4.6) and CAI was 2.29 (±2.4) in UC. 218 (73.9%) patients admitted to use CAM in the past or the present and only 80 (26.1%) patients did never use CAM at all. Eighty-nine patients used CAMs without being aware that the applied method was recognised as such. Phytotherapies (173 (61.3%)) were most frequently used, followed by probiotics (122 (45.7%)), relaxation techniques (121 (45.3%)), homeopathy (74 (29.5%)), and acupuncture (52 (19.9%)). The main reasons why patients would take CAM in the past, present, or future were, above all, concerns about the further course of the disease (112 (40.1%)), a desired holistic approach (92 (33.0%)) and on the recommendation of attending physicians (83 (29.7%)). 172 (58.9%) patients received or wanted to receive information about CAM preferably from their attending physician. The second most popular source of information was the Internet for 163 (56.0%) patients. 210 (72.9%) patients could imagine using CAM in the future. In addition, 220 (78%) patients would use CAM without further concerns about efficacy or safety.

Conclusions: German IBD patients widely use CAM. Although the Internet is often used as a source of information, patients like most to receive information about CAM from their attending IBD physician. Therefore, IBD specialists should become more involved with the subject to be able to help their patients with their best advice on CAM.

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Pulmonary function tests in asymptomatic patients with inflammatory bowel disease: preliminary results of a single-centre cohort study

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Background: Pulmonary dysfunction is frequently underestimated in inflammatory bowel disease (IBD) patients. The aim of this study was to investigate pulmonary function in IBD patients and identify possible risk factors for pulmonary dysfunction.

Methods: Consecutive informed and consented IBD patients < 60 years old followed up in our centre underwent pulmonary function tests (PFTs) during their regular follow-up visit. Measurements conducted were forced vital capacity (FVC), forced expiratory volume in one sec (FEV1) and maximal mid-expiratory flow (MMEF 75/25). Exclusion criteria were an acute or chronic respiratory disease as well as the presence of an established pulmonary extra-intestinal manifestation.

Results: Sixty-four IBD patients have been enrolled so far (males: 53.1%, Crohn's disease: 62.5%, mean age at IBD diagnosis: 35.5 years [SD ± 12.7], median [IQR] duration of IBD: 7.2 months [3.3–12.0], extraintestinal manifestations: 39.1%). Seventeen patients (26.5%) had never smoked with the rest being either active (42.2%) or ex- (31.3%) smokers. Twenty-four patients (37.5%), including 6/17 (35.3%) non-smokers, revealed abnormal PFTs (males:14/24, Crohn's disease: 16/24); 7 (29.1%) exhibited a restrictive pattern, 7 (29.1%) an obstructive pattern (57.1% mild and 42.9% moderate GOLD stage) and 10 (41.7%) small airway disease. Interestingly, appendectomy was more commonly reported in non-smokers with abnormal LFTs compared with those without ($p = 0.04$). IBD was active at baseline in 4/24 and extraintestinal

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manifestations were present in 10/24 patients. Anti-TNFα agents were administered in 11/24 patients. Three patients were under combination therapy with an IMS. There was no association of abnormal PFTs with gender, disease sort or location or behaviour or activity, tonsillectomy, IBD therapy either as monotherapy or as combination therapy and the presence of anaemia.
Conclusions: More than one-third of our IBD patients in total and of non-smokers in particular demonstrate abnormal LFTs measured in a random outpatient visit without any symptoms, signs or history of respiratory disease. Appendectomy was associated with LFTs abnormality in non-smokers perhaps revealing an immunologic defect influencing the development of obscure primary or secondary pulmonopathy on the background of IBD. These results should of course be interpreted with caution for the time being, while awaiting those of a larger cohort.

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Clinical outcomes of 2012 ECCO/ESPGHAN guidelines in a large cohort of children with ulcerative colitis

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Background: Therapeutic strategies for children with ulcerative colitis (UC) have changed after the publication of the first ECCO/ESPGHAN guidelines on medical management.[1] Our main aim was to evaluate the impact of those recommendations on significant clinical outcomes: colectomy rate, number of acute severe colitis episodes and disease extension, in a large cohort of children with UC over a 3-year follow-up.
Methods: Retrospective analysis of children diagnosed with UC between 2006 and 2011 (Group 1) and 2012 and 2016 (Group 2) and identified at our department database. Records were reviewed for disease location and severity, laboratory and endoscopic findings, treatments and rate of surgery, hospitalisation and disease extension at the diagnosis and every year.
Results: One hundred fifty-seven patients were identified (45% F; median age 11, IQR 1,2–16.7; 80 Group 1, 77 Group 2). A significant higher use of infliximab was found at 1 and 2 years in Group 2 (18% vs. 6%, $p = 0.02$ and 25% vs. 11%, $p = 0.04$, respectively), while no significant differences were found at 3 years (27% vs. 17%, $p = 0.30$). Immunomodulator use was significantly higher in Group 1 at the end of follow-up ($p = 0.001$). Fourteen patients (9%) needed surgery at follow-up, with no significant differences between eras (10% Group 1, 8% Group 2, $p = 0.83$). The number of episodes of acute severe colitis decreased from 23% to 10% ($p = 0.05$) between the first and the second period, while no significant differences were found for disease extension ($p = 0.83$).
Conclusions: After 2012, a significant reduction of episodes of acute severe colitis and an increased early use of infliximab have been observed in this large cohort of children with UC. Nevertheless, the rate of colectomy remained unchanged.

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P247

Understanding patient perspectives on dysplasia cancer risk and its management

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Background: Uncertainty in inflammatory bowel disease (IBD) dysplasia prognosis makes management decision-making challenging. Further understanding of patient preferences is required to help clinicians support this process.
Methods: A web survey, evaluating views on dysplasia, was administered via IBD charity social media in November 2018, to UK IBD patients who have had colorectal cancer (CRC) surveillance. Validated scores assessed whether their decisions were influenced by concerns about developing CRC (Cancer Worry Scale, CWS), their dispositional optimism (revised Life Orientation Test, LOT-R), numerical ability (Subjective Numeracy Scale, SNS) and health-related quality of life (Short IBD Questionnaire, SIBDQ).
Results: There were 50 respondents (see Table 1). Being told that a dysplastic lesion was 'high risk' or 'low risk' in words, corresponded with a mean perceived risk of 56% and 17%, respectively. Of the patients who were dysplasia-naïve ($n = 29$), the mean CRC risk would have to be 50% in order for them to accept colectomy. Pain, lack of bowel control and inability to do things they enjoyed were the top-most concerns in >70%. If they were told that they had unresectable dysplasia, 34% would choose to have a colectomy and 28% would choose frequent surveillance instead. Those who preferred colectomy were significantly more likely to be employed or a full-time carer (80% vs. 25%; $p = 0.02$), were more likely to believe that dysplasia progressed to CRC within a year (50% vs. 0%; $p = 0.02$) and that the words 'high risk' meant that their mean CRC risk was 70%, whereas those preferring surveillance perceived 'high risk' to be a mean of 47% ($p = 0.01$). Of the patients with prior dysplasia diagnoses ($n = 21$), 90% were first told by a gastroenterologist. A substantial minority did not feel well informed about the risk of CRC (24%) and the management of dysplasia (29%). Fifty-five per cent felt their relationship with their doctor in the final management decision-making process was equal but 45% did not. Sixty-seven per cent chose to have a colectomy. Those who remained on surveillance listed lack of symptoms and concerns about requiring a stoma or developing complications as deterrent factors for surgery. There was no significant mean difference in LOT-R, SNS, SIBDQ, CWS or Decision Regret Scale scores between all subset groups.
Conclusions: This survey has suggested that about a quarter of IBD dysplasia patients did not feel well informed about their cancer risks and management. Further qualitative work is required to understand how best to support shared decision-making in IBD dysplasia.

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Correlation of faecal calprotectin levels and sonographic measurements in patients with inflammatory bowel diseases

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Background: Bowel ultrasound is becoming an useful tool in managing inflammatory bowel diseases (IBD). Sonographic measurements

Abstract P247 – Table 1. Demographics and responses of survey respondents ($n = 50$).

IBD type	Ulcerative colitis: $n = 37$ (74%); Crohn's colitis: $n = 11$ (22%); Indeterminate colitis/ Unknown: $n = 2$ (4%)
Mean age	55 years
Female	$n = 27$ (54%)
Mean duration of IBD colitis	22 years
Reported flares requiring steroids in last year	$n = 11$ (22%)
Respondents who believe their chance of getting CRC in their lifetime is 0–10%	$n = 31$ (62%)
Respondents who identified dysplasia as a risk factor for cancer	$n = 26$ (52%)
Respondents who believe endoscopic resection of dysplasia STOPS patients from getting colorectal cancer	$n = 26$ (52%)
Mean Short IBD Questionnaire score (min. score 1; max score 7)	4.9
Mean Cancer Worry Scale score (min. score 6; max score 24)	9.8

superpose with endoscopic findings and other imagistic methods (MRI, CT). Faecal calprotectin level correlates significantly with endoscopic disease activity in IBD and the test is useful in clinical practice for assessment of endoscopic activity and remission.

Methods: 32 IBD patients were included in the study (2 diagnosed with ulcerative colitis, 30 with Crohn's disease). Diagnosis was established endoscopically and histologically and both patients with active and inactive disease were included. Patients with other causes of inflammatory syndrome were excluded (Clostridium Difficile and viral infections). Patients were prospectively evaluated sonographically using a 4–8 MHz micro-convex transducer. The examiner was blinded to biological data. Patient were examined in supine position with no special preparation before. For each subject, three sonographic measurements of bowel wall thickness were noted and the preserved stratification of the intestinal wall was assessed. The sonographic measurements were noted in the corresponding regions according to endoscopic observations. Mean value of BWT was calculated. Faecal calprotectin levels were obtained for each patient.

Results: A strong correlation was observed for the three measurements of the bowel wall thickness (Spearman's equation, $r = 0.720$, $r = 0.740$ and $r = 0.750$, $p < 0.001$) and the value of the faecal calprotectin. A mean calculated value of the 3 measurements of BWT was correlated strong with the level of calprotectin too ($r = 0.749$, $p < 0.001$). The observation that the higher the value of the faecal calprotectin the greater the disturbance of the wall stratification (CI 95% [–610.6 –251.3], $p < 0.001$) suggested a relationship between the presence of a stratified wall appearance and calprotectin levels.

Conclusions: Sonographic findings (BWT and bowel stratification) strongly correlates with faecal calprotectin making this two associated tests an useful tool in IBD patients management.

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Validation of a Novel Integral Disease Index (NIDI) for evaluating the grade of activity in Mexican patients with ulcerative colitis: a prospective cohort study

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Background: ulcerative colitis (UC) is a chronic condition characterised by affecting the colon. Clinical disease activity is a complex concept that relies on clinometric assess tools that can be traduced into a score to be used objectively to predict the risk of an individual patient with variables obtained from routine medical visit. However, clinical evaluation with current index scores could have a poor concordance with objective diagnostic tools such as serological biomarkers, colonoscopy and histology findings. The aim of this study was to validate an integral activity index for UC patients.

Methods: This is a prospective cohort study that included 222 patients with definite diagnosis of UC confirmed by histopathology where 546 evaluations were analysed at basal and at least one follow-up visit for each patient. NIDI index was made up considering six categories: (1) Number of stools with blood per day; (2) haemoglobin; (3) high-sensitive C-reactive protein; (4) albumin; (5) endoscopic findings and (6) histological findings. Each variable was graded on a score from 0 to 3. The range of the NIDI Index is from 0 points to 18 points and it was distributed in four categories: (1) remission (0 to 3 points); mild activity (4 to 6 points); moderate activity (7 to 12 points) and severe activity (13 to 18 points). The validation and reliability analysis was done with the principal components analysis and Cronbach A coefficient for internal consistency and average correlation of individual items. Finally, we calculated the receiver-operating characteristic (ROC) based analysis to define their sensibility, specificity, positive predictive value (PPV), negative predicted value (NVP) and area under the ROC curve (AUC) with 95% confidence intervals (CI). The STATA SE 11.1 statistical Programme was used.

Results: The main component analysis of the six items included in the NIDI Index revealed that the scale is most likely unidimensional with 49.9% of the variance explained by a unique component. An adequate internal consistency was observed with a Cronbach α of 0.78 and an acceptable average inter-correlation for the typified items ($r = 0.47$, $p < 0.05$). A good internal consistency was found with a Cronbach α of 0.78 and an acceptable average inter-correlation for the typified items ($r = 0.47$, $p < 0.05$). The overall efficacy of the new score was 87.2% of correctly classified patients with an AUC according to the three scenarios described of 0.93, 0.92 and 0.96, respectively. All items analysed had a good discriminative capacity with specificity range between 0.61 and 0.93 and sensibility from 0.25 to 0.94.

Conclusions: The NIDI provides an integral view of UC activity and it will be useful in the optimisation of medical treatment in UC patients.

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Use of complementary and alternative medicine is associated with chronic fatigue and lower health-related quality of life in patients with inflammatory bowel disease 20 years after diagnosis: results from the IBSEN study

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Background: Use of complementary and alternative medicine (CAM) is common among inflammatory bowel disease (IBD) patients.[1] The CAM modalities used include a wide range of healthcare practices and therapies.[2] The aim of this study was to examine possible associations between CAM use, clinical, and psychological factors, including health-related quality of life (HRQOL), 20 years after diagnosis.
Methods: The Inflammatory Bowel South-Eastern Norway (IBSEN) study is a population-based study with a prospective design. From January 1990 to December 1993, all newly diagnosed patients with IBD from a well-defined area in South Eastern Norway were included in the cohort. The 20-year follow-up was conducted between 2011 and 2014 and included a structured interview, a review of patient records, a clinical examination, laboratory tests, and patient-reported questionnaires. To measure chronic fatigue, HRQOL, anxiety and depression, we used the Fatigue Questionnaire, the Short - Form 36 (SF-36) and the Hospital Anxiety and Depression Scale (HADS), respectively. Additionally, patients answered a questionnaire about CAM use.
Results: Of the 599 patients invited to the 20-year follow - up visit, 78.5% (UC 314, CD 156) participated. Altogether, 439 of the patients had evaluable questionnaires (response rate 93%), and of these 49% were men. In total 28% (122/439) reported the use of CAM for their IBD. Women were more likely to report CAM use than men (60% vs. 40%, $p = 0.02$), and CAM users were younger (mean age 49 years) than the non-users (mean age 56 years), $p < 0.001$. Those who reported more than one relapse the last year were more likely to report CAM use compared with patients in clinical remission (35% vs. 21%, $p < 0.01$). A significantly higher proportion of CAM users reported chronic fatigue compared with non-users (30% vs. 20%, $p = 0.02$). Compared with non-users, CAM users had significant lower SF-36 scores in the dimensions Vitality (51 vs. 57, $p \leq 0.01$), Physical functioning (85 vs. 89, $p = 0.04$), and Social functioning (77 vs. 84, $p = 0.01$). There were no differences in anxiety and depression scores between CAM users and non-users.
Conclusions: One third of the IBD patients reported CAM use 20 years after diagnosis. CAM use was associated with female gender, younger age, disease activity, chronic fatigue and lower HRQoL scores in 3 out of 8 dimensions.

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RAID Dx: the first test based on faecal microbiota to differentiate irritable bowel syndrome from inflammatory bowel diseases

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Background: The irritable bowel syndrome (IBS) is a functional disorder affecting up to 20% of world population. So far, there is not a specific diagnostic test. Diagnosis is based on the characteristic symptoms systematized in the Rome IV criteria and excluding main organic diseases. However, the overlap of IBS symptoms with other intestinal diseases, such as inflammatory bowel disease (IBD), requires to complement Rome IV criteria with biological markers such as faecal calprotectin (FC). Nevertheless, IBS is still one of the main reasons of unnecessary colonoscopies. RAID-Dx is a new non-invasive method for positive IBS diagnosis and its differential diagnosis with IBD patients. This test is based on detecting the specific IBS bacterial signature on stool samples. The aim of this study was to evaluate the potential of RAID-Dx as a diagnosis tool for IBS in comparison to FC.
Methods: RAID-Dx was tested in 39 IBS patients and 51 IBD patients recruited from 5 Catalan hospitals. IBS patients met Rome IV criteria and presented a colonoscopy without valuable macroscopic lesions. IBD patients had clinical (Harvey–Bradshaw Index >4 and Mayo Partial Index >1) and endoscopic activity (SES-CD> 0 and Endoscopic Mayo Index >0 points). A stool sample from each subject, prior to the realisation of the colonoscopy, was obtained to determine RAID-Dx and FC.
Results: RAID-Dx shows a high potential to distinguish between IBS and IBD patients with a sensitivity of 88.2% for IBS and a specificity of 89.2% for IBD. In contrast, the sensitivity and specificity of the FC (pre-determined cut-off 50 µg/g) was 51.5% and 92.2%, respectively. These results represent a substantial increase of the Negative Predictive Value of the RAID-Dx (94.3%) compared with that obtained with FC (74.6%). In addition, FC is analysed with a cut-off point of 150 µg/g as a hypothetical situation of maximum contingency. There is a significant increase in sensitivity for IBS (81.8%); however, the specificity decreases to 84.3% for the diagnosis of IBD.
Conclusions: RAID-Dx is an accurate marker to diagnose IBS with high sensitivity and specificity, which makes it a candidate to become the diagnostic method of IBS. The use of this new tool will allow to reduce 75% of the unnecessary colonoscopies from IBS misdiagnosed patients by FC and its associated costs, time and risks.

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Measuring the mediating effects of Mayo score components for tofacitinib on disease-specific quality of life in ulcerative colitis: data from the OCTAVE programme

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Background: Composite efficacy endpoints in ulcerative colitis (UC) clinical trials are typically based on the Mayo score (MS), which includes 4 components: stool frequency, rectal bleeding, endoscopic appearance, and physician assessment. Although disease-specific quality of life (QoL) measures like the Inflammatory Bowel Disease Questionnaire (IBDQ) are also frequently included, it is unclear whether treatment effects on QoL are fully explained by MS changes or if there are other unobserved variables in play. The current study explored the interrelationship among treatment, IBDQ scores, and MS components using a mediation modelling framework.
Methods: Pooled data at the end (Week 8) of the two double-blind, identically designed induction studies of tofacitinib (OCTAVE Induction 1 and 2, NCT01465763 and NCT01458951) were used. Tofacitinib is an oral, small-molecule Janus kinase inhibitor approved in several countries for the treatment of ulcerative colitis (UC). A mediation model was specified such that the MS components served as the mediators between treatments (active treatment vs. placebo) and IBDQ domain scores (bowel symptoms, systemic symptoms, emotional functioning, and social functioning). Our primary interest was the extent to which treatment affects the IBDQ domains outside of any change in MS components (ie, the direct path).
Results: In total, 1079 patients with moderately to severely active UC at baseline were included. Majority of treatment effect on the IBDQ was mediated by MS components. For all IBDQ domains, the indirect path (ie, the pathway from treatment to MS component and then to each IBDQ domain score) was significant (all $p < 0.05$) and explained 71.6 to 84.7% of the total effect of treatment on IBDQ domains. Yet, for bowel symptom, systemic symptom, and social functioning IBDQ domains, the direct paths (ie, the pathways from treatment directly to each IBDQ domain) were also significant and explained the remaining 21.0 to 28.4% of the total effect of treatment on IBDQ domains (all $p < 0.05$). The largest direct effects were observed for systemic symptoms (28.4%) and social functioning domains (27.7%). The smallest direct effect of 15.3% (not significant, $p = 0.29$) was observed for emotional functioning.
Conclusions: Our study suggests that the MS, while important in capturing disease activity, does not fully mediate the treatment effects on IBDQ scores. The results indicate that tofacitinib affects certain aspects of disease-specific QoL—bowel symptom, systematic symptom, social functioning—outside of any benefit from improving stool frequency, rectal bleeding, endoscopic assessment, or physician assessment. These results reinforce the value of disease-specific QoL measures such as the IBDQ in capturing the full benefit of UC treatment.

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The impact of storage time and freeze–thaw cycles on faecal calprotectin concentration in inflammatory bowel disease patients and controls

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Background: Faecal calprotectin (FCal) is considered the best surrogate marker of mucosal inflammation and therefore routinely used for diagnosis and follow-up of inflammatory bowel disease (IBD). For practical reasons, freezing the faecal sample prior to FCal extraction would be beneficial. However, freeze–thawing might degrade neutrophils, potentially leading to false-positive FCal measurement. We investigated the effect of multiple freeze–thaw cycles as well as long-term storage on FCal stability in frozen faecal samples and FCal extracts.
Methods: Fresh faecal samples from 10 healthy controls (HC) and 10 active IBD patients were collected in March 2017 and immediately split into five tubes which were processed differently (conditions I–VI, Table 1). During a freeze–thaw cycle, the tubes of all samples were thawed for 1 h, a FCal extract was prepared from one tube. The remaining tubes were stored at –80°C. Bühlmann® Smart Prep Faecal Sample Preparation Kit and Bühlmann® FCALTM ELISA kit were used for FCal extraction and measurement, respectively. From condition I-IV, an additional aliquot of FCal was stored at –20°C for 1.5 years (VI). Statistical analyses were performed in JMP. Linear regression analysis was performed to compare FCal concentrations. Root mean square errors (RMSE) demonstrate the average difference between FCal measurements.
Results: The median FCal concentration in, respectively the HC and IBD group were 30 and 852 µg/g faeces. The RMSE's comparing the fresh FCal concentrations (I) with the FCal concentrations II-VI are presented in Table 1.
Freeze–thawing resulted in both ascending and descending deviations from the fresh FCal concentration. In HC, FCal concentrations did not exceed 100 µg/g faeces, neither after different freeze–thaw cycles nor after long-term storage, except for one sample that went up to 123 µg/g faeces after three freeze–thaw cycles. One IBD patient switched from a commonly regarded positive calprotectin to a negative calprotectin (254 vs. 154 µg/g faeces) after 1.5 years storage.
Conclusions: Multiple freeze–thaw cycles and long-term storage of faecal samples and FCal extracts influence FCal concentrations only moderately, and without influence on clinical decision-making. The non-consistent variation between different conditions is more likely caused by existing within-stool variability and variation in technical execution, rather than by freeze–thawing or storage duration. For further clinical use and research, freezing and long-term storage are acceptable to perform reliable FCal measurements.

Abstract P253 –Table 1. Characteristics of the different storage conditions (I–VI) and RMSEs of the fresh FCal concentrations (I) compared with FCal concentrations after freeze–thawing (II–IV) and long-term storage (V and VI).

Conditions		(I)		(II)		(III)		(IV)		(V)		(VI)	
Median baseline FCal concentrations: **30 (HC) and 852 (IBD)** µg/g faeces.		Controls	IBD	Controls	IBD	Controls	IBD	Controls	IBD	Controls	IBD	Controls	IBD
Sample Size		10	10	10	10	10	10	10	10	10	6	10	10
Storage	Temperature	4°C		-80°C								-20°C	
	Sample type	Faecal sample										FCal extract	
	Freeze-thaw cycles	0		1		2		3		1		1	
	Time stored	1 day		1 week		2 weeks		3 weeks		1.5 years		1.5 years	
RMSE (µg/g faeces) Comparing the FCal conc of (I) with subsequent conditions				11.5	327	18	71	27	274	20	179	9	105

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Re-defining the concept of endoscopic and histological healing by using electronic virtual chromoendoscopy and probe confocal endomicroscopy in ulcerative colitis

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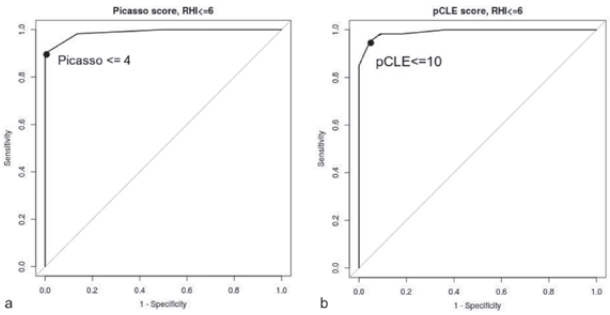
Background: The treatment goal of UC has shifted from symptomatic remission alone to endoscopic and recently histological healing.[1] The new validated Virtual Chromoendoscopy (VCE) score, PICaSSO (Paddington International virtual ChromoendoScopy ScOre)[1] offering detailed mucosal and vascular assessment, and probe confocal laser endomicroscopy (pCLE) as real time in vivo histology, aimed to re-define the concept of mucosal healing (MH). We specifically explored the magnitude of difference between endoscopy and histology defined MH using refined endoscopic assessments.

Methods: In total, 82 UC, 8 controls, male 65.6%; mean age 49.9, SD 14.8 were prospectively enrolled at endoscopy unit, University of Calgary. The endoscopic activity was evaluated by Mayo Endoscopic Score (MES) and PICaSSO mucosal and vascular pattern 1 and thereafter with pCLE (Cellvizio, Paris) after IV fluorescein. The pCLE findings were graded as (A) crypt architecture (Grades 1–4); (B) leakage of fluorescein (Grades 1–4); (C) vessel architecture (Grades 1–4); (D) blood flow (Grades 1–4). Histological score (Robarts histological index, RHI) was used to score histological inflammation. Receiver-operating Characteristic (ROC) curves were plotted to calculate the best cut-off threshold of PICaSSO and pCLE scores to predict histological healing.

Results: For overall PICaSSO score, the optimum cut-off threshold for predicting histological healing defined as RHI ≤ 6 was 4, with sensitivity of 90.0% (95% CI 75.6–96.2) specificity 100% (95% CI 84.6–100), and accuracy of 92.7% (95% CI 84.8–97.3). The overall PICaSSO score of 4 or less was associated with all patients having an RHI ≤ 6. The best cut-off threshold for pCLE score was 10, with sensitivity 95.0% (95% CI 86.0%–99.0%), specificity 95.5% (95% CI 77.2–99.8) and accuracy of 95.1% (95% CI 88.0–98.7). The accuracy of predicting histological healing using PICaSSO or pCLE were superior to MES 0, which had sensitivity of 80% (95% CI 67.6–89.2), specificity 95.5% (95% CI 77.2–99.9), and accuracy of 84.2% (95% CI 74.4–91.3).



ROC curve of PICaSSO and pCLE for predicting histological healing.

Conclusions: The new VCE PICaSSO score and pCLE score can predict histological healing defined by RHI accurately. Advances in endoscopy enable close approximation to histology and can accurately re-define in real-time MH. Overall PICaSSO score of 4 or less was associated with RHI ≤ 6 in all patients. Large prospective studies are necessary to ascertain whether, with new endoscopic technologies such as readily available VCE, histology can still provide additional information about course of UC.

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Perceived disease severity and treatment satisfaction among patients with ulcerative colitis in Europe

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Background: Although ulcerative colitis (UC) trials emphasise rectal bleeding and stool frequency as subjective disease activity measures, there are many clinical manifestations of UC. The current study explored how patients perceive their disease severity and treatment experiences, and how these perceptions are related to symptom reporting.
Methods: Data from the 2015 and 2017 Adelphi Inflammatory Bowel Disease Specific Programmes (IBD-DSP) were used. The IBD-DSP is a database of patient chart information abstracted by gastroenterologists across the European Union Five (ie, France, Germany, Italy, Spain, and the UK). Eligible gastroenterologists were asked to complete patient record forms for their next seven consecutive eligible adult patients with UC. Patients were then invited to complete a survey including their disease perceptions and symptom experiences. Only patients with moderate-to-severe UC were included in the analysis (defined as those who had used either an immunomodulator or a biologic). The concordance between physician and patient perceptions of current severity was examined as well as the relationship between disease severity, treatment satisfaction, and symptom reporting. Statistical differences among groups were examined using chi-square and one-way analysis of variance tests.
Results: In total, 518 patient record forms with linked surveys were included (55.2% male, mean age: 38.7 years, mean disease duration = 4.9 years). Physicians categorised their patients as 51.0% mild, 44.7% moderate, and 4.3% severe; patients assessed their severity as 48.0% mild, 45.5% moderate, and 6.5% severe (kappa = 0.64; moderate agreement). Of the 23 symptoms assessed, 18 varied significantly ($p < 0.05$) by patient self-reported severity. UC-related symptoms were common even among patients who perceived their disease as mild: rectal urgency = 14.5%, bloody diarrhoea = 10.0%, and tenesmus = 10.0%. Additionally, 11.2% of these patients reported their current pain level at 5 or above (worse) on a 0–10 numerical rating scale; 10.3%, 9.7%, and 20.3% reported their sleep disturbance, sexual dysfunction and fatigue levels, respectively, at 5 or above (worse). Similar findings were observed for treatment satisfaction; 18 of 23 symptoms varied significantly ($p < 0.05$) by satisfaction levels. Patients who reported being satisfied and 'at the best level of what treatment can achieve' still reported a number of UC-related symptoms: rectal urgency = 18.1%, bloody diarrhoea = 16.1%, and tenesmus = 14.5%.
Conclusions: Large proportions of patients in Europe with a history of advanced therapy perceive their disease severity to be mild and are satisfied with their current therapy. Nonetheless, even among these patients, symptoms remain.

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Bowel contrast-enhanced ultrasound perfusion imaging in the evaluation of Crohn's disease patients

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Background: Evaluation of inflammation in Crohn's disease (CD) is crucial for treatment planning and monitoring. The use of contrast enhanced ultrasound (CEUS) could be important in the diagnosis and follow-up since it is a non-invasive and easily repeatable method. We aimed to prospectively evaluate the role of CEUS in CD.
Methods: In total, 54 patients with active ileal CD starting infliximab were enrolled. Clinical assessment, laboratory tests and CEUS were performed at baseline (T0) and after 2 (T1), 6 (T2) and 12 weeks (T3) of treatment to assess variations in peak intensity (PI), area under the curve (AUC), slope of wash in (Pw), time to peak (TP), mean transit time (MTT). Deep remission was defined as SES-CD = 0 or decreased of at least 1 unit plus CDAI < 70 at T3. Clinical relapse was assessed up to 3 months.
Results: 70% of patients achieved deep remission (responders). The delta between T0 and T1 was significantly different in responders and non-responders in PI, AUC, Pw, and MTT. Ninety-five per cent of patients showed a reduction in PI, 100% in AUC, 84% in Pw, 26% in TP and 50% in MTT. There was a good correlation between ratio in CEUS parameters between T1-T0 and T2-T0 and T3-T0. The eight patients who relapsed showed lower mean percentage reduction in delta PI between T1 and T0 and between T2 and T0 compared with patients in remission (–8.4 vs. –20.76, $p = 0.038$) and a new increase at T3 (15.6 vs. –62.9, $p < 0.001$). No significant differences in delta AUC have been found in relapsers and non relapsers at T1 (–25 vs. –23.7, p = ns), but reduction in AUC values are lower at T2 (–53 vs. –32.1, $p = 0.007$) and T3 (–62.4 vs. –3.9, $p < 0.001$) in relapsers. About Pw, at T1 and T2 mean percentage of reduction are higher in patients who will maintain remission (–23.2 vs. –1.9, $p = 0.008$ and –38.6 vs. –15.8, $p = 0.006$, respectively) with a return to results similar to baseline at T3 in relapsers (–51 vs. –0.42, $p < 0.001$).
Conclusions: CEUS could be useful as reliable predictor of deep remission and clinical relapse in patients with CD treated with infliximab.

P257

Monitoring of calprotectin levels in IBD patients with point-of-care test CalproSmart™

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Background: Monitoring of mucosal inflammation makes a pivotal contribution to the therapy of irritable bowel disease (IBD). This requires frequent endoscopic procedures, which are tedious and

carry high burden for patients and health services. Therefore, there is a need for an improved non-invasive monitoring method based on a reliable IBD marker, such as calprotectin (CP). Activation of the intestinal immune system during IBD leads to recruitment of neutrophils. CP comprises 60% of cytosol proteins in these cells, thus the amount of CP is proportional to the number of neutrophils and eventually to the degree of the gut inflammation.

Methods: The correlation between routine CalproLab ELISA-based laboratory test for CP and the new point-of-care test (CalproSmart™) was evaluated. The latter consists of a faeces extraction device prefilled with a buffer, a rapid lateral flow test, a support frame and a smartphone application. The study was performed by trained personnel on both fresh and frozen/thawed stool samples from 50 IBD patients during a 2 weeks period. Upon completion of the study, the operator was asked to fill out a survey evaluating design and user experience with the new test.

Results: 93% of the CP values measured by the new CalproSmart™ and the routine ELISA test were in good agreement with each other. The deviation between the measurements was less than 15% for the majority of the samples (67% of the total) and less than 25% for the rest of them. The average sensitivity and specificity of CalproSmart™ was calculated as 93% and 78%, respectively; the average positive and negative predictive values were 87% and 88%, respectively. CP values measured by CalproSmart™ and the routine method were scrutinised for fitting into the correct diagnostic window. This demonstrated that the results of the tests coincide in 100% of the cases when it comes to measuring samples from acute patients (CP level above 500 mg/kg); therefore, there were no false negative results. CalproSmart™ and the routine method placed patients with moderate CP levels into the same category in 73% of the cases and healthy individuals—in 86% of the cases. No 'bleeding through' between the acute and healthy patients category was observed.

Conclusions: CalproSmart™ demonstrated reliability, high degree of accuracy and correlation with the routine test. It received a positive feedback on its design and user experience—in principle, the test can be used even by patients with no previous experience in using smartphone applications. The new test is economically beneficial, it costs about 10- to 30-fold less than the enormous cumulative price of a single day in at a hospital. The test helps to improve compliance, reduce periods of pain and amount of drugs needed due to monitoring of CP.

P258

Abdominal pain and its relationship with clinical outcomes, biomarker levels, and health-related quality of life in patients with moderate to severe ulcerative colitis: data from U-ACHIEVE, a Phase 2b study of upadacitinib

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Background: Abdominal pain (AP), a common symptom in Crohn's disease, is reported but not thoroughly assessed in patients with ulcerative colitis (UC). We evaluated the impact of AP in UC and its relationship with other clinical outcomes, biomarker levels, and health-related quality of life (HRQOL) in the 8-week induction period of the upadacitinib trial U-ACHIEVE (NCT02819635).

Methods: In the Phase 2b study U-ACHIEVE, we evaluated data from adults with moderate-to-severe UC (adapted Mayo score [Mayo score without Physician Global Assessment] of 5–9 points and endoscopy subscore of 2–3) who randomly received upadacitinib or placebo for 8 weeks. AP (0=none, 1=mild, 2=moderate, 3=severe) was collected in the patient daily diary. Average AP score over the most recent 3 days before study visits was calculated. Impact of AP on HRQOL was assessed by comparing baseline (BL) Inflammatory Bowel Disease Questionnaire (IBDQ) and Short Form 36 Health Survey (SF-36) scores with AP severity. AP scores were calculated for patients in clinical remission and clinical response per adapted Mayo score at Week 8. Correlations between AP and clinical outcomes, HRQOL measures, and biomarker levels were evaluated with Spearman's correlation coefficients at Week 8.

Results: Among 250 patients, 82% reported any level of AP at BL (7% severe, 34% moderate, 41% mild); 8% had no AP; 10% had missing data. A trend was observed that patients with more severe AP had more impaired HRQOL at BL (Table 1). At Week 8, significantly lower AP scores were reported for patients with vs. without clinical remission (0.28 vs. 0.73; $p < .001$); improvement of AP score from BL to Week 8 was significantly greater in patients with vs. without clinical response (–0.94 vs. –0.36; $p < .001$). At Week 8, AP had a moderate to strong correlation with Mayo rectal bleeding subscore, IBDQ, and SF-36 Physical Component Summary scores (Table 2) but a weak correlation with Mayo endoscopic subscore and faecal calprotectin (f-cal).

Conclusions: Over 80% patients with UC reported experiencing AP, with higher AP severity linked to impaired HRQOL. AP was correlated moderately to strongly with HRQOL, clinical response and remission, but weakly correlated to proxy indicators of inflammation (endoscopy subscore and f-cal), inspiring future study on alternative mechanistic explanations for AP relief in UC.

P259

Systematic assessment of patient self-reported signs, symptoms, and nutrition behaviour

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Background: Symptom-based patient-reported outcomes (PROs) measurements are currently being investigated and re-assessed with the goal to be more appropriate in clinical trials as well as in daily practice. Our objectives were to assess the prevalence of patient-reported signs, symptoms - as collected in traditional disease activity scores for CD and UC/IBDU (labelled as UC), to assess nutrition behaviour of patients and its association with the other PROs.

Methods: We conducted a cross-sectional study among patients enrolled in the Swiss IBD cohort. We collected patient self-reported signs and symptoms, as used in the CDAI and MTWAI activity indexes. In addition, we collected information on needs, reasons, and frequency of diet adaptations. Descriptive statistics included numbers and percentages. Generalised ordered logit regression was used to assess associations between nutrition behaviour and PROs.

ABSTRACT P258-Table 1. Quality of life measures by level of abdominal pain at baseline (as observed data)

Measure	Average AP Score at Baseline			
	No pain	Mild	Moderate	Severe
	AP = 0 (n=21)	0 < AP < 1 (n=99)	1 < AP < 2 (n=80)	2 < AP < 3 (n=18)
IBDQ score, mean ± SD	156.3 ± 23.7	136.3 ± 28.3	107.2 ± 24.9	84.7 ± 23.2
p value[a]	reference	.002	<.001	<.001
IBDQ ≥170, n (%)	6 (29%)	11 (11%)	0 (0%)	0 (0%)
p value[b]	reference	.031	<.001	<.001
SF-36 PCS, mean ± SD	50.1 ± 5.0	44.5 ± 7.1	38.9 ± 7.4	33.5 ± 5.8
p value[a]	reference	.002	<.001	<.001
SF-36 MCS, mean ± SD	48.0 ± 8.6	43.6 ± 10.9	37.8 ± 10.9	33.2 ± 8.1
p value[a]	reference	.096	<.001	<.001

AP, abdominal pain; IBDQ, Inflammatory Bowel Disease Questionnaire; MCS, Mental Component Summary; PCS, Physical Component Summary; SD, standard deviation; SF-36, Short Form 36 Health Survey.
[a]Mann–Whitney U test.
[b]Chi-square test.

ABSTRACT P258-Table 2. Correlation of AP scores and clinical outcomes, biomarker levels, and HRQOL at Week 8 (as observed data).

Measures	N	Spearman Correlation (95% CI)
Full Mayo score	206	0.41 (0.28, 0.53)
Mayo RBS	210	0.43 (0.31, 0.54)
Mayo SFS	210	0.35 (0.21, 0.47)
Mayo PGA	210	0.42 (0.29, 0.53)
Mayo endoscopic subscore	222	0.20 (0.05, 0.33)
IBDQ	214	–0.55 (–0.64, –0.20)
SF-36 PCS	214	–0.52 (–0.62, –0.41)
SF-36 MCS	214	–0.31 (–0.44, –0.16)
HS-CRP	231	0.32 (0.18, 0.44)
Fecal calprotectin	211	0.22 (0.08, 0.36)

AP, abdominal pain; CI, confidence interval; HRQOL, health-related quality of life; HS-CRP, high-sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; MCS, Mental Component Summary; PCS, Physical Component Summary; PGA, physician global assessment; RBS, rectal bleeding subscore; SFS, stool frequency subscore.
Estimates between 0 and 0.3 (–0.3) indicate weak convergent validity; 0.3 to 0.5 (–0.3 to –0.5) indicate moderate convergent validity, and >0.5 (or <–0.5) indicate strong convergent validity.

Results: In total, 1215 patients answered to the questionnaire (54% females, 54% CD, mean age 49 years). The following signs and symptoms were reported: mild-to-severe abdominal pain: 45% (CD: 49%/UC: 41%, $p = 0.008$), faecal incontinence: 17% (CD: 19%/UC: 14%, $p = 0.017$), blood in stools: 22% (CD: 20%/UC: 25%, $p = 0.045$) and nocturnal diarrhoea: 16% (for both). Patients reported a mean of seven liquid or very soft stools in the last week (range CD: 0–112/UC: 0–89). Diet restrictions in the last week was reported by 41% of the patients (CD: 46%/UC: 36%, $p = 0.004$). One third of CD patients reported restrictions on a quarter (UC: 27%) and 14% on half-all foods (UC: 10%). Reasons for restrictions were: diarrhoea control (CD: 27%/UC: 21%, $p = 0.007$), poor digestion (CD: 43%/UC: 31%, $p < 0.001$), pain control (CD: 17%/UC: 9%, $p < 0.001$), limitations after resection surgery (CD: 5%/UC: 1%, $p < 0.001$), weight control (CD: 20%/UC: 16%, NS), prevention of relapses (CD and UC: 16%), prevention of diarrhoea (CD: 11%/UC: 8%, NS) and prevention of bloating/vomiting (CD: 25%/UC: 19%, $p = 0.013$). A third of all patients reported mild frustration about the need to adapt their diet while 11% were moderately to extremely frustrated. One third of patients adapted their diet when meals were taken out of home (8% did it more than half of the time), and one third had to adapt their meals in terms of time or quantity. Diet restriction significantly increased with nocturnal diarrhoea (CD), number of liquid/soft stools (UC) and abdominal pain (both), and decreased with higher general well-being (both).
Conclusions: We observed a high prevalence of the PROs used in CDAI and MTWAI clinical activity indexes in our patients. Diet adaptation was frequent and highly associated with several self-reported symptoms. It may potentially bias the levels of reported PROs, used to calculate activity scores. Therefore, it should be collected as an additional PRO.

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Disease duration in Crohn's disease is a strong determinant for having a colectomy in geriatric population

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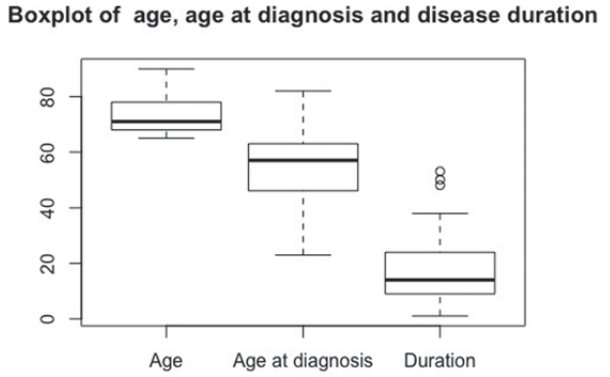
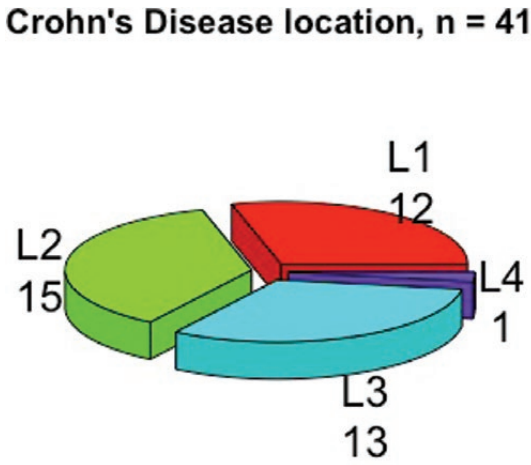
Background: Geriatric population is swiftly growing in most developed countries. Looking after inflammatory bowel disease (IBD) in elderly population has become a clinical challenge due to their co-morbidities, frailty, polypharmacy with multiple drug interactions. In our study, we evaluate the clinical course, treatment, and outcome in our geriatric IBD population in a large district general hospital.

Methods: We identified an IBD geriatric group with age 65 and above from our existing database from 2014 onward. Data were extracted from electronic database. Extracted data included gender, age of diagnosis, duration of disease, disease characteristics using Montreal classification, and surgical outcomes. χ^2-test was performed on non-parametric data using R studio program.
Results: Since 2014, we identified 105 IBD patients with age above 65 years. Forty-one out 105 (39%) have Crohn's disease. Sex ratio is equally distributed (M:F= 21:20).



Boxplot of age, age of diagnosis, and disease duration.
Age ranges from 65 to 90 with median age of 71. Age of diagnosis ranges from 23 to 82 with median age of 59. Disease duration ranges from 0 to 58 years with a median age of 14.



Disease location, n = 41.
Of 41, 12 (29%) had colectomies and 8 (67%) has L1 disease and 4 (33%) had L3 disease.
Colectomy is associated with disease duration of more than 10 years (29% vs. 0%, χ^2 = 5.94, p value = 0.015). However, there is no statistically significant association between colectomies and age of disease onset age (<65 years) (33% vs. 13%, p = 0.47) or disease behaviour (stricturing and stenotic vs. non-structuring and non-stenotic) (47% vs. 19%, p = 0.13).
Conclusions: In our cohort of Crohn's disease, patients aged above 65 years, regardless of the age of disease onset, longer disease duration is associated with colectomies mainly in L1 and L3 disease.

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Frequency of B-cell subsets in infliximab-treated paediatric IBD patients

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Background: The role of B cells in IBD is ambiguous, as B cells may have both pathogenic as well as protective functions in IBD. On the one hand, autoreactive B cells may contribute to mucosal inflammation via secretion of autoantibodies. On the other hand, B cell subsets with regulatory properties like transitional B cells are thought to provide an anti-inflammatory milieu by producing IL10 and TGF-β. The aim of the study was to investigate in a first step frequency patterns of B cell subsets in paediatric IBD patients undergoing a treatment with Infliximab (IFX).
Methods: The numerical distributions of transitional, naïve and memory B cells as well as antibody-secreting cells like plasmablasts and plasma cells were assessed at initiation of therapy and in the longitudinal course by FACS multi-colour analysis. The study included 9 children with UC and 13 with CD and 9 age-matched healthy controls. Blood samples were obtained at baseline, before fourth infusion at the end of induction phase and after 6 and 12 months under therapy maintenance. With regard to clinical and biochemical remission, we categorised every patient with a faecal calprotectin level below 100 µg/g or a decrease of <10% of the baseline value after 12 months as responder.
Results: Compared with healthy controls, FACS analysis revealed significantly low percentages of transitional B cells in UC (p = 0.001), whereas in CD patients we detected either low or highly increased frequencies of transitional B cells. In addition, frequencies of memory B cells were highly elevated in UC patients in (p = 0.0357). We also observed highly increased numbers of antibody-secreting B cell subsets in a small number of patients from both entities at the end of induction phase. With regard to therapeutic effects we could show that successful IFX therapy was associated with increased numbers of CD19+ B cells in those patients that reached clinical and biochemical remission.
Conclusions: The results of our study suggest an involvement of B cells in the pathogenicity of IBD. Especially the findings in UC patients with high frequencies of antigen-experienced memory B cells in contrast to reduced percentages of transitional B cells point towards a disbalance between pro- and anti-inflammatory elements in paediatric IBD. In CD, our findings within all B cell subsets are more ambiguous, suggesting a rather heterogenous B cell spectrum in CD patients.

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Systematic review of development and content validity of patient-reported outcome measures in inflammatory bowel disease: do we measure what we measure?

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Background: Patient-reported outcome measures (PROMs) are increasingly important in IBD-research and daily care. Many commonly used PROMs predate the current standards for development. This review summarises the evidence on development and content validity of IBD-specific PROMs.

Methods: MEDLINE, EMBASE and PsycINFO were searched up to July 2017 using the combined concepts: adults, IBD, PROMs, psychometric properties. Articles were included if the PROM is IBD-specific, measures a form of disability, QOL or disease activity and its development and/or content validity was reported. Evidence was synthesised according to the COSMIN methodology for development and content validity (relevance/comprehensiveness/comprehensibility), using a modified GRADE approach.[1]

Results: From 4673 screened hits, 45 eligible articles were identified representing 32 PROMs. Three PROMs measure a form of disability, 10 disease activity and 19 QOL. The development process was reviewed for 21 PROMs, the remaining 11 are modifications for which the development study of the original was used. The development studies were of doubtful (n = 4) or inadequate quality (n = 17), the latter due to not clearly defined constructs (n = 8) and/or no patient involvement (n = 14). Sixteen content validity studies were found on 9 PROMs, 11 studies were solely on comprehensibility. The studies were of doubtful (n = 15) or inadequate quality (n = 1). Based on the development and content validity studies and our own judgement, 16 PROMs have sufficient content validity. Moderate quality of evidence was found for the comprehensibility and relevance of three IBDQ versions,[2–4] the comprehensiveness of the IBDQ-36[7] and the comprehensibility of two more IBDQ versions.[5,6] All other aspects in those 16 were also sufficient, but with low or very low quality of evidence (judgement of reviewer was decisive). The remaining 16 PROMs did not show sufficient content validity in all aspects, most were rated incomprehensive (n = 15) but comprehensible (n = 12) and some relevant (n = 8). Moderate quality of evidence for sufficient comprehensibility was found for 3 of the 12 comprehensible PROMs. Again, the other aspects had low or very low quality of evidence.

Conclusions: Most of the identified IBD-related PROMs do not meet current standards for development. Content validity studies are scarce and poorly described resulting in a limited body of evidence. There is some evidence for comprehensibility in IBD-specific PROMs, future studies should also focus on relevance and comprehensiveness to strengthen content validity.

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Association between inflammatory bowel diseases and the non-classical histocompatibility complex HLA-G

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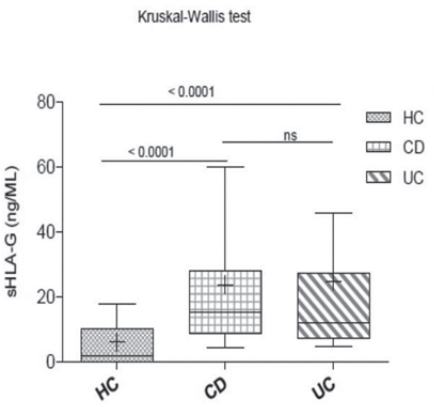
Background: HLA-G is a non-classical major histocompatibility complex (HLA) class I molecule with immunomodulatory properties. Considering that inflammatory bowel diseases (IBD), represented mainly by Crohn's disease (CD) and ulcerative colitis (UC), have immune-mediated mechanisms in their pathogenesis, the aim of this study was to determine the association between soluble (s) HLA-G production and the HLA-G expression in patients with IBD in a tertiary IBD unit in Southeastern Brazil.

Methods: sHLA-G levels were measured with ELISA in plasma of IBD patients (n = 199; 54.4% female; mean age at diagnosis: 32.84 ± 13.37 years) and healthy controls (n = 120). Tissue expression of HLA-G was assessed by immunohistochemistry in samples of the colon and terminal ileum from 152 patients (91 CD; 62 UC) and 24 healthy controls. We evaluated sHLA-G levels and HLA-G expression in patients with IBD (CD and UC) when compared with healthy controls. We also determined the relationships between sHLA-G levels and tissue HLA-G expression and CD phenotype and localisation, and UC extension.

Results: There was a significant increase ($p < 0.0001$) in sHLA-G levels in IBD patients when compared with healthy controls (Figure 1).



	HC	CD	UC
Number of values	120	111	88
Minimum	0.0	0.0	0.0
25% Percentile	0.0	8.580	7.193
Median	1.809	15.31	12.03
75% Percentile	10.11	27.85	27.27
Maximum	54.50	146.8	426.3
Mean	6.000	23.65	24.62
Std. Deviation	8.689	26.08	50.05
Std. Error of Mean	0.7932	2.476	5.335
Lower 95% CI	4.429	18.74	14.02
Upper 95% CI	7.570	28.55	35.23

Dunn's multiple comparisons test	Mean rank diff.	Significant	Summary	Adjusted P Value
HC vs. CD	101.7	Yes	****	< 0.0001
HC vs. UC	92.11	Yes	****	< 0.0001
CD vs. UC	9.555	No	ns	> 0.9999

Boxplot of serum sHLA-G concentrations in patients with IBD and in healthy controls.

There were no significant differences between CD and UC patients. No differences were observed between the various CD phenotypes and localisation patterns, neither between subgroups of UC patients with different disease extent. HLA-G was similarly expressed (p = 0.21) in the epithelial cells of the colon and terminal ileum in IBD patients (CD: 64.8%; UC: 70.5%) and in healthy controls (83.3%). Regarding inflammatory cells (plasma cells and lymphocytes), HLA-G was highly expressed in IBD intestinal tissue samples (CD: 73.3%; UC: 80.3%; $p > 0.05$), which was not found in any sample (0%) of healthy controls ($p < 0.001$). In CD, expression of HLA-G in tissue inflammatory cells was found more frequently in the inflammatory phenotype than in patients with stenosis (94.1% vs. 61.1%; p = 0.03). No differences were observed between the various CD localisation patterns, neither between subgroups of UC patients with different disease extent.

Conclusions: Higher levels of sHLA-G and increased tissue expression of HLA-G in patients with IBD suggest that this molecule may play a role in disease pathogenesis. Measurement of sHLA-G production may comprise a novel non-invasive diagnostic tool in IBD.[1,2]

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Assessing the risk for an intra-abdominal abscess in patients with Crohn's disease presenting to the emergency department

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Background: The aim of the present study was to generate a simple non-invasive scoring model to predict the presence of an intra-abdominal abscess in Crohn's disease (CD) patients who present to the emergency department with disease exacerbation.

Methods: We performed a retrospective case–control study at two Israeli hospitals (Hadassah Medical centre in Jerusalem, and Nazareth Hospital in Nazareth) from January 2010 to 30 May 2018. Inclusion criteria included patients with an established diagnosis of CD and patients who had abdominal computed tomography or magnetic resonance imaging performed. Patients were excluded if they had IBD-undefined, severe liver, or haematological diseases.

Results: Three hundred and twenty-two patients were included; of these, 81 patients (25%) were diagnosed with an intra-abdominal abscess. In univariate analysis, ileo-colonic location (OR 1.88, 95% CI 1.131–3.12, p = 0.0148), perianal CD (OR 7.01, 95% CI 2.38–20.66, p = 0.0004), fever (above 37.5°C) (OR 1.88, 95% CI 1.08–3.25, p = 0.0247), neutrophil-to-lymphocyte ratio (NLR) (OR 1.12, 95% CI 1.81–1.17, $p < 0.0001$), and C-reactive protein (CRP) (OR 1.10, 95% CI 1.06–1.14, $p < 0.0001$) were significantly associated with abscess formation, while, current use of corticosteroids was negatively associated with abscess formation (OR 0.46, 95% CI, 0.2–0.88, p = 0.0192). We developed a diagnostic score that included the 5 parameters that were significant on multi-variate regression analysis, with assignment of weights for each variable according to the co-efficient estimate. For ileo-colonic location (1 point), peri-anal disease (3 points), absence of current steroids (2 points), CRP > 0.5 mg\dl (5 points) and NLR > 11.75 (3 points) (defined by the Youden J index with corresponding sensitivity of

53%, and specificity of 85%). By ROC analysis, the area under the curve for this score was 0.83. A low cut-off score of <7 was associated with a negative predictive value of 93% for abscess formation, while a high cut-off score >9 was associated with positive predictive value of 65% (see Table 1).

	Low cut-off ≤7	Intermediate cut-off >7 and ≤9	High cut-off >9	Total
Total	157	91	58	306
Abscess –ve\Abscess +ve	146\11	50\41	20\38	234\72
Sensitivity	85%		53%	
Specificity	62%		91%	
Positive predictive value	41%		65%	
Negative predictive value	93%		86%	
Likelihood ratio (+)	2.24		5.89	
Likelihood ratio (–)	0.24		0.52	
Interpretation	Absence of an abscess (93% certainty)		Presence of an abscess (65% certainty)	

Predictive value of the scoring system. https://planner.smart-abstract.com/ecco2019/submission/en/abstract/12120/content#

Conclusions: We recommend incorporating this scoring model into daily clinical practice in the ED as an aid for stratifying CD patients with low or high probability for presence of an intra-abdominal abscess.

Reference

1. Khoury T. Predictive value of the scoring system. 2018.

P265

Pharmacokinetic and pharmacodynamic evaluation of radiological healing in Crohn's disease patients treated with Infliximab: a TAILORIX MRE substudy

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Background: Higher infliximab (IFX) trough levels (TL) are associated with clinical and endoscopic remission in Crohn's disease (CD). The relationship between pharmacokinetic (PK) and pharmacodynamic (PD) monitoring and radiological healing evaluated by magnetic resonance enterography (MRE) are unknown. We here assessed the correlation between IFX TL and radiologic remission in a post hoc analysis of the prospective randomised TAILORIX trial.[1]

Methods: This study included all patients from TAILORIX that had baseline and Week 54 MRE available. The MARIA score was calculated by two independent blinded central readers (CR). In case of discrepancy a third CR provided adjudication. Radiologic response and remission were defined as MARIA in all segments <11 and <7, respectively. Prospectively collected PK markers (IFX TL), PD markers (CRP and Faecal Calprotectin [FC]) and endoscopic remission (CD endoscopic index of severity, CDEIS <3) were used for the analysis.

Results: Thirty-six patients were included in the analysis (50% female; median age 35.7 years IQR 25.6–48.6; median disease duration 1.44 months IQR 0.6–22.4). Radiologic response and remission at w54 was 32.3% and 25.8%, respectively; endoscopic remission was 67.7%. The correlation between CDEIS and MARIA at w0 was moderate (Pearson 0.46; $p = 0.008$), but was absent at w54. No correlation could be found between endoscopic and radiologic remission. Radiological remission at w54 was correlated with IFX TL at Week 14 ($p = 0.049$) with a ROC based IFX TL cut-off value of 7.8 µg/ml (AUC 0.74 sens 75% and spec 86%; NPV 90% and PPV 67%). Radiologic response at w54 was correlated with IFX TL at w14 ($p = 0.048$) with a ROC based IFX TL cut-off value of 7.8 µg/ml (AUC 0.73 sens 75% and spec 90%; NPV 87% and PPV 78%) and with continuous pharmacological response (IFX TL >5.0 µg/ml at all time points) ($p = 0.034$). No difference was found in IFX TL comparing patients with or without radiologic remission or response at W54. A subgroup of 21 patients needed dose escalation. In this subgroup continuous pharmacological response (IFX >7 µg/ml at all time points) was associated with radiological response ($p = 0.042$) and remission ($p = 0.010$). CRP and FC were not associated with radiological remission or response at any given time point.

Conclusions: In this post hoc analysis of TAILORIX, radiologic response and remission following infliximab induction and maintenance were observed in 32 and 26% of patients. IFX TL >7.8 µg/ml at the end of induction therapy predicted both radiologic remission and response at w54 in patients with CD.[1]

Reference

1. D'Haens G, Vermeire S, Lambrecht G, *et al*. Increasing infliximab dose based on symptoms, biomarkers, and serum drug concentrations does not increase clinical, endoscopic, and corticosteroid-free remission in patients with active luminal Crohn's disease. *Gastroenterology* 2018;154:1343–1351.e1.

P266

Clinical significance of granulomas in Crohn's disease: a meta-analysis

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Background: Epithelioid granuloma is one of the hallmarks in histological diagnosis of Crohn's disease (CD). However, the clinical significance of granulomas in CD is still unclear. We performed a meta-analysis to compare the clinical characteristics and prognosis of patients with CD according to the presence of granulomas.
Methods: A literature search in PubMed, EMBASE, and Cochrane database was performed published until December 2017. We included studies that met the following inclusion criteria; (1) patient: patients with CD; (2) exposure: granulomas on the endoscopic or surgical pathology; (3) comparator: no granulomas on the pathologic finding; (4) outcomes: the clinical features (location of disease, presence of perianal disease, extraintestinal manifestations, and disease activity at presentation) and prognosis (CD-associated surgery, hospitalisation, and use of biologics).
Results: We identified 20 studies meeting inclusion criteria. In terms of the clinical features, the presence of granulomas in patients with CD was associated with a higher proportion of disease involving both small and large intestine (odds ratio (OR): 1.49, 95% confidence interval (CI): 1.21–1.83, $p < 0.001$), a higher prevalence of perianal disease (OR: 2.47, 95% CI: 1.49–4.10, $p < 0.001$), and a higher severity index at presentation (standardised mean difference: 0.21, 95% CI: 0.03–0.40, $p = 0.02$). The pooled prevalence of extraintestinal manifestations was not significantly different according to the presence of granuloma (OR: 1.21, 95% CI: 0.79–1.84, $p = 0.38$). Regarding the factors related to prognosis, CD-associated hospitalisation (risk ratio (RR): 1.84, 95% CI: 1.09–3.11, $p = 0.02$) and use of biologics (RR: 1.30, 95% CI: 1.01–1.66, $p = 0.04$) were more common in CD patients with granuloma when compared with patients without granulomas. CD-associated surgery showed an increasing trend in CD patients with granuloma, but was not significant (RR: 1.41, 95% CI: 0.97–2.06, $p = 0.07$).
Conclusions: This meta-analysis demonstrated that the clinical features and prognosis in patients with CD were significantly different according to the presence of granulomas; it may indicate a more aggressive phenotype of CD.

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Relationship between morphological alteration of paneth cells and dysbiosis in patients with inflammatory bowel disease

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Background: Inflammatory bowel disease (IBD) is broadly categorised into Crohn's disease (CD) and ulcerative colitis (UC). The causal factors underlying IBD pathology remain unclear, however a relationship between microbiota and intestinal immunity is one of pathological factors. Paneth cell is a key player in innate gut immunity, and reported to contribute to the pathogenesis of CD, whereas the association between Paneth cell and UC remains unclear.
The aims of this study were therefore to verify whether measurements of the granule diameter of Paneth cells corresponding to Paneth cell morphology using biopsy samples could be used clinically as a pathological evaluation tool and to clarify the relationship between Paneth cells and intestinal microbiota in IBD by conducting 16S rRNA sequencing of intestinal bacteria in stool samples collected from the same patients at the same time.
Methods: Endoscopic biopsy specimens and stool samples were collected from 20 patients with each condition treated at Hokkaido University Hospital. Controls included stool samples from 20 volunteers and endoscopic biopsy specimens from 20 non-IBD cases. Paneth cell morphology evaluation in biopsy specimens focussed on pathological granule aspects; stool samples underwent 16S rRNA sequencing of microbiota.
Results: Paneth cell granule diameter was significantly smaller, and atypical Paneth cell proportions was significantly larger in the CD group. Stool samples of the CD group showed dysbiosis with significantly reduced intestinal microbiota α diversity, with a low degree of β diversity similarity. Firmicutes, Clostridiales, Ruminococcae, and Faecalibacterium were significantly reduced, whereas Proteobacteria, Gammaproteobacteria, Enterobacteriaceae, and Bacteroides were increased. Conversely, a lower degree of β diversity similarity was observed in the UC group than Control groups. Clostridiales, Lachnospiraceae, Faecaribacterium, and Coprococcus were significantly reduced, whereas Bacilli and Lactobacillales were significantly increased. For the CD group, Paneth cell granule diameter positively correlated with Clostridiales occupancy, whereas Paneth cell morphology did not correlate with microbiota in the UC group.
Conclusions: Paneth cells with altered granular morphology i.e., having smaller granules were found only in the CD group, and the alteration correlated with dysbiosis, indicating that Paneth cells are strongly involved in the pathology of CD. In contrast, no correlation was found in the UC group between the morphological changes of Paneth cells and dysbiosis, suggesting that major factors contributed to dysbiosis in UC might not be Paneth cells. Our results further suggested that the cause of dysbiosis in UC may differ from that of CD.

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Eosinophil-derived neurotoxin (eosinophil protein x) showed higher specificity and positive predictive value for detecting disease activity in inflammatory bowel disease compare to faecal calprotectin

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Background: Colonoscopy with multiple biopsies represents the gold standard to diagnose patients with chronic diarrhoea and to assess disease activity and severity. However, it is invasive and costly. Faecal calprotectin (FC) is used as a biomarker for intestinal inflammation in inflammatory bowel disease (IBD) but there is no reliable marker for microscopic colitis (MC). Moreover, the best biomarker for distinguishing functional from organic intestinal disorders is elucidated.
Methods: The AIM is to evaluate the diagnostic accuracy of faecal eosinophil-derived neurotoxin/eosinophil protein x (EDN/EPX) and to compare it to FC in patients with chronic diarrhoea. In this

prospective study, we enrolled 40 adult patients with chronic diarrhoea who underwent standard laboratory test, colonoscopy, faecal EDN/EPX and FC at 'Tsaritsa Yoanna – ISUL' University Hospital, Sofia, Bulgaria. We divided the patients into five groups: 14 patients with active IBD, 5 patients with quiescent IBD, 5 patients with IBD after surgery, 11 patients with IBS-D, and 5 patients with MC. We used ELISA to detect EDN/EPX and quantitative immunochromatographic to evaluate FC.

Results: Of this 40 patients included in the analysis, elevated levels of EDN/EPX was confirmed in 25% (10) of the patients and excluded in 75% (30). We found a EDN/EPX cut-off level of 1357 ng/ml for IBD activity with sensitivity of 50.00% (95% CI 23.04% to 76.96%), specificity 88.46% (95% CI 69.85% to 97.55%), negative predictive value 76.67% (95% CI 65.65% to 84.96%) and positive predictive value (PPV) of 70.00% (41.61% to 88.43%). EDN/EPX showed higher specificity and PPV for detecting disease activity in IBD patients compared with FC.

Conclusions: Combination of EDN/EPX and FC should be used for identifying patients with active IBD and they could possibly be used as biomarkers for differentiating IBD from IBS-D or MC with high diagnostic accuracy. Combination of both EDN/EPX and FCP can be used as a screening and monitoring surrogate markers for non-invasive disease activity evaluation in patients with active IBD using both their NPV and PPV. Furthermore, bigger studies are needed to establish the efficacy of EDN/EPX.

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Utility of capsule endoscopy in the diagnosis of inflammatory bowel disease and its disease extent

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Background: Capsule endoscopy is an established non-invasive tool for the evaluation of small bowel due to its ability to visualise subtle mucosal abnormality that may not be detected by cross-sectional imaging. We aim to evaluate its utility in patients with suspected inflammatory bowel disease (IBD) and in known IBD patients in a single tertiary hospital.

Methods: Retrospective analysis was done for all patients who underwent capsule endoscopy with PillCam™ SB video capsule system from the National University Hospital, Singapore from January 2006 to December 2016. Clinical data, laboratory results, and medications were assessed using electronic medical records and electronic prescription. Statistical analysis was done using SPSS. Categorical variables were compared using χ^2 test with Fisher exact test and continuous variables were compared using Student's *t*-test where appropriate.

Results: There were 426 patients who underwent capsule endoscopy from January 2006 to December 2016. Among these, 35 (8.2%) patients underwent capsule endoscopy for suspected IBD while 16 (3.8%) patients underwent capsule endoscopy for known IBD. There were 19 (37.3%) patients in the paediatric age group and 32 (62.7%) patients in the adult age group. Thirty-one (60.7%) patients were males and 20 (39.2%) patients were females. Of the 35 patients with suspected IBD, 7 (20.0%) patients were diagnosed with IBD after capsule endoscopy was done. Suspected IBD patients who were subsequently diagnosed with IBD following capsule endoscopy had a significantly lower mean albumin level (39 ± 4.41 g/l) compared with patients who were not diagnosed with IBD (39.0 ± 4.41 g/l vs. 43.0 ± 3.28 g/l; $p = 0.039$), and were more likely to have hematochezia (3/7; 42.9% vs. 2/28; 7.1%, $p = 0.044$). There were no significant difference in haemoglobin, white cell count, C-reactive protein, creatinine, presence of diarrhoea, and weight loss, between patients who were subsequently diagnosed with IBD and those who were not. Among the 16 patients with known IBD, there was a change in IBD phenotype following capsule endoscopy in 2 (12.5%) patients, with extension of involvement from Montreal L2 (colonic) to L3 (ileocolonic) . Four (25.0%) patients had intensification of treatment following capsule endoscopy: one patient was started on biologics and 3 others were started on immunomodulators.

Conclusions: Although IBD-related evaluation compromised a small proportion of overall capsule endoscopy referrals, capsule endoscopy is a useful tool in making the diagnosis of IBD, and in the evaluation of the extent of IBD, resulting in optimisation of treatment.

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Clinical and radiologic characteristics of intra-abdominal fistulising Crohn's disease

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Background: Few studies describe the radiographic and laboratory characteristics of patients with Crohn's disease (CD) with intra-abdominal fistulae. We therefore aimed to describe a cohort of CD patients with intra-abdominal fistulae and determine characteristics associated with complex fistulae.

Methods: Data were gathered retrospectively from the medical records and imaging studies of CD patients. Once patients with fistulae were identified, the radiographic studies were re-read by abdominal radiologists. The review included evaluation of the type of fistula, number of fistulae, and radiological characteristics. Clinical and imaging study characteristics were then compared between groups of patients with fistulae.

Results: Among 1233 patients with CD, a total of 205 fistulae in 132 patients were identified with an average patient age of 31 (±12) years. The average time from CD diagnosis to fistula development was 7 years. The most common type of fistula was entero-enteric (53%). Most CD patients in our cohort with an intra-abdominal fistula had only one fistula (54%), while patients with an extra-intestinal fistula presented with an average of 1.96 fistulae, compared with an average of 1.28 fistulae for those with a fistula limited to the bowel ($p = 0.01$). Aside from the number of fistula, no other significant differences were observed in radiological characteristics of patients who were diagnosed with a fistula at the time of CD diagnosis when compared with those diagnosed with a fistula subsequent to CD diagnosis. C-reactive protein (CRP) levels were above the upper limit of normal at time of fistula diagnosis in 66% of patients and albumin levels were below the lower limit of normal in 41% of patients.

Conclusions: This study reports data of a relatively large cohort of CD patients with intra-abdominal fistulae and may be used to help predict the course of fistulising CD. The most common CD-associated intra-abdominal fistulae are entero-enteric and entero-colonic fistulae. An extra-intestinal fistula and diagnosis of a fistula subsequent to diagnosis of CD were associated with an increased number of fistulae per patient, but were not associated with the development of fistula associated stenosis or abscess.

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Role of magnetic resonance in imaging of mesentery in Crohn's disease

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Background: Mesenteric adipocites, fat tissue and mesenteric lymph nodes (MLN) are believed to be the origins of the intestinal wall destruction. MRI is the best imaging modality for assessment of the mesentery due to its high tissue contrast resolution. Moreover, MRI utilises no ionised radiation. There are no uniform imaging criteria for assessment the activity of CD in MRI. The aim of the study was to evaluate the role of MRI in assessment of disease activity based on evaluation of mesentery.
Methods: The study was approved by The Bioethical Committee. A group of 30 adults with diagnosed CD was enrolled into the study. All patients had MRI performed on 3T scanner in enteroclysis protocol with the application of spasmolytic agents and gadolinium intravenous contrast medium. MRI images where reviewed for following radiologic signs of mesenteric abnormalities: comb sign, mesenteric lymph node (MLN) size and number, MLN enhancement, mesenteric fat creeping, mesenteric oedema. The results were compared with clinical data and CD course severity, based on age, sex, CD duration, conservative and surgical treatment, CDAI and SES-CD. Mann–Whitney *U* test, multivariate regression and Spearman correlation of imaging and clinical findings (a type of treatment, CDAI, SES-CD and simplified Geboes index) have been performed on Statistica 13.
Results: The mean age of the analysed group was 34 years. The mean calprotectin level on the time of MRI examination was 364 mg/dl. More than half of the patient suffered from chronic abdominal pain. Thirty-one per cent underwent anti-TNF therapy, and 15% were on steroids administration on the time of MRI. In SES-CD score 29% was in remission, 23% had mild CD, 47% moderate or severe CD course. Forty per cent underwent surgical treatment before MRI. The comb sign was associated with higher SES-CD score, as well as with increased MLN enhancement ($p < 0.05$). Mesentery of patients after biological treatment and on steroids was characterised by higher multiplicity of MLN (over 10 and 5, respectively) ($p < 0.05$) and vivid contrast enhancement of MLN ($p < 0.01$).
Conclusions: Assessment of mesentery in MRI can serve as an independent tool in CD activity evaluation. Comb sign, MLN enhancement and number were related to the severity of CD.

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Developing a novel medication adherence index to determine reasons for nonadherence in inflammatory bowel disease

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Background: Medication nonadherence is a significant challenge in inflammatory bowel diseases (IBD), and associated with high costs and negative outcomes. The vast majority of studies report nonadherence in IBD in the range of 30–45%. With increased adaptation of electronic health (e-health) technologies, there is a significant opportunity to monitor patient adherence behaviours remotely. However, no tool exists that can both determine adherence levels and quantify patient-specific reasons for nonadherence. We developed a medication adherence index to categorise adherence and assess nonadherence factors in patients with Crohn's disease (CD) or ulcerative colitis (UC) for use in e-health applications.
Methods: We performed a cross-sectional study to develop a medication adherence index (MAI) for CD and UC that accurately screens for medication adherence in the IBD population. Our MAI was developed using 27 patient-reported outcomes measures collected from the literature and its predictive performance was compared with the widely used Morisky Medication Adherence Scale-8 (MMAS-8). Data were captured from IBD patients through an electronic questionnaire via email or during clinic visits at the University of California, Los Angeles, Center for IBD from June 2017 to November 2017.
Results: In total, 133 patients (65 UC and 68 CD) were included in this study. Our population had 44 (33%) non-adherent and 89 (67%) adherent patients. Our cohort was primarily Caucasian, non-Hispanic, non-smoking and privately insured. No patient characteristics were associated with significant higher nonadherence. Our final 6-item survey for assessing adherence had an area under the curve (AUC), sensitivity, and specificity of, respectively 0.90, 0.87, 0.79, with a score of ≥9 as adherent, and <9 as non-adherent. An additional 4-item survey was developed for nonadherent patients to delineate reasons for their nonadherence.
Conclusions: Implementation of this novel tool in e-health applications promising for the monitoring of nonadherence in IBD. Compared with existing scales our new index showed comparable AUC, sensitivity and specificity. There is a potential for more widespread use due to its shorter length and development in a prototypic chronic disease. Additionally, quantifying the reasons for nonadherence can lead to more effective and personalised interventions and education for non-adherent patients. With more tailored solutions for non-adherence, there is a great potential for more patient empowerment, improved clinical outcomes and decreased costs.

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Investigations of the characteristics and efficacy of anti-TNFα agents for optimising treatment in paediatric patients with new-onset Crohn's disease

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Abstract P272 –

Question	Response score	Factor type	Specific factor
Do you ever find yourself not as careful about taking your medications?	Yes(0): +0 No(1): +1	General	General
When you feel better do you sometimes stop taking your medicine?	Yes(0): +0 No(1): +4	Intentional	Lack of understanding of disease/medication
Does your physician offer choices in medical care?	Yes(1): +1 No(0): +0	Intentional	Lack of involvement in the treatment decision-making process
Sometimes if you feel worse when you take the medicine, do you stop taking it?	Yes(0): +0 No(1): +1	Intentional	Avoidance of side effects
Do you ever forget to take your medication?	Yes(0): +0 No(1): +4	Unintentional	Forgetfulness
Does your physician explain treatment alternatives?	Yes(1): +2 No(0): +0	Unintentional	Poor patient–physician communication

The AUC, sensitivity, and specificity of this model are, respectively, 0.90, 0.87, 0.79, and the final scoring guide is as follows: score ≥ 9 is adherent, score < 9 is non-adherent.

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Background: We investigated the characteristics of paediatric Crohn's disease (CD) patients and the efficacy of anti-TNF-α agents in our hospital specialising in inflammatory bowel diseases to illustrate real-world data.

Methods: In this single-centre retrospective case–control study, we investigated 236 CD patients newly diagnosed at our hospital from January 2007 to December 2017. The patients were divided into the paediatric group (≤17 years of age) and the non-paediatric group (>17 years of age). We compared clinical characteristics and investigated the efficacies of anti-TNF-α agents. Clinical remission was defined as a Pediatric Crohn's disease Activity Index (PCDAI) ≤10, while loss of response (LOR) was defined as requiring additional or increasing doses of concomitant therapy. Mucosal healing was defined as no active inflammation at any site based on conventional ileocolonoscopy.

Results: The paediatric group accounted for 22.9% of CD patients (54/236) and the observational period was 3.9 ± 2.0 years. The age at diagnosis was 14.8 ± 1.9 years in the paediatric CD patients, and males accounted for 66.7% (36/54). The complications of extraintestinal manifestations were significantly more common in the paediatric group (22/54, 40.7%) than in the non-paediatric group (13/182, 7.1%) ($p < 0.001$). The inflammatory type of behaviour was significantly more frequent in the paediatric group than in the non-paediatric group (90.7% vs. 59.9%; $p < 0.001$). In the paediatric group, 78.8% (42/54) of patients were administered anti-TNFα agents (30 cases given infliximab, 12 cases given adalimumab), and 92.9% (39/42) of them were administered without immunomodulators. The rates of achieving remission induction and mucosal healing within a year were 89.2% (33/37) and 75.0% (18/24), respectively. Among 33 primary responders in the paediatric group, the cumulative LOR rate was 21.2% (7/33) at 1 year, 33.3% (11/33) at 2 years and 39.4% (13/33) at 5 years. Significantly lower haemoglobin (10.4 ± 3.1 g/dl vs. 12.5 ± 1.5 g/dl, $p < 0.05$), higher C-reactive protein (5.5 ± 5.5 mg/dl vs. 2.4 ± 2.3 mg/dl, $p < 0.05$) and higher PCDAI (41.3 ± 13.4 vs. 28.2 ± 13.8, $p < 0.05$) at baseline were observed in the LOR group than in the remission maintenance group. There tended to be more females in the LOR group (53.8% vs. 20.8%, $p = 0.07$).

Conclusions: The inflammatory type of behaviour and the complications of extraintestinal manifestations were frequent in our paediatric CD cohort. Although a higher rate of anti-TNF agent administration depends on the special support system covering the medical costs for CD patients in Japan, LOR developed. The introduction of anti-TNF agents as combination therapy with immunomodulators should be considered to avoid LOR in high-risk paediatric CD patients.

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The association between the severity of histological lesions with the disease location and presence of colonic lesions in patients with ulcerative colitis

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Background: Multiple histological scores evaluate the disease activity UC including GEBOES, GUPTA, Gramlich, amongst others. The objective of this study was to assess the severity of histological lesions in patients with UC using these three scores and to check if there is an association with disease location, presence of polyps, dysplasia and cancer

Methods: This is a retrospective study whereby all UC pathology reports, in the biggest pathology centre in Beirut between 2006 and 2016, were reviewed and subjected to a second reading. Several variables were analysed: age, sex, extent of lesions, and presence

of polyps, dysplasia and cancer. GEBEOS, GUPTA, and Gramlich scores were used to evaluate the severity of the histological lesions.
Results: In total, 1096 patients were diagnosed with UC during the period ranging from 2006 to 2016. Mean age was 42 years and 48.9% were females. Sixty-one per cent of patients had their first disease flare, 26.6% had a relapse and 9.9% had the disease controlled on treatment. For disease location, pancolitis was present in 53% of patients, left sided colitis in 20.2% and proctitis in 26.8% of patients. Hyperplastic polyps were present in 1% of patients with a mean age of 45 years, adenomas in 2.6% with mean age of 56 years and inflammatory pseudopolyps in 6.1% with a mean age of 47 years. There was no difference between the sexes. The majority of inflammatory polyps arised in patients with pancolitis with significant difference when compared with the two other locations. There was no difference in the presence of hyperplastic polyps and adenomas in regards to the different disease locations. In patients with adenomas, low-grade dysplasia was noted in 82.8%, high-grade dysplasia in 10.3% and cancer in 6.9%, whereas 1.6% of patients with inflammatory pseudopolyps had dysplasia. The presence of dysplasia and cancer was 0.8% and 0.9%, respectively, with a mean age of 63 years for patients with dysplasia and 56 years for patients with cancer. Regarding histological severity, 2%, 74.5%, 20.2% 2%, 8% and 1.1% were graded as 5, 4, 3, 2, 1 and 0, respectively, using the GEBOES score. 74.7%, 8.8% et 11.8% and 2.1% had Gramlich scores of 3, 2, 1 and 0, respectively and finally 74.7%, 8.6%, 12% and 2.% had a GUPTA score of 3, 2, 1, and 0, respectively, Lesions' severity was not linked to the disease location but the presence of adenomas, inflammatory pseudopolyps and hyperplastic polyps was significantly higher in patients with elevated histological scores.
Conclusions: The majority (>75%) of UC patients had severe lesions according to the different scores (GEBOES, Gramlich, and GUPTA). Histological severity was not linked to disease location, but was associated with a higher prevalence of inflammatory pseudopolyps, adenomas and dysplasia.

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The emotional impact of diagnosis on patients with ulcerative colitis in the UK

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Background: The diagnosis period can mark a turning point in life for patients diagnosed with chronic conditions. Being diagnosed with ulcerative colitis (UC) can be a stressful and disruptive time for patients, not only because of the effects of symptoms and disease activity, but also because of the need to understand and adapt to the implications of diagnosis more broadly. Very little qualitative research focussing on patients' experience of diagnosis with UC has been conducted to date. Such research might help us understand these processes more fully.
The aim of this presentation is to explore qualitative research data collected from patients resident in the UK describing their perspectives on the period immediately pre and post diagnosis with UC.
Methods: In-depth semi-structured interviews were carried out with 40 UC patients as part of qualitative studies integrated with two separate pilot trials. Patients who withdrew from the trials, or who declined to take part, were also interviewed.
Results: The majority of patients had no awareness or knowledge of UC before being diagnosed with the condition. This contributed to patients being anxious about how the disease would advance and what to expect in the future. Prior to diagnosis, some primary care physicians dismissed patients' reported symptoms, thereby increasing the length of time it took to be referred to a gastroenterologist and adding to their distress. Finally, patients reported feeling a range of emotions after being diagnosed with UC, including shock, relief, and confusion about whom to turn to for help. They also expressed a lack of emotional support during this particularly upsetting and difficult time.
Conclusions: The diagnosis period is a very emotional time for patients who suffer from UC. In addition to feeling distressed before being diagnosed and anxious about their future, patients also felt isolated and lacked emotional support after their diagnosis. Some emotional support is currently available from various sources throughout the diagnosis period, including health services (IBD nurse, hotline), charities (peer support groups, hotline), and families and friends. However, these support initiatives do not seem to meet all the patients' requirements. Having an early multi-disciplinary assessment as soon as possible after diagnosis could be vital to minimise the psychological impact of the diagnosis. Future research should concentrate on how patients' needs could be met more efficiently to improve patients' experience of being diagnosed with UC. In turn, this may help patients adapt more effectively and rapidly to their diagnosis.

P276

Extraintestinal manifestations in paediatric patients with inflammatory bowel disease

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Background: More than half of the paediatric patients with inflammatory bowel disease (IBD) develop extraintestinal manifestations (EIMs). The frequency varies depending on the used definition. Some authors differentiate 'extraintestinal manifestations' and 'extraintestinal complications', others use more broad term. EIMs may occur before or after IBD diagnosis and usually parallel the disease activity. The aim of our study was to assess the prevalence of EIMs in paediatric patients with IBD and to analyse the connections between EIMs and disease type, duration, extent and activity.
Methods: A single-centre retrospective observational study including children and adolescents diagnosed with IBD, treated in the Department of Gastroenterology and Hepatology at the University Paediatric Hospital 'Prof. Ivan Mitev', Sofia for the period March 2011–October 2018. All observed EIMs were analysed.
Results: Totally 91 children were included in the final analysis—51 with ulcerative colitis (UC) and 40 with Crohn's disease (CD). The median age of the participants at IBD diagnosis was 14 years (range 2–17 years). The median follow-up was 36 months (1–180 months). Fifty-five patients (60.4%) experienced at least one EIM. The most prevalent EIMs were anaemia 34.1% (31/55), growth failure 6.6% (6/55), and arthritis 5.5% (5/55). Other rare EIMs such as glomerulonephritis (2/55) and pyoderma gangrenosum (1/55) were also

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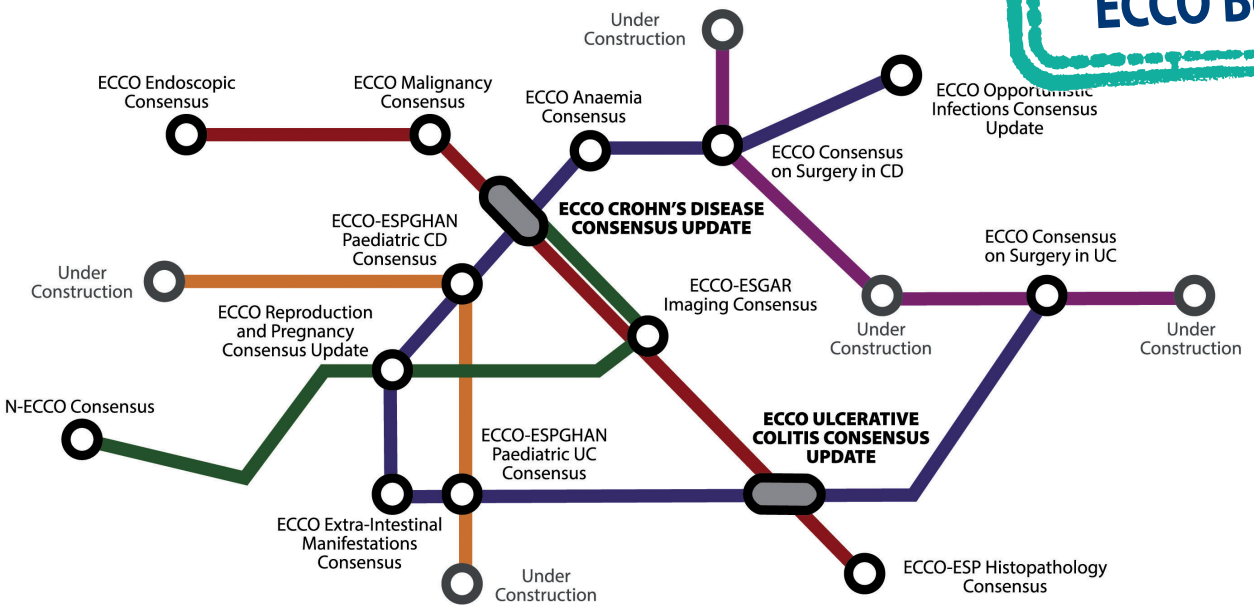

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observed in our patients. In 18.2% (10/55) of the cases, the EIMs preceded the IBD diagnosis, in 32.7% (18/55) were identified at IBD diagnosis and in 49.1% (27/55) EIMs developed subsequently within the disease course. There were no statistically significant differences in the rates of EIMs between UC and CD patients (60.8% vs. 60%, $p = 0.938$). Of the UC patients with EIMs 61.3% (19/31) were girls and 38.7% (12/31) were boys; 58.1% (18/31) had pancolitis, 12.9% (4/31) extensive colitis, 25.8% (8/31) left sided colitis and 3.2% (1/31) ulcerative proctitis. Of the CD patients with EIMs 41.6% (10/24) were girls and 58.4% (14/24) were boys; 70.8% (17/24) had ileocolonic disease, 16.6% (4/24) colonic disease and 12.6% (3/24) ileal disease. The majority of EIMs observed were associated with an active underlying disease.

Conclusions: EIMs are common in paediatric patients with IBD. Children with longer disease duration and more extensive disease are at higher risk to develop EIMs.

P277

Real life effectiveness and safety of vedolizumab induction and maintenance therapy for Korean IBD patients in whom anti-TNF treatment failed: a prospective cohort study

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Background: Vedolizumab (VDZ) is a gut-selective monoclonal antibody blocking α4β7 integrin, which can be effective for patients with inflammatory bowel disease (IBD). We aimed to investigate the clinical effectiveness and safety of VDZ therapy for Korean patients with Crohn's disease (CD) or ulcerative colitis (UC) in whom anti-tumour necrosis factor therapy (TNF) failed previously.

Methods: Between August 2017 and October 2018, a total of 54 patients with CD ($n = 36$) or UC ($n = 18$) were started on VDZ therapy and prospectively enrolled in the ASAN VDZ registry. Of those, data of patients who were evaluated at Week 14 after completing induction therapy and those evaluated at Week 53–57 were analysed. The co-primary outcomes were corticosteroid-free clinical remission (both for CD and UC) and endoscopic remission/response (for UC) at Week 14 and Week 53–57, respectively. Safety after initiating VDZ was also evaluated.

Results: A total of 47 patients were evaluated at Week 14 (CD, 30 [63.8%]; male, 31 [66.0%]; median age, 36 years [range, 19–71]; median disease duration, 8.9 years [range, 0.1–26.7]). At Week 14, corticosteroid-free clinical remission/response rates in CD and UC patients were 37.5%/37.5% and 11.8%/35.3%, respectively. In patients with UC, endoscopic remission and response rates defined by Mayo endoscopic subscore (MES)/ulcerative colitis endoscopic index of severity (UCEIS) were 23.5%/5.9% and 47.1%/29.4%, respectively. Twelve out of 47 patients (25.5%, 7 CD and 5 UC) were evaluated at Week 53–57. Corticosteroid-free clinical remission/response rates in CD and UC patients at Week 53–57 were 50%/50% and 20%/40%, respectively. In patients with CD, combined endoscopic mucosal healing and radiologic healing were observed in one patient (14.3%). In patients with UC, endoscopic remission and response rates at Week 53–57 defined by MES/UCEIS were 40%/20% and 60%/40%, respectively. Out of 47 patients, shortening of VDZ dosing interval was required in 17 patients (36.2%) and five patients (10.6%) discontinued VDZ therapy after a median period of 41 weeks (range, 26–46 weeks) due to poor response. IBD exacerbation was the most common adverse events which was observed in 21 patients (44.7%). Arthralgia, nasopharyngitis, and headache were observed in 13 (27.7%), 10 (21.3%), and 8 patients (17.0%), respectively. IBD-related admissions occurred in 6 patients (12.8%).

Conclusions: In Korean IBD patients with prior failures to anti-TNF therapy, VDZ induction and maintenance therapy may be effective with acceptable safety profile. Further long-term follow-up studies with larger number of patients are required to prove the effectiveness and safety of VDZ.

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Comparison of long-standing paediatric-onset and adult-onset inflammatory bowel disease

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Background: Inflammatory bowel diseases (IBD) are chronic autoimmune conditions of the gut affecting both paediatric and adult patients. Multiple studies show that onset of IBD during childhood has a different disease pattern and more aggressive evolution compared with adult onset. The aim of the study was to analyse the natural history and the rate of complications of childhood-onset disease and to compare them with characteristics of adult-onset disease in patients.

Methods: A retrospective comparative study was conducted from January 2014 to December 2016. Seventy-nine patients with Crohn's disease (CD) and 50 patients with ulcerative colitis (UC) were retrospectively divided into paediatric onset (age at diagnosis ≤ 18 years) and adult onset (>18 years) patients.

Results: Among the CD patients, 13 (16, 4%) had paediatric-onset. There was no significant difference in the location of the disease between paediatric-onset patients (L1: 46%, L2: 15%, L3: 38%, L4: 7%) and adult onset patients (L1: 34%, L2: 13%, L3: 53%, L4: 5%) at diagnosis or during follow-up. The comparison of the rate of intestinal complications between age groups yielded the following results: strictures were more frequent in adult-onset patients (66.6% vs. 46.1%, $p = 0.1$).The overall prevalence of abdominal penetrating disease was the same between the 2 groups (53.8% vs. 43.9%, $p = 0.2$). In addition, the rate of perianal fistulising disease was similar (30.7% vs. 28.7%, $p = 0.1$). The rate of resectional surgery was not different in paediatric- and adult-onset CD patients (61.5% vs. 68.1%, $p = 0.1$). The rates of the assessed treatments with anti-TNF-α antibodies were higher in paediatric CD onset (69.2% vs. 46.9%, $p = 0.04$). During the follow-up, the presence of extra intestinal manifestations was observed more often in the paediatric-onset group without significant difference (38.4% vs. 27.2%, $p = 0.3$). In UC patients, 20%($n = 10$) of patients had a paediatric-onset disease. At the diagnosis, 23% had proctitis, 35%

left-sided colitis and 42% extensive colitis. Paediatric-onset disease was associated with a higher rate of acute severe colitis (60% vs. 23%, $p = 0.006$) at diagnosis and increased risk for colectomy (30% vs. 10%, $p = 0.004$) .The rate of treatments with anti-TNF-α antibodies was higher in paediatric-onset patients without colectomy (60% vs. 22%, $p = 0.03$).

Conclusions: In our study, patients with paediatric-onset IBD exhibit a more severe disease: more stricturing in paediatric onset CD and more acute severe colitis in paediatric onset UC, explaining the more frequent require of immunomodulators therapy in this population.

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Interest of serum calprotectin in inflammatory bowel disease (IBD): a prospective monocentric study

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Background: Faecal calprotectin (FC) is the most effective non-invasive biomarker for the diagnosis and monitoring of inflammatory bowel diseases (IBD). It is a major marker in the 'Treat to Target' strategy. However, in clinical practice, the faecal sample appears to be restrictive for patients. The aim of our study was to evaluate the diagnostic performance of serum calprotectin (SC) to predict clinical remission (CR) and mucosal healing (MH) in IBD patients.

Methods: It was a prospective monocentric study. We have consecutively included any patient with either ulcerative colitis (UC) or Crohn's disease (CD) and followed in our IBD centre. Exclusion criteria were: inflammatory rheumatism, *Clostridium difficile* infection, recent treatment with non-steroidal anti-inflammatory, pregnancy, age <16 years, patients with exclusive ano-perineal lesions for CD. The main objective was to search for predictive values of SC for RC and MH and to compare it with other biomarkers (CRP, FC). In secondary analysis, we searched for a correlation between SC, FC, and protein C reactive (CRP). The analysis technique for the SC and FC was performed by the Bühlmann Quantum Blue® rapid test. All measurments (SC, FC, and PCR) were performed at the same time.

Results: From June 2017 to June 2018, 82 patients (60.2% CD, sex ratio M/F = 0.74, mean age 42.19 ± 15.4 years) were included and we performed 123 SC assays. Of the 123 assays of SC, 87 (70.7%) were performed in patients with CR. With respect to the prediction of CR, SC had an area under the curve (AUC) of 0.67. A cut-off value of 5.3 mg/ml predicted a clinical remission with a sensitivity (Se) of 65.6%, a specificity (Sp) of 67.6%, conferring diagnostic performance not inferior to other biomarkers such as CRP ($p = 0.80$) and CF ($p = 0.42$). This predictive value was more favourable in UC than in CD. With regard to the prediction of MH, the diagnostic performance of SC was good (AUC = 0.73), with a threshold of 4.8 mg/ml to predict MH with a Se of 61.9% and a Sp of 80.9%. These results were similar to those of CRP ($p = 0.48$) and CF ($p = 0.23$). There was a correlation between the endoscopic score during UC and SC levels ($r = 0.59$) which was greater than with FC ($r = 0.46$). No significant correlation was reported between SC and FC ($r = 0.16$) and between SC and CRP ($r = 0.35$).

Conclusions: This study has shown that SC is a predictive biomarker of CR and MH in IBD patients. This biomarker was not inferior to other biomarkers in terms of prediction. Further studies involving more patients are needed to confirm the future role of SC in IBD management.

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Prediction factors for low bone mineral density in children with Crohn's disease

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Background: Since bone mass is almost exclusively accrued during childhood, early recognition and treatment of osteopenia is paramount in paediatric Crohn's disease (CD). We aimed to identify variables predictive of moderate–severe osteopenia to guide screening to those who most need it.

Methods: Retrospective review of medical records of children (2–18 years) diagnosed with CD at Shaare Zedek and Schneider medical centres. Demographic, anthropomorphic, clinical, biochemical, radiological, and endoscopic features at diagnosis were recorded along with bone mineral density (BMD) z-scores based on whole-body dual-energy X-ray absorptiometry (DEXA) scans corrected to gender and height.

Results: In total, 155 children were included (mean age 13 ± 3 years, 91 (59%) males, mean body mass index (BMI) 17.2 ± 2.9, median paediatric Crohn's disease activity index (PCDAI) 25 (IQR 17.5–37.5). Eighteen children (12%) had stricturing or penetrating disease, 36 (23%) had perianal and 59 (38%) had growth delay. Mild osteopenia (z-score −1 to −2) was observed in 36 (23%) children and moderate–severe (z-score <−2) in 53 (34%). Based on unadjusted BMD z-scores, children with moderate–severe osteopenia had a higher mean PCDAI score (32 ± 16 vs. 27 ± 13, $p = 0.036$), platelet count (432×10^3/μl ± 119 vs. 400 ± 100, $p = 0.013$), a higher incidence of growth delay (56% vs. 13%, $p < 0.001$), lower mean BMI (16.3 ± 2.6 vs. 18.4 ± 3.0, $p = 0.001$) and lower serum albumin (3.5 g/dl ± 0.7 vs. 3.8 ± 0.4, $p = 0.019$) than those with normal BMD (z-score > −1). However, when BMD z-scores were corrected for height the only significant association was with PCDAI (34 ± 15 vs. 24 ± 16, $p = 0.027$) and BMI (16 ± 2 vs. 19 ± 2, $p < 0.001$). There was no association between the presence of osteopenia and disease extent or location, age or presence of perianal disease.

Conclusions: Osteopenia is a frequent finding in paediatric CD and is associated with several variables at disease onset. Appropriate referral practices and early identification of patients with moderate–severe osteopenia is important, and accurate prediction of patients may assist timely intervention.

P281

Endoscopic healing assessed by advanced optical enhancement techniques combined with faecal calprotectin (FCP) can accurately assess histological healing in ulcerative colitis patients

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Background: Mucosal healing (MH) is considered a key target of therapy in ulcerative colitis (UC) but there is debate about endoscopic healing, histological healing, and surrogate marker of MH using faecal calprotectin (FC). We have recently described and validated endoscopic MH using high-definition electronic chromoendoscopy. In this study, we aimed to investigate MH using multiple endoscopic scorings, FC, and validated histological scores.

Methods: We prospectively obtained clinical data, endoscopic scores [Mayo Endoscopic Score (MES), Ulcerative Colitis Endoscopic Index of Severity (UCEIS) PICaSSO score (Paddington International virtual ChromoendoScopy ScOre)] and FC for UC patients undergoing colonoscopy using high-definition (Pentax) iScan optical enhancement (OE) or NBI near focus (Olympus). Histological scorings were assessed using Robarts Histological Index (RHI) and Nancy index (NI). Receiver-operating characteristics (ROC) curves were plotted to determine operating characteristics of FC alone or in combination with endoscopic scores to predict histological healing.

Results: In total, 44 patients (mean age 45 years, 52% men) were included. By partial Mayo score <2, 30 patients (68.2%) were in remission; however, endoscopic remission was seen in only 21(47.7%) with MES = 0 and UCEIS ≤ 1 and 18 (40.9%) with PICaSSO ≤ 2. The mean ± sd of FC was 465.5 ± 703.3 μg/g and 20 (45.5%) patients had FC ≤ 100 μg/g. The histological healing, defined as RHI ≤ 6 was seen in 21 (47.7%) patients and NI ≤ 1 was seen in 19 (43.2%). The threshold for FC alone as a predictor of histological healing using RHI was 313 μg/g with an accuracy of 84.1% (95% CI 69.9–93.4%) and AUROC of 87% (95% CI 75–98%), whilst for NI it was 112 μg/g, with accuracy of 81.8% (95% CI 67.3–91.8%) and AUROC 85% (95% CI 73–96%). The accuracy of predicting histological healing using a combination of PICaSSO and FC(≤100 μg/g) is 93.2% (95% CI 81.3–98.6%) with AUROC 96% (95% CI 91–100%) for both RHI and NI (formula used for NI=FC+1.5*Picasso). The combination of UCEIS and FC (≤100 μg/g) had an accuracy of 90.9% (95% CI 78.3–97.5%) in predicting histological healing for both RHI and NI, with an AUROC of 95% (95% CI 89–100%) and 94% (95% CI 87–100%), respectively. MES was not modelled in combination with FC as the best 2 endoscopy scores were modelled further.

Conclusions: The combination of PICaSSO and FC could help to identify UC patients with histological healing accurately than FC alone. PICaSSO with FC had better operating characteristics for prediction of histological healing than UCEIS and FC when using advanced endoscopic imaging with either iscan OE or NBI near Focus.

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Combination of biomarkers reflecting type IV collagen degradation and citrullinated vimentin predicts response to adalimumab with high diagnostic accuracy, in patients with Crohn's disease

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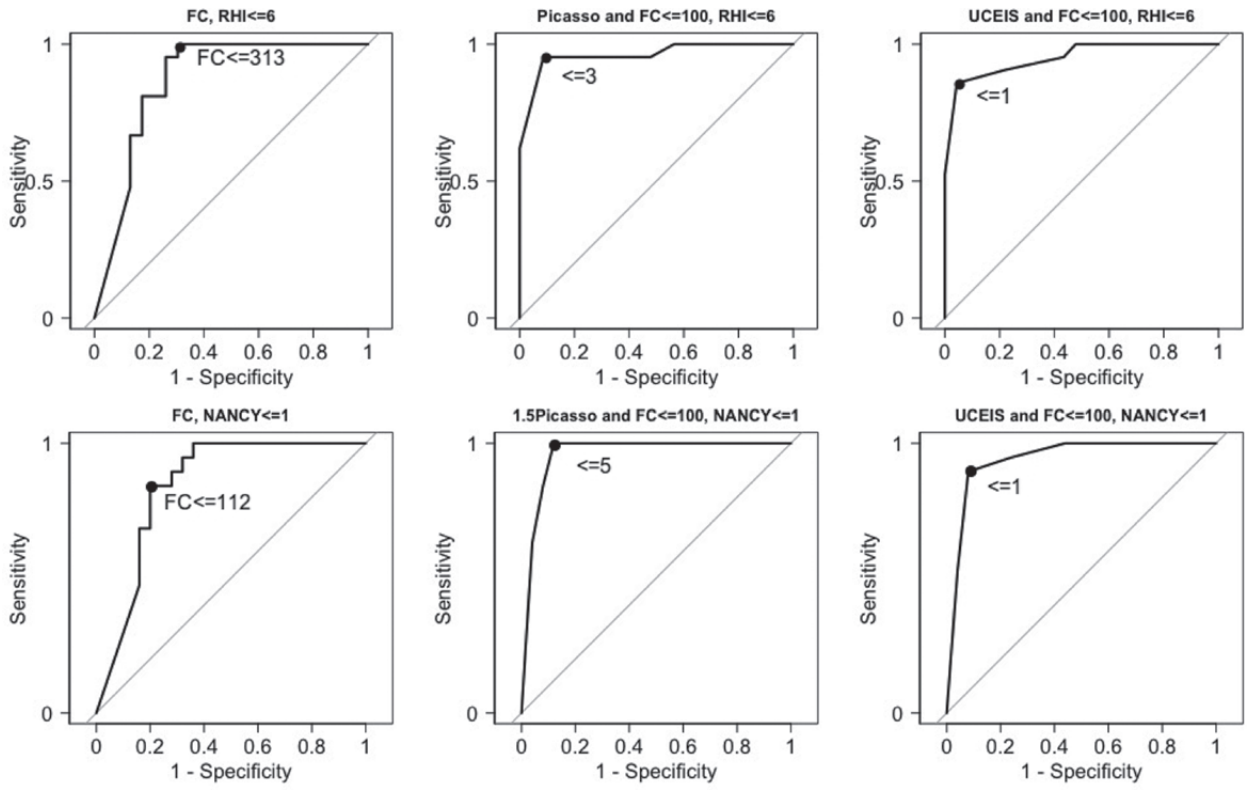

Abstract P281 – ROC curves predicting histological healing.

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Background: In inflammatory bowel diseases (IBD), up to 40% of patients do not respond to biologic treatment, eg, anti-TNFα antibodies. A personalised medicine approach may facilitate the best possible treatment option for IBD patients. Currently, no biomarkers have sufficient sensitivity to separate responders from non-responders within the first weeks of anti-TNFα therapy, which limits the personalised medicine approach for IBD patients. We investigated serum biomarkers that reflect basement membrane degradation (C4M: MMP mediated degradation of type IV collagen) and citrullinated vimentin (VICM: activated macrophages), and their ability to predict response to anti-TNFα treatment in Crohn's disease.

Methods: This was a single-centre cohort study. We measured clinical response to adalimumab at Week 8 after treatment induction in 22 patients with Crohn's disease, using the Harvey–Bradshaw Index (HBI). Response was defined as clinical remission (HBI<5) at Week 8. ELISA was applied to quantify the degradation of type IV collagen (C4M) and macrophages activity (VICM). Inflammation was estimated by C-reactive protein (CRP). The biomarkers were combined in a backwards multi-variate regression model to increase the prediction value for non-response to anti-TNF.

Results: At baseline, C4M serum levels was significantly higher in non-responders compared with responders (AUC: 0.81 [CI: 0.58–1.00], $p = 0.027$). VICM serum levels were not significantly different at baseline between responders and non-responders but was modulated in patients who responded to anti-TNF and was significantly lower at Week 1 compared with non-responders (AUC=0.89 [CI: 0.69–1.00], $p = 0.007$). CRP did not demonstrate any predictive value at baseline (AUC=0.65 [CI: 0.42–0.89], $p = 0.301$) or Week 1 (AUC=0.66 [CI: 0.38–0.94], $p = 0.282$).

C4M and VICM were included in the final model. The combination of C4M and VICM increased the predicted value to identify patients that do not respond to anti-TNF treatment (AUC=0.94 [CI: 0.75–1.00], $p = 0.005$), with an odds ratio of 22 (CI: 2.70–313).

Conclusions: The combination of baseline serum levels of C4M and Week 1 serum levels of VICM demonstrated high accuracy to predict who will respond to anti-TNFα treatment in Crohn's disease, and was superior to CRP. Thus, baseline levels of C4M in combination with Week 1 levels of VICM may be used to predict response to anti-TNFα and may therefore aid in a more personalised treatment approach.

P283

Bowel urgency in patients with moderate to severe ulcerative colitis: prevalence and correlation with clinical outcomes, biomarker levels, and health-related quality of life from U-ACHIEVE, a Phase 2b study of upadacitinib

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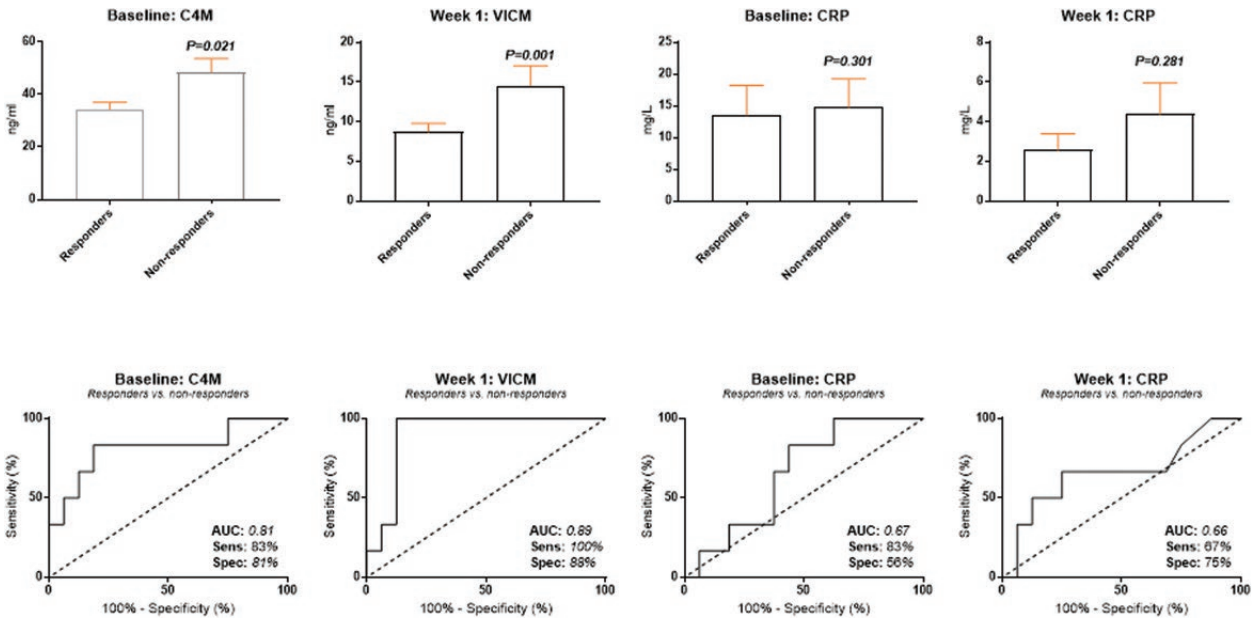
Background: Frequent bowel movement is a common symptom in ulcerative colitis (UC), and is usually accompanied by urgency. However, bowel urgency (BU) is not a component of UC activity indices commonly used. We assessed the prevalence of BU and its associated burden and impact in patients with UC using the 8-week (week) induction period of the upadacitinib trial U-ACHIEVE (NCT02819635).

Methods: This post hoc analysis evaluated data from adults with moderate to severe UC (adapted Mayo score [Mayo score without Physician Global Assessment] of 5–9 points and endoscopy subscore of 2–3) who randomly received upadacitinib or placebo



Abstract P281 –Figure 1. The figure depicts C4M, VICM, and CRP's ability to predict response at baseline or Week 1 after adalimumab treatment.

for 8 weeks. BU (yes/no) was collected in the patient daily diary. Number of days with BU over the most recent 3 days before study visits were calculated (BU days range: 0–3). Prevalence of BU and its impact on health-related quality of life (HRQOL) were assessed; inflammatory bowel disease Questionnaire (IBDQ) and Short Form 36 Health Survey (SF-36) scores were compared in patients with vs. without BU. At Week 8, number of BU days was compared between patients who achieved clinical response and remission based on adapted Mayo score and those who did not. Correlations between BU and clinical outcomes, HRQOL measures, and biomarker levels were evaluated using Spearman's correlation coefficients at Week 8.

Results: Among 250 patients, 83% reported experiencing BU over 3 days at baseline (71% for 3 days, 8% for 2 days, 4% for 1 day); 7% had no BU; and 10% had missing data. Pts with any BU days at baseline reported significantly impaired HRQOL in IBDQ and SF-36 Physical Component Summary (PCS) vs. no BU (Table 1). By Week 8, 28% reported no BU. Fewer BU days were observed in patients with vs. without clinical remission (0.52 vs. 1.80, $p < 0.001$); change in BU days from baseline to Week 8 was significantly greater in patients with vs. without a clinical response (–1.62 vs. –0.26; $p < 0.001$). BU days had a strong correlation with Mayo stool frequency subscore and IBDQ, and moderate correlation with Mayo endoscopic subscore, rectal bleeding subscore, faecal calprotectin levels, and high-sensitivity C-reactive protein levels (Table 2).

Table 1. Burden associated with bowel urgency on quality of life measures at baseline and Week 8 (as observed data).

Baseline Measures	BU day = 1 or 2 or 3 at Baseline (n=208)	BU day = 0 at Baseline (n=16)	p value
IBDQ score, mean ± SD	121.8 ± 32.4	142.1 ± 35.1	0.025 [a]
IBDQ ≥170, n (%)	14 (7%)	3 (19%)	0.090 [b]
SF-36 PCS, mean ± SD	41.6 ± 8.1	47.8 ± 6.6	0.005 [a]
SF-36 MCS, mean ± SD	40.9 ± 10.9	42.2 ± 14.1	0.584 [a]
Week 8 Measures	**BU day = 1 or 2 or 3 at Week 8 (n=106)**	**BU day = 0 at Week 8 (n=67)**	**p value**
IBDQ score, mean ± SD	152.18 (35.90)	186.70 (28.42)	<0.001 [a]
IBDQ ≥170, n (%)	43 (40.6%)	54 (80.6%)	<0.001 [b]
SF-36 PCS, mean ± SD	45.88 (8.47)	52.62 (5.22)	<0.001 [a]
SF-36 MCS, mean ± SD	44.20 (12.06)	50.93 (8.97)	<0.001 [a]

BU, bowel urgency; IBDQ, Inflammatory Bowel Disease Questionnaire; MCS, Mental Component Summary; PCS, Physical Component Summary; SD, standard deviation; SF-36, Short Form 36 Health Survey.
[a] Mann–Whitney U test.
[b] Chi-square test.

Table 2. Correlation of bowel urgency days and clinical outcomes, biomarker levels, and HRQOL at Week 8 (as observed data).

Measures	N	Spearman Correlation (95% CI)
Full Mayo score	206	0.59 (0.49, 0.68)
Mayo RBS	210	0.40 (0.27, 0.51)
Mayo SFS	210	0.55 (0.45, 0.65)
Mayo PGA	210	0.50 (0.38, 0.60)
Mayo endoscopic subscore	222	0.42 (0.30, 0.54)
IBDQ	214	–0.50 (-0.61, -0.38)
SF-36 PCS	214	–0.41 (-0.53, -0.28)
SF-36 MCS	214	–0.27 (-0.41, -0.13)
HS-CRP	231	0.34 (0.21, 0.46)
Fecal calprotectin	211	0.41 (0.28, 0.53)

BU, bowel urgency; CI, confidence interval; HRQOL, health-related quality of life; HS-CRP, high-sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; MCS, Mental Component Summary; PCS, Physical Component Summary; PGA: physician global assessment; RBS, rectal bleeding subscore; SFS, stool frequency subscore.
Estimates between 0 and 0.3 (-0.3) indicate weak convergent validity; 0.3 to 0.5 (-0.3 to -0.5) indicate moderate convergent validity, and > 0.5 (or <-0.5) indicate strong convergent validity

Conclusions: A high prevalence of BU (>80%) was observed in patients with moderate to severe UC. BU was correlated with UC disease activity and biomarker levels and had a high impact on patients' HRQOL. Improvements in BU paralleled clinical response and remission.

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Assessment of prothrombotic tendency in IBD pregnant patients and its associated risk factors

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Background: Inflammatory bowel diseases (IBD) are an established risk factor for thrombotic complications. IBD pregnant patients are at even greater risk for thrombosis. Nevertheless, the risk factors associated with this prothrombotic tendency among IBD parturient are not well-established. The objective of our study was to examine the characteristics associated with hypercoagulability in pregnant women with IBD.

Methods: A prospective cohort study, performed during 2017–2018 at a university hospital, of women attending a specialised, multi-disciplinary clinic for the preconception, antenatal and postnatal treatment of IBD women. Women were consecutively recruited and tested for thrombin generation, a global marker of the coagulation system, expressed as the endogenous thrombin potential (ETP).

Results: One hundred and forty-five women with IBD were enrolled in this study; 100 had Crohn's disease, 43 ulcerative colitis and 2 indeterminate colitis. The median age of this cohort was 29 [26–33] years. In univariate analysis that included all measured clinical and laboratory parameters, ETP levels were directly correlated with duration of pregnancy ($p < 0.0001$), disease activity as assessed by physician global assessment ($p = 0.005$), extra-intestinal involvement ($p = 0.04$), C-reactive protein level ($p < 0.0001$), erythrocyte sedimentation rate ($p < 0.0001$), white blood cell count ($p = 0.008$), body mass index ($p = 0.02$) and inversely correlated with haemoglobin level ($p < 0.0001$). ETP level did not correlate with any of the other clinical and laboratory characteristics assessed. In multivariate analysis, duration of pregnancy ($p < 0.0001$), active disease ($p = 0.009$), extra-intestinal involvement ($p = 0.02$) and body mass index ($p = 0.05$) were the only independent predictors of ETP level.

Conclusions: As determined by thrombin generation, IBD pregnant patients have an enhanced procoagulant potential which increased throughout gestation. This enhanced hypercoagulability was independently associated with disease activity, body mass index, and the

presence of extra-intestinal disease involvement. Future prospective studies are warranted to confirm our findings and better delineate the optimal antithrombotic prophylactic strategy in this setting

P285

Deep learning for automated detection of mucosal inflammation by capsule endoscopy in Crohn's disease

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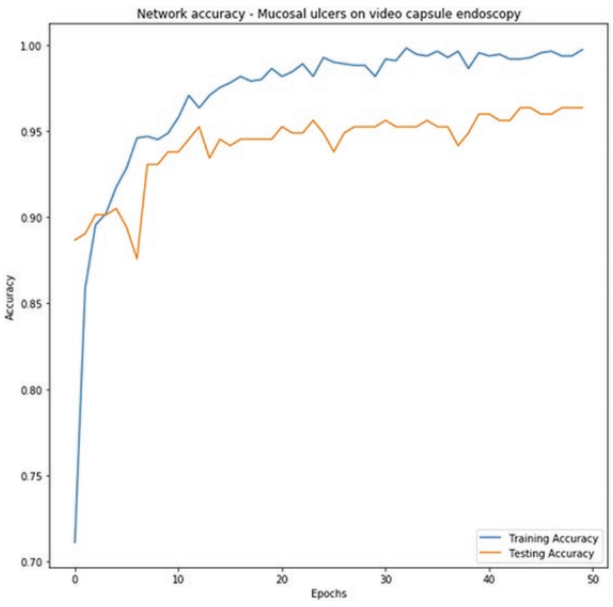
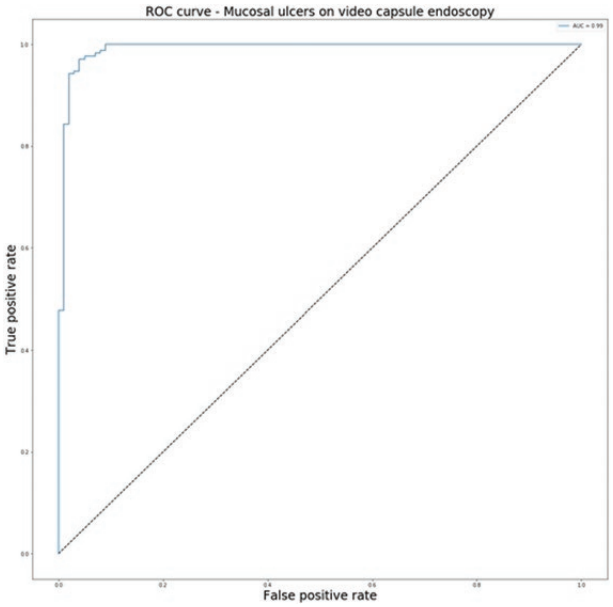
Background: Capsule endoscopy (CE) is a prime modality for diagnosis and monitoring of Crohn's disease. However, lack of standardisation and prolonged reading time are among the limitations of CE. Recent advancements in artificial intelligence deep learning algorithms present opportunity for utilising this technology in different medical tasks. Utilisation of deep learning techniques may allow for standardised and automated processing of capsule images.
The aim of our study was to evaluate the utility of a deep learning module for detection of small bowel ulcers on CE images.
Methods: We retrospectively collected capsule endoscopy images produced by SB III capsule (Medtronic). Each image was labelled by an expert gastroenterologists either as normal mucosa or containing mucosal ulcers. A state-of-the-art Xception Convolutional Neural Network classified images into either image of normal mucosa or images with mucosal ulcers. The network's weights were pre-trained on ImageNet data and training was limited to the top fully connected layers. Each capsule image was resized into a 299 × 299 matrix. A fivefold cross-validation, with an 80/20 training/testing split for each fold, was used to evaluate the mean area under the curve (AUC) and accuracy and Youden's index was used to find the models' best sensitivity and specificity for detecting images with mucosal ulcers.
Results: Overall, our dataset included 1363 capsule endoscopy images; 861 normal mucosa images and 502 mucosal ulcers images. Assessment of network training was conducted using plotting of loss and accuracy for training and testing data. The curves of the testing dataset closely follow the curves of testing datasets, which indicates a low degree of overfitting. The mean AUC, accuracy, sensitivity and specificity of the fivefold cross-validation tests for detection of small bowel ulcers were 0.992 ± 0.005, 0.959 ± 0.017, 0.969 ± 0.017, and 0.966 ± 0.023, respectively





Conclusions: Deep learning technology provides highly accurate automated detection of mucosal ulcers on capsule endoscopy CE images. This technology may allow for standardised and automated diagnosis and follow-up of Crohn's disease by CE in the near future.

P286

Bariatric surgery in inflammatory bowel disease: outcome and safety from a GETAID registry population

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Background: Morbid obesity increased in the past 2 decades including in the inflammatory bowel disease (IBD) population with up to 15 to 20% of obese IBD patients in Europe and 20 to 40% in the USA. Bariatric procedures dramatically changed the management of obesity. Few data are available on the feasibility and the safety of these procedures in the IBD population. The aim of this work was to assess the safety and the efficacy of bariatric surgery (BS) in IBD patients and to describe the outcomes of IBD after BS.

Methods: IBD patients with a history of BS were recruited in GETAID centres. The demographic and the disease characteristics were retrospectively reviewed. The type of BS, the early post-operative complications and the long-term IBD outcomes were recorded.
Results: In total, 57 patients (44 Crohn's disease, 12 ulcerative colitis and 1 unclassified colitis) from 14 GETAID centres underwent a BS after the diagnosis of IBD. At the time of BS the mean age was 39 years (SD ±11), the mean disease duration was 122 months (SD ±77) and 42% were on biologic therapy. The BS was a sleeve gastrectomy in 44/57 (77.2%), an adjustable gastric banding in 10/57 (17.5%) and a gastric bypass in 3/57 (5.3%). Five patients (8.8%) experienced an early post-operative complication including 1 abscess with septic shock, 1 stricture of the sleeve with secondary bypass, 1 bypass converted to sleeve for peroperative technical reasons, 1 abdominal wall infection and 1 banding narrowing. The mean weight and BMI at the time of BS were 120 kg (SD ±19) and 42 kg/m^2 (SD ±5.7), respectively. The mean weight loss at maximal follow-up (median: 37.8 months–SD ±35.6) post-BS was 28.3 kg (SD ±15). Regarding IBD outcomes, 12 (21%) patients required a treatment modification during the follow-up period, 1 was operated for an IBD flare (ileo-caecal resection for active Crohn's disease) and 3 experienced new perianal lesions. Anaemia was more frequent after BS (14.3% vs. 5.3% pre-BS).
Conclusions: In the IBD population, BS is feasible and the sleeve gastrectomy has become the most common procedure. Close to 10% of early post-operative complications were observed in our cohort. The course of IBD was stable after the procedure with low rates of IBD complications and treatment escalations.

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The clinical utility of low radiation dose computed tomography as a first-line investigation for evaluation of small bowel pathology

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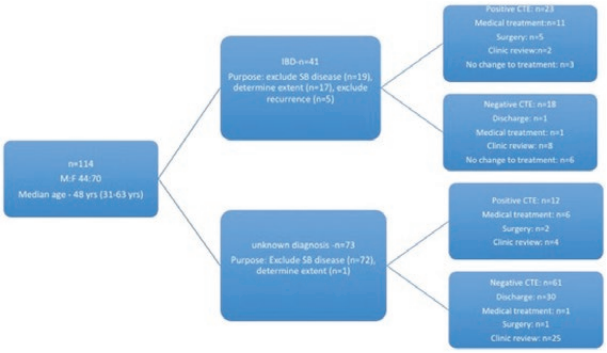
Background: Small bowel cross-sectional imaging is usually performed with either magnetic resonance (MRE) or computed tomography enterography (CTE). Whilst MRE avoids exposure to radiation, CTE is faster, cheaper and employs a shorter image acquisition time that results in less motion artefact and better resolution. However, concern regarding radiation exposure has resulted in clinicians preferring MRE. The aim of this study was to determine whether a low radiation dose CTE was effective at identifying small bowel pathology.
Methods: Retrospective review of all patients undergoing CTE at our institution from November 2015 to June 2018. A low radiation dose CTE protocol was devised which involves a portal venous phase CT scan with oral contrast (gastrografin). Data on CTE outcomes and subsequent need for further imaging were obtained from electronic case records.
Results: 114 patients were included (M:F 44:70, median age 48 years). Forty-one had known inflammatory bowel disease (34 Crohn's disease, 2 ulcerative colitis, 5 indeterminate colitis). CTE was performed successfully in 100/114 (88%) patients. In 14, there was poor small bowel opacification with limitations on image quality. All patients tolerated the procedure well. In comparison, there were 4/114 patients who could not tolerate MRE. Mean radiation exposure was 281 mGy/cm compared with 523 mGy/cm for conventional CT abdomen and pelvis.



Outcomes of patients undergoing CTE.
The sensitivity, specificity, positive predictive value, and negative predictive value of CTE was 93.5%, 92.8%, 82.9%, and 97.5%, respectively. Overall, 19/114 (17%) patients underwent further imaging within 12 months of CTE, which included MRE (n = 7), CT abdomen/pelvis (n = 4) and capsule endoscopy (n = 8). In total, 8 patients underwent surgical resection, with operative findings matching imaging in 7 (88%). In patients not known to have small bowel disease, CTE was diagnostic in 12/73 (16%) patients. In those with negative findings, 30/61 (49%) were discharged from further follow-up; 25/61 (41%) remain under clinical review; and 1 (1.6%) patient has been started on treatment for inflammatory bowel disease based on colonoscopy findings prior to CTE.
Conclusions: Our results suggest CTE is a valuable imaging modality, particularly as a first-line investigation to exclude small bowel pathology. It is well tolerated and has a low failure rate. Subsequent small bowel imaging in those patients diagnosed with Crohn's disease can be with MRE to decrease cumulative radiation exposure.

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Is there any value of preoperative small bowel evaluation in patients with ulcerative colitis about to undergo ileal pouch-anal anastomosis?

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Background: Ileal pouch-anal anastomosis (IPAA) is the standard operative approach to ulcerative colitis (UC) patients requiring surgery for medically refractory disease or dysplasia. Despite excellent long-term outcomes, pouchitis or *de novo* Crohn's disease (CD) are adverse outcomes that occur frequently after IPAA. Little is known regarding the utility of small bowel evaluation (SBE) before IPAA. The aim of this study was to assess the value of preoperative SBE in predicting adverse outcomes in UC patients undergoing IPAA.
Methods: Consecutive UC patients undergoing IPAA between 2000 and 2017 were identified. SBE included endoluminal imaging via wireless capsule endoscopy (WCE) or radiographic imaging via small bowel follow through (SBFT), magnetic resonance enterography (MRE), or computed tomography enterography (CTE). Abnormal preoperative imaging alone without other clinical manifestations was not sufficient for the diagnosis of CD or inflammatory bowel disease unclassified (IBDU), both of which were excluded. Adverse

outcomes were assessed prospectively and included no pouchitis (NP), acute pouchitis (AP; antibiotic responsive), chronic pouchitis (CP; antibiotic dependent/resistant) or *de novo* CD (five or more mucosal ulcers proximal to the ileal pouch or perianal complication 3 months after ileostomy closure).

Results: Of the 328 study patients, 190 (58%) had preoperative SBE and 138 (42%) had no preoperative SBE. Preoperative SBE included WCE (n = 72), SBFT (n = 64), CTE/MRE (n = 54). Only 19 (10%) patients with preoperative SBE had an abnormal study. Clinical and disease characteristics were not statistically different between patient groups with or without preoperative SBE. After a median follow-up of 41 (range 3–260) months, outcomes included AP (n = 58; 18%), CP (n = 27; 8%) and *de novo* CD (n = 50; 15%). There was no significant difference in AP, CP, or *de novo* CD between patient groups with or without preoperative SBE (p = 0.17). Additionally, there were no significant associations between any abnormal preoperative SBE study and the incidence of AP, CP and *de novo* CD (p = 0.19).

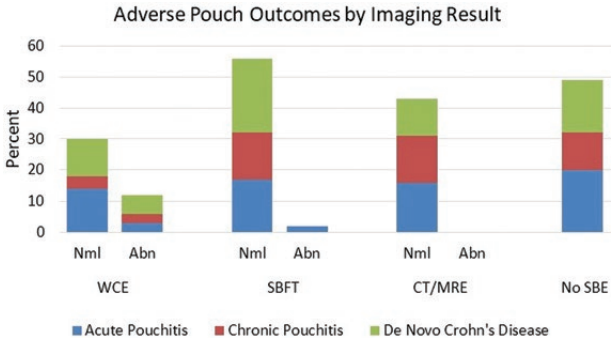

Figure 1. Adverse pouch outcomes by imaging result. Nml: normal, Abn: abnormal, WCE: wireless capsule endoscopy, SBFT: small bowel follow through, CT/MRE: computed tomography/magnetic resonance enterography, SBE: small bowel evaluation. All $p > 0.05$.

Conclusions: In this largest to date prospective series investigating the value of preoperative SBE in UC, only 10% of patients had an abnormal study. Outcomes of IPAA were not significantly different between UC patients with or without preoperative SBE, nor were they different between patients with abnormal and normal preoperative SBE. Taken together, there appears to be little value in performing preoperative SBE in UC patients about to undergo IPAA.

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The initial development of a Chat-Bot for inflammatory bowel disease (IBD) patients for use in e-health applications

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Background: The emergence of Chat-Bots in healthcare through mobile applications is fast-approaching. A Chat-Bot is a natural language processor that attempts to simulate a conversation with a human user. While there have been many attempts to develop Chat-Bots that interpret and triage common symptoms and ailments, data on the feasibility of Chat-Bot development for chronic diseases like inflammatory bowel diseases (IBD) is scarce. In this study, we attempt to explore the feasibility of creating a Chat-Bot specifically for patients with IBD by categorising retrospective electronic dialogue data between patient and healthcare providers (HCP).

Methods: We used electronic dialogue data collected between 2013 and 2018 from a care management platform (eIBD) at a tertiary referral centre for IBD at the University of California, Los Angeles (UCLA). The platform includes a portal for providers and a mobile application with messaging functionality for patients. We focussed on patient to HCP dialogues only. A sample of the data were manually reviewed and an algorithm for categorisation was established. This algorithm was applied to the entire set via programming code. We successfully placed all relevant dialogues into a number of categories. Additionally, we tested the accuracy of our program by having three independent doctors evaluate the appropriateness of the categorisation by manually categorising 100 lines of randomly picked dialogue and comparing it to the categorisation of our algorithm.

Results: In total, 16453 lines of dialogue from 1712 patients interacting with 3 IBD physicians, 3 nurses and 3 administrative assistants were collected. 8324 of these were patient to HCP interactions and we determined that 6193 were relevant for our categorisation. Ultimately, we were able to categorise the messages into seven categories, there was overlap in these categories, so we measured their frequencies independently into: symptoms (32.8%), medications (38.7%), appointments (24.5%), labs (34%), finance/insurance (7.2%), communications (34.9%), procedures (10%), and miscellaneous (10%). Additionally, our algorithm showed 94% similarity in categorisation compared with our three independent physicians.

Conclusions: With increased adaptation of electronic health (e-health) technologies, Chat-Bots could have great potential in interacting with patients, collecting data, and increasing efficiency. Our categorisation showcases the feasibility of using large amounts of electronic dialogue for the development of a Chat-Bot algorithm. Text-based Chat-Bot interventions in healthcare for chronic diseases such as IBD would allow for the monitoring of patients beyond consultations and potentially empower and educate patients and improve clinical outcomes.

P290

Compliance to vaccination guidelines in patients with immune-mediated inflammatory diseases: a cross-sectional, single-centre study

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Background: Despite the elevated risk for vaccine-preventable diseases and infection-related complications in patients with immune-mediated inflammatory diseases (IMID), vaccination coverage is still far from optimal. In 2015, we reported that only 32% of our patients with inflammatory bowel disease (IBD) were completely vaccinated according to guidelines.[1] We evaluated the evolution of vaccination coverage between 2015 and 2018 in IBD patients, and compared the current coverage with other IMID patients.

Methods: Between August 2018 and October 2018, the vaccination status of 829 consecutive IMID patients (43% male, median age

50 years) was collected at the outpatient clinics of a tertiary referral centre (63% gastroenterology, 34% rheumatology, 3% dermatology). A one-page vaccination questionnaire was completed by the treating physician and reasons for non-vaccination were recorded. Missing data were added after contact with the general practitioner.
Results: Among IBD patients, vaccination rates had increased significantly from 2015 to 2018, namely 62% vs. 74% for pneumococci ($p < 0.001$), 53% vs. 67% for hepatitis B ($p < 0.001$), and 32% vs. 45% for all vaccines ($p < 0.05$) (see Image 1). One hundred and one patients were included in both IBD cohorts. Sixty-seven were not completely vaccinated according to guidelines in 2015 and 30 of them (45%) changed vaccination behaviour in the last 3 years. Analysis of the current vaccination status demonstrated that overall 39% of the IMID patients were completely vaccinated according to guidelines (see Image 1). Vaccination rates were significantly greater in IMID patients followed at the gastroenterology department vs. patients followed at rheumatology, namely 74% vs. 36% for pneumococci ($p < 0.001$), 67% vs. 45% for hepatitis B ($p < 0.001$), 82% vs. 73% for tetanus ($p < 0.01$), and 45% vs. 27% for complete vaccination according to guidelines ($p < 0.001$) (see Image 1). Regarding dermatology patients, IBD patients more frequently received a hepatitis B vaccination (67% vs. 46%, $p < 0.05$). Scepticism (24% for influenza) and non-awareness (47% for pneumococci, 38% for hepatitis B and 42% for tetanus booster) were the most commonly reported reasons for non-vaccination.

	DERMATOLOGY (n=26)	RHEUMATOLOGY (n=283)	IBD (n=520)	ALL IMID PATIENTS (n=829)	IBD 2015 (n=505)	IBD 2018 (n=520)
Influenza	77%	69%	76%	74%	80%	76%
Pneumococcus	65%	36%	**74%**[b]	61%	62%	**74%**[d]
Hepatitis B*	46%	45%	**67%**[a,b]	60%	53%	**67%**[d]
Tetanus	79%	73%	**82%**[c]	79%	82%	82%
All vaccines	46%	27%	**45%**[b]	39%	32%	**45%**[e]

* recommended in all seronegative IBD patients and in rheumatology/dermatology patients at risk
[a] p<0.05 compared to dermatology
[b] p<0.001 compared to rheumatology
[c] p<0.01 compared to rheumatology
[d] p<0.001 compared to IBD 2015
[e] p<0.05 compared to IBD 2015

Vaccination rates.
Conclusions: Approximately 40% of all IMID patients were completely vaccinated according to guidelines. Although recent efforts on vaccination education in IBD patients have significantly improved vaccination rates, there is still need for awareness in both patients and healthcare professionals.

Reference

1. Coenen S, Weyts E, Jorissen C, *et al*. Effects of education and information on vaccination behavior in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2017;23:318–24.

P291

Improvements in access to IBD care following the implementation of a novel tiered triage model

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Background: Inflammatory bowel disease (IBD) requires early disease identification and close monitoring of disease activity. Centralised referral systems offer benefits in reduced wait times and opportunities for refinements in referral management. The Vancouver Island IBD Clinic obtains referrals through the regional gastroenterology (GI) group which receives an average of 750 referrals per month. In 2018, our intake system, GI Central Access and Triage (GICAT), was migrated onto a new platform within our electronic medical record allowing us to optimise referral management system-wide. As part of innovative changes to GICAT, we initiated distribution of all IBD referrals directly to IBD specialists for immediate triage. Along with review and prioritisation, immediate specialist triage facilitates proactive ordering of subsequent tests such as faecal calprotectin in a 'tiered' triage model to further refine referral management decisions. The aim of this study was to evaluate the short-term impact of our novel electronic tiered triage model on the processing of IBD referrals.
Methods: Referrals received by central fax were immediately distributed to GIs for triage, requiring identification of referral indication, pathway, urgency, and outstanding information or lab testing. Referrals were then expedited or returned to a common pool for distribution, with triages displayed on a real-time dashboard. Outstanding information was requested either prior to triage completion or scheduling. To understand enhancements to referral refinement, timing of referrals received and cancelled was measured over 10 months following implementation, as were changes to urgency and requests for information or testing. The number of weeks to initial consult for urgent IBD referrals and from referral date to GI triage were compared 6 months pre and post-implementation.
Results: In the first 10 months following the transition to GICAT, 7940 referrals were received with 18% per cent immediately cancelled or redirected via GICAT. Immediate triage facilitated requests for information and testing prior to consult in 29% of cases and changes to urgency in 62%. Time-to-triage was on average 22 weeks shorter for IBD referrals (24.3 vs. 2.2 weeks; $p < 0.001$) post-implementation. Wait times for urgent IBD consults were 2.4 weeks shorter in the post implementation audit (3.9 vs. 6.3; $p = 0.044$).
Conclusions: The transition to a novel triage management system decreased both time-to-triage and urgent wait times for IBD referrals. This process also expedited proactive testing, changes to urgency, and cancellation of inappropriate referrals. Centralised electronic tiered referral systems show great potential as innovative platforms for the rapid adaptive triage of IBD referrals in high volume centres.

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Immunomodulator and biological therapy are increased in inflammatory bowel disease patients with associated immune-mediated inflammatory diseases

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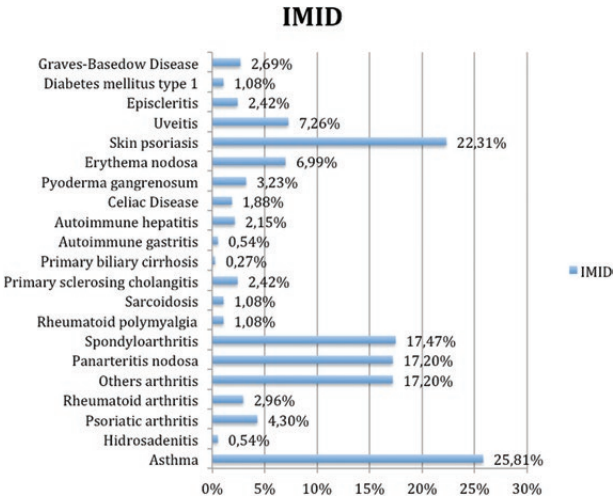
Background: Immune-mediated diseases (IMIDs) include a heterogenous group of chronic diseases that are characterised by the loss of the immune system tolerance causing inflammation and organs tissue damage. Inflammatory bowel diseases (IBD) belong to IMIDs group together with other autoimme diseases. Literature data showed an IMID prevalence of 9–15% in IBD, depending of the region studied. The objective of our study is to describe the prevalence and influence of IMIDs in IBD.

Methods: A retrospective and descriptive study was designed to evaluate the influence of IMIDs in IBD. In total, 1448 IBD patients were studied to evaluate the different clinical characteristics and evolution course of the disease depending on the associated IMIDs

Results: In total, 1448 patients were analysed of whom 46.96% (n = 680) were diagnosed with Crohn's disease, 48.34% (n = 700) with ulcerative colitis and 4.7% (n = 68) with IBD unclassified. A IMID prevalence of 25.69% (n = 372) was present in IBD patients compared with 74.31% (n = 1076) of IBD patients without IMIDs. The most prevalent IMIDs were intrinsic asthma and skin psoriasis following rheumatoid conditions.



Prevalence of IMID's in inflammatory bowel diseases.

An increased risk of IMIDs was observed in IBD women (OR 1.37 (IC 95%: 1.07–1.75) p = 0.009). Furthermore, more proportion of IMIDs patients was observed in Crohn's disease compared with ulcerative colitis (OR 1.32 (IC 95% 1.03–1.70) p = 0.02). It is important to highlight that IMIDs patients had a higher intestinal perforation risk than other patients (OR 2.72 (IC 95%: 1.04–7.09), p = 0.04). Extraintestinal manifestations were associated with IMIDs group and they also required more immunomodulator (OR 1.70 (IC 95%: 1.33–2.17), p = <0.01) and biological therapy (OR 2.03 (IC 95%: 1.56–2.63) $p \leq 0.01$).

	IMID (%)	NO IMID (%)	OR	P
Sex: Women	55.11	47.21	1.37 (1.07 – 1.75)	0.009*
Smoker	20.67	17.59	1.05 (0.81 - 1.38)	0.463
Crohn's Disease	52.69	44.98	1.32 (1.03- 1.70)	0.020*
Complications	8.03	6.29	1.3 (0.79- 2.08)	0.255
Perforation	2.15	0.84	2.6056 (0.87 - 7.67)	0.043*
Immumodulator therapy	49.46	36.52	1.70 (1.33 - 2.17)	<0.000*
Biogical therapy	37.63	22.96	2.03 (1.56 - 2.63)	<0.000*
Surgery	21.77	19.33	1.2 (0.89 - 1.62)	0.309

Odss ratio of clinical characteristics and therapy.

No statistically significant association was observed between IMIDs patients and clinical characteristics of the disease or IMIDs patients and smoking habit. Age or evolution time of the disease was neither correlated to suffering IMIDs.

Conclusions: (1) There is an increased IMIDs prevalence in IBD patients. (2) Crohn's disease patients and women have a higher risk of associated IMIDs to their IBD. (3) IBD patients with associated IMIDs require more immunomodulator therapy or biological therapy to control their disease, probably caused by a more aggressive course of IBD. (4) More studies are necessary to increase the knowledge in IBD patients with associated IMIDs.

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Prognosis of small intestinal ulcers (SIUs) on capsule endoscopy when magnetic resonance enterography is normal

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Background: Small intestinal ulcers (SIUs) are often identified during capsule endoscopy (CE) in patients whose MR enterography (MRE) is normal during evaluation of established, or suspected, Crohn's disease. The prognostic implications of SIUs in this setting are unknown.

Methods: We undertook longitudinal follow-up on a cohort of patients at two academic centres. CE databases were used to identify patients with SIUs and linked to the electronic medical record to identify patients with an MRE within 12 months of the CE study. This cohort was further narrowed to patients with established or suspected Crohn's disease based on ordering details for the CE study. Follow-up data on hospitalisations, emergency visits and clinic visits after the CE study was collected in this cohort. Dichotomous data were analysed by 2 × 2 tables and ×2 or Fisher exact test for significance.

Results: We identified 85 subjects with established or suspected CD, a normal MRE, and a completed CE study. Of these, 35 had SIUs (CE+), and 50 did not have SIUs (CE-). Table 1 summarises their baseline characteristics; mean ESR and CRP were similar in both groups. The mean duration of follow-up was 40 months ±27 months. In patients with established CD, CE+ patients had non-significant differences in rates of healthcare visits to CE- patients (60% vs. 45%, p = 0.4), and similar rates of hospitalisation (29% vs. 13%, p = 0.3). In contrast, amongst all patients investigated, CE+ patients were more likely to be hospitalised during follow-up (16% vs. 2%, p = 0.02), or require healthcare visits (49% vs. 16%, p = 0.001) than CE- patients.

Conclusions: Symptomatic patients with SIUs on CE, but normal MRE, have increased healthcare utilisation when compared with those without SIUs. Further studies would be required to determine whether this cohort would benefit from therapeutic intervention.

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Microscopic colitis: a missed opportunity to diagnose during colonoscopy

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Background: British Society of Gastroenterology (BSG) guidelines on chronic diarrhoea state biopsies should be taken from both the left and right colon to exclude microscopic colitis (MC). There is a paucity of work assessing biopsy adherence rates, and whether this is influencing detection of MC.
Methods: A UK study from 2 hospitals in South Yorkshire of retrospectively collected data between 2007 and 2017 of all patients referred for colonoscopy with chronic diarrhoea, IBS type symptoms or suspected inflammatory bowel disease (IBD). Data were analysed using IBM SPSS v25 to complete χ^2 where required. Data were also collected on patients diagnosed with MC.
Results: A total of 10 015 lower gastrointestinal endoscopies (84.3% colonoscopies and 15.7% flexible sigmoidoscopies) were performed (59.3% female, median age 57 years, IQR 43–69 years). Colonoscopies were performed for investigation of chronic diarrhoea, IBS-diarrhoea (IBS-D), IBS-mixed (IBS-M), or suspected IBD (22.4%, 59.0%, 14.6% and 3.9%). Cancer exclusion pathways accounted for 28.3% of patients. Endoscopies were performed by consultants, trainees, clinical nurse specialists (CNS), and others including GPs (34.3%, 31.6%, 30.4%, and 3.7%, respectively). In total, 19.5% of colonoscopies conformed to biopsy guidelines. In the other cases biopsies were taken from incorrect sites including: only left or right sides of the colon, the rectum and randomly (15.8%, 10.7%, 24.2%, and 58.7%, respectively). In 8.6% of colonoscopies, no biopsies were taken. There was a significant difference in the adherence to guidelines by consultants, trainees, CNS and others including GPs (11.6%, 17.8%, 29.2%, 18%, respectively, $p < 0.005$). CNS also adhered to guidelines significantly more often than gastroenterologists and general surgeons (29.2% vs. 19.1% and 6.8%, respectively, $p < 0.005$). Patients on cancer exclusion pathways were less likely to have biopsies as per guidelines (16.8% vs. 20.0%, $p < 0.005$). The highest adherence to guidelines (48%) occurred in a subgroup of IBD where the indication was to rule out MC. The adherence to biopsy guidelines differed for chronic diarrhoea, IBS-D, IBS-M, or IBD (17.1%, vs. 20.7%, 14.8%, 31.5%, respectively, $p < 0.005$). In the same study period, 402 patients had been diagnosed with MC of which 24.4% had at least 1 previous colonoscopy, which may be a missed opportunity to diagnose MC.
Conclusions: Biopsies are not currently taken in accordance with guidelines, which may cause delays or missed diagnoses of MC. This is likely to impact estimates of the prevalence of this disease. This study suggests the importance of classifying MC as a subtype of IBD to improve the adherence to guidelines in patients presenting with chronic diarrhoea or IBS type symptoms.

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Impact of superimposed cytomegalovirus infection on the outcomes of ulcerative colitis flare-up

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Background: The aim of this study was to identify the impact of CMV infection on disease outcome of UC flare-ups and to investigate clinical significance of CMV viral load and antiviral treatment during UC flare-ups.
Methods: We retrospectively searched the electronic pathologic database of our tertiary academic hospital. Between January 2007 and July 2017, all colonoscopic biopsies specimens that were assessed for CMV infection were evaluated. CMV colitis was diagnosed as having one or more positive inclusion bodies on histological tests including H&E stain or immunohistochemical stain (IHC) in colonic tissues. CMV viral load was classified as low- or high-grade (5 or more inclusion bodies per section). To classify the CMV viral load, a single, independent gastrointestinal pathologist prospectively reviewed all biopsy specimens. We investigated long-term disease outcomes of UC patients with flare-ups according to their CMV infection status. Poor outcomes were defined as the following: hospitalisation, colectomy, or death. Subgroup analysis was performed according to CMV viral load and antiviral treatment status.
Results: Among 844 cases with final pathologic results for their CMV status, a total of 257 patients with moderate-to-severe UC flare-ups were finally included. Mean age was 43.20 ± 14.68 years and 56.4% were male. Their median follow-up duration was 46 ± 39.01 months. CMV colitis were diagnosed in 36 patients (prevalence of 14%). Compared with patients without CMV colitis, both mean age and mean age at diagnosis were higher in patients with CMV colitis (all $p < 0.001$). The patients with CMV colitis showed significantly higher disease activity by total Mayo score and Mayo endoscopic sub-score (all $p < 0.05$), when compared with those without CMV colitis. Additionally, the patients with CMV colitis were more likely to receive systemic steroids, immunosuppressants, and anti-TNF agents (all $p < 0.5$). Collectively, CMV infection was an independent predictor of poor outcomes (Hazard ratio 2.27, 95% confidence interval 1.12–4.60) and the cumulative probability of poor outcome was significantly higher in the CMV positive group ($p < 0.001$, log-rank test). Twenty-three patients of CMV colitis was graded as low density and 13 patients were high grade. No significant difference was observed in clinical outcome according to CMV density. Despite successful initial treatment with antiviral agents, the rates of CMV recurrence (57.14% vs. 22.73%; $p = 0.0361$) and hospitalisation (22.73% vs. 64.29%; $p = 0.0126$) were higher in the treated group.
Conclusions: Superimposed CMV colitis is an independent predictor of poor outcome in moderate to severe UC flare-ups. Antiviral agent does not seem to improve the long-term outcome of UC patients regardless of CMV load.

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Effect of upadacitinib on patient-reported symptoms by the new Ulcerative Colitis Symptoms Questionnaire (UC-SQ) in patients with moderate to severe ulcerative colitis: data from the Phase 2b study U-ACHIEVE

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Background: The Ulcerative Colitis Symptoms Questionnaire (UC-SQ) is a new disease-specific instrument developed to assess patient-reported outcomes in UC. We examined the impact of upadacitinib (UPA) on patient-reported outcomes utilising the UC-SQ in an 8-week (week) Phase 2b induction study (U-ACHIEVE, NCT02819635).
Methods: Adults with moderate-to-severe UC (defined by adapted Mayo score [Mayo score without Physician Global Assessment] 5–9 points and Mayo endoscopy subscore 2–3) were randomised to receive extended-release UPA 7.5, 15, 30, 45 mg once daily (QD) or placebo (PBO) for 8 weeks. The UC-SQ contains a 17-item assessment of intestinal and extra-intestinal symptoms such as bowel movements, abdominal pain, blood/mucus in stool, fatigue, and difficulty sleeping. Items are rated on a five-point Likert scale to assess the frequency/intensity of individual symptoms. Overall scores of UC-SQ range from 17 to 85; higher scores indicate greater symptom burden. Patients at selected study sites completed the UC-SQ at baseline (BL) and Week 2, 4, and 8. Mean change from BL was calculated for UC-SQ total score and individual items at Week 2, 4, and 8; comparisons between UPA dosage groups and PBO were based on analysis of covariance, and missing data were imputed with the last observed value.
Results: A total of 110 patients completed the UC-SQ questionnaire. At BL, >50% of patients reported often or always having a sudden/intense need to have a bowel movement (73%), blood in stool (62%), diarrhoea (59%), difficulty sleeping (55%), mucus in stool (54%), or felt tired/lack of energy (53%). At Week 2, 4, and 8, respectively, significant improvement (decrease in mean score from BL, $p < 0.05$) was observed in UC-SQ total score in patients receiving UPA 15, 30, and 45 mg QD vs. PBO (table). Significant improvements were seen as early as Week 2 in the majority of the individual items of the UC-SQ in patients receiving UPA 30 and/or 45 mg QD vs. PBO, including intestinal symptoms of blood in stool, mucus in stool, bowel movement frequency, urgency for bowel movement, need for bowel movement even if bowel is empty, abdominal pain, and rectal pain. A positive impact on fatigue and sleep quality was also observed in patients receiving UPA vs. PBO.

Table. Mean change from baseline in UC-SQ total score and individual items at Week 8 (LOCH).

	PBO n=22	UPA 7.5 mg QD n=21	UPA 15 mg QD n=25	UPA 30 mg QD n=23	UPA 45 mg QD n=19
UC-SQ total score	−6.0	−9.3	−15.2*	−20.6*	−15.3*
Intestinal symptoms					
Have blood in stool	−0.6	−0.9	−2.0*	−1.8*	−1.9*
Have mucus in stool	−0.2	−1.0	−1.4*	−1.8*	−1.8*
Bowel movement frequency	−0.3	−1.1*	−1.4*	−1.6*	−1.6*
Have diarrhea	−0.4	−0.7	−1.3*	−1.9*	−1.5*
Have a sudden or intense need to have a bowel movement	−0.5	−0.5	−1.2*	−1.7*	−1.5*
Need for bowel movement even if bowel is empty	−0.5	−0.8	−0.8	−1.6*	−1.3*
Loss of appetite	−0.3	−0.3	−0.6	−1.0	−0.9*
Have abdominal pain	−0.4	−0.8	−1.1*	−1.6*	−0.8
Have rectal pain	−0.3	−0.3	−0.6	−1.5*	−0.6
Have cramping	−0.7	−0.5	−0.7	−1.8*	−0.5
Feel nauseated	−0.1	0.0	−0.3	−0.9*	−0.5*
Pass gas more than usual	−0.6	−0.5	−0.6	−0.5	0.5
Experience bloating	−0.4	−0.5	−0.4	−0.6	−0.4
Were constipated	0.0	−0.2	0.0	−0.5	−0.3
Extra-intestinal symptoms					
Feel tired or lack energy	−0.6	−0.2	−1.2	−1.5*	−0.8
Have difficulty sleeping	−0.3	−0.6	−1.2*	−1.1*	−0.9
Have joint pain	0.2	0.0	−0.3	0.1	−0.5

*p<0.05 treatment group vs PBO. LOCF: last observations carry over; UC-SQ: ulcerative colitis symptom questionnaire. P values for UC-SQ score are from analysis of covariance with treatment, randomisation factors (previous biologic use, baseline corticosteroid use, and baseline adapted Mayo score [≤7 and >7]), and UC-SQ baseline value as covariates.

Conclusions: More than half of UC patients suffered in both intestinal and extraintestinal symptoms. Patients with moderate-to-severe UC treated with 8-week induction UPA therapy vs. PBO reported a reduction in UC-related symptoms and in the impact of these symptoms on their lives.

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The change of bone mineral density in patients with inflammatory bowel disease

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Background: There is limited data regarding the impact of treatment for IBD on the BMD status. Therefore, this study aimed to identify the change of BMD in the patients with IBD after treatment including 5-aminosalicylic acid, thiopurine, and anti-TNF agents.
Methods: The cases were retrieved from 442 patients who were diagnosed with IBD in a single university hospital. Of those, 119 patients (CD 84, UC 35) had the follow-up BMD with at least 1-year interval. The associations between BMD, BMI and disease activity parameters including CDAI, Mayo-score, haemoglobin (Hb), c-reactive protein(CRP), serum albumin were evaluated as Pearson correlation analysis and partial correlation; BMD was measured as Z- score and low BMD was defined as less than −1.
Results: In enrolled 84 patients with inactive CD, the baseline mean of BMD Z score at the lumbar spine and femur neck were −0.44 ± 1.36, −0.13 ± 1.28; the follow-up mean of BMD Z score at the lumbar spine and femur neck were −0.47 ± 1.21 ($p = 0.512$), −0.18 ± 1.17 ($p = 0.304$). In enrolled 35 patients with inactive UC, the baseline mean of BMD Z score were −0.20 ± 1.04, −0.11 ± 1.06; the follow-up mean of BMD Z score at the lumbar spine and femur neck were −0.26 ± 1.05 ($p = 0.145$), −0.08 ± 1.06 ($p = 0.633$). The proportion of low BMD patients of CD and UC at the baseline were 30(35.7%), 11(30.6%); the number of low BMD patients with CD and UC at the disease controlled-status were 31(36.9%, $p = 0.873$), 9(25%, $p = 0.599$), respectively. Only in the low BMD group of CD, the BMD of femur neck was correlated with BMI, Hb, CRP, and albumin. (0.517: $p = 0.003$, 0.423: $p = 0.02$, −0.394: $p = 0.031$, 0.378: $p = 0.039$). However, there was no correlation with disease activity parameter and BMD status in partial correlation, using BMI as control variable.
Conclusions: There is no correlation with improvement of disease and BMD status after treatment in patients with IBD. However, in low BMD group of CD, treatment itself could improve the status of BMD of femur neck.

P298

Wall thickness ratio, a new magnetic resonance parameter, predicts the outcome of biological therapy in patients with ileal and ileocolonic Crohn's disease

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Background: Magnetic resonance enterography (MRE) is a non-invasive useful tool for assessing the transmural and extraintestinal lesions in Crohn's disease (CD). The absolute measure of transmural healing (TH) has been recently associated to improved long-term outcome in CD. However, a not negligible proportion of patients responding to biological therapy does not achieve TH. The aim was to identify a new MRE parameter assessing clinical outcome of biological therapy in patients with active ileal or ileocolonic CD.

Methods: Consecutive patients with ileal or ileocolonic involvement, attending our IBD unit and scheduled for anti-TNF (Infliximab, Adalimumab) or anti-integrin therapy (Vedolizumab), were enrolled. All patients underwent MRE at baseline (T0) and after 1 year (T1). CRP and Harvey–Bradshaw index (HBI) were measured at T0, T1, and after 2 years of treatment (T2). Non-response to therapy was defined at T2 as: <3-point change in HBI (T0-T2), need for steroids, optimisation/change of treatment or surgery. TH, defined as wall thickness ≤3 mm without ulcers, oedema, enhancement and complications, was evaluated by MRE at T1. Wall thickness ratio (WTR) was calculated as wall thickness (mm) at T1/wall thickness at T0.
Results: A total of 103 patients were enrolled: 56 were responders and 47 non-responders to biological therapy after 2 years of treatment. The median (±interquartile range) values of CRP and HBI were 15.0 mg/l [2–19] and 8.27 mg/l [6–10] at T0, 8.92 mg/l [1–4] and 4.95 [2–7.5] at T1 and 3.73 mg/l [1–4.5] and 4.54 mg/l [2–7.25] at T2. Overall, 16 out of 56 responders and 3 out of 47 non-responders achieved TH (28% and 6%, respectively, $p < 0.01$). Mean (±SD) WTR was 0.64 ± 0.23 in responders and 0.97 ± 0.26 in non-responders. According to the upper value of 95% confidence interval in non-responders, the WTR cut-off value of 0.87 was calculated. Therefore, 44 (78%) responders had a WTR < 0.87 and 20 (74%) non-responders had a WTR >0.87. In the group of responders, the proportion of patients with a WTR <0.87 was significantly higher than the proportion of patients achieving TH (78% vs. 28%, $p < 0.01$). The presence of a WTR <0.87 at T1 was significantly associated to a response to biological therapy at T2 (RR 3.6, 1.7–7.2) with a sensitivity of 74% and a specificity of 77%. Positive and negative predictive values were 71% and 80%, respectively.
Conclusions: Wall thickness ratio appears to be a useful MRI variable as it discriminates responders to biological therapy, also in patients not achieving transmural healing. This novel variable accurately predicts a favourable response to biological therapy in CD patients and may be considered a useful parameter for monitoring patients during therapy.

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A novel ileocolonic Crohn's staging tool: the development and validation of an evidence-based, end-user informed radiological decision-aid

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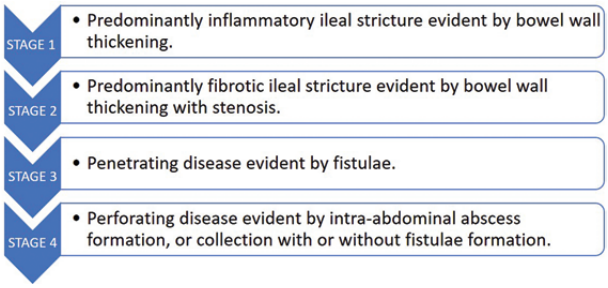
Background: Consensus guidelines emphasise the importance of multi-disciplinary team driven care for patients with complex Crohn's disease (CD). There are, however, no clear definitions of complex ileocolonic CD beyond the presence or absence of preoperative intra-abdominal sepsis. This study aims to develop a staging instrument (The St Mark's – Amsterdam tool) for complex ileocolonic CD based upon best evidence and end–user expert opinion and provide validation and reliability evidence for this tool.
Methods: Items for the staging tool were developed using literature review and semi-structured interviews. Validity was tested using surgical outcome measures which were reviewed against intra-operative and histopathologically (IoH) assigned stages. Reliability was tested against IoH assigned stages using cross-sectional imaging, which were used to provide an objective pre-operative stage for patients who have undergone ileocolonic resection.
Results: A 4 stage tool was constructed.



The St Mark's – Amsterdam tool consists of 4 stages of escalating disease advancement mirroring radiological features identified from literature review and end user opinion.
Validity testing with 324 patients demonstrated greater proportions of males ($p < 0.005$), patients without preoperative biologics ($p < 0.05$), patients with preoperative anaemia ($p < 0.001$), leukocytosis ($p < 0.001$), thrombocytosis ($p < 0.001$), hypoalbuminaemia ($p = 0.001$), CRP > 10 ($p < 0.001$), emergent surgery ($p < 0.001$), open surgery ($p < 0.001$), concomitant sigmoidectomy ($p < 0.001$), and pre-emptive stoma formation ($p < 0.001$), with increasing IoH stage, respectively. Eighty-four patients had preoperative cross-sectional imaging prospectively staged. Further testing demonstrated greater proportions of preoperative anaemia ($p = 0.03$), concomitant sigmoidectomy ($p = 0.01$), and pre-emptive stoma formation ($p < 0.001$), with increasing preoperative radiological stage. As an overall measure of morbidity, pre-emptive stoma formation and postoperative intra-abdominal septic complication were combined, demonstrating higher morbidity rates per increment IoH ($p < 0.001$) and radiological ($p < 0.05$) stage increase. Reliability was demonstrated, with 44(52%), 6(7%), 25(30%) and 9(11%) patients per increment radiological stage increase, and 26(39%), 14(21%), 20(30%), and 7(10%) per increment IoH stage increase, respectively ($R = 0.8$; $p < 0.001$).
Conclusions: This novel staging tool has been validated to show greater morbidity with increasing stage severity. It can reliably be used to preoperatively stage patients, estimate morbidity, and inform surgical decision-making through a tailored operative risk management approach. Further multi-centre prospective validation of this tool is required for both clinical and research purposes.

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Long-term surgical outcomes following restorative proctocolectomy with ileal pouch-anal anastomosis for ulcerative colitis in a tertiary IBD centre in Brazil

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Background: Present the experience of a tertiary Brazilian centre in surgical management of inflammatory bowel disease (IBD) focussing on the long-term outcomes of IPAA.
Methods: Retrospective analysis of medical records of all patients with Ulcerative colitis (UC) who underwent surgical treatment with IPAA at Clinical Hospital of Ribeirão Preto Medical School, University of São Paulo, Brazil. Electronic medical records consisted of sex, age, average hospital stay, post-operative complications such as pouchitis, nocturne diarrhoea, faecal incontinence, pouch failure and definitive ileostomy.
Results: Fifty-four (n = 54) patients with UC had been submitted to IPAA between 1987 and 2018. Thirty-four (63%) were female and the mean age at IPAA was 36.4 years. The most common indication for surgery was failure of medical treatment (57.8%), followed by fulminant colitis or toxic megacolon (22.2%), refractory intestinal bleeding (14.8%) and high-grade dysplasia (3.8%). All patients with toxic megacolon, fulminant colitis or severe intestinal bleeding were submitted to total colectomy (first stage) and then to IPAA. The surgical approach for IPAA was via laparotomy in all patients except for 2 patients who had the operation by laparoscopic technique. All patients had a J-shaped pouch configuration. The majority of patients had a defunctioning ileostomy added to IPAA (98.1%). Mean hospitalisation length was 9.87 days (2–42) and the mean time to ileostomy closure was 163 days (14–650 days). Mean surgical time was 243.7 min (165–425). Early complications after IPAA occurred in 35.3% of patients and included pelvic sepsis (n = 5), pouch fistula (n = 5). Anastomotic stricture occurred in 15 patients and was successfully treated by anal dilatation under anaesthesia as an outpatient procedure. Median post-IPAA stool frequency was six motions at daytime (4–10). Nine patients had nocturne evacuation and six patients had faecal incontinence. Four patients (7.4%) developed Crohn's disease (CD) at postoperative follow-up. Pouch failure and excision had been reported in five patients, one due to post-operative complications and others due to severe pouchitis or development of CD. Pouchitis was reported in 66.6% of patients; however, it was considered severe only in five (9.2%) patients. There were three deaths in the follow-up (two related to post-operative complications and one due to suicide).
Conclusions: Ileal J-pouch anal anastomosis is a major surgery with potential complications. However, short- and long-term results are acceptable and present good functional results, if well indicated and performed in referral IBD centres.[1]

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P301

A serological biomarker of type VIII collagen that contains the anti-angiogenic signalling molecule, vastatin, is associated with the extension of disease in ulcerative colitis

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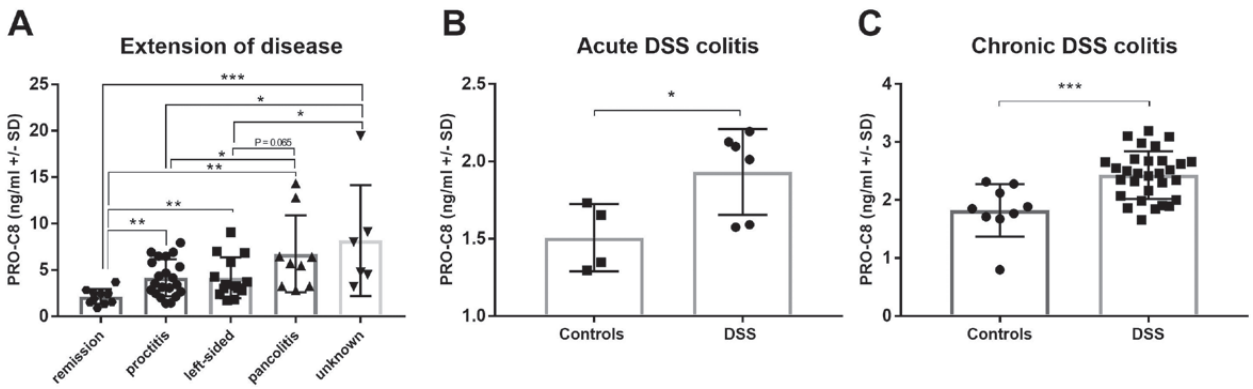
Background: Ulcerative colitis (UC) is characterised by superficial inflammation that starts in the rectum and can extend proximally to affect the entire colon. Endoscopy is used to diagnose patients in terms of extension of disease; however, this is invasive and cannot always be completed, for example, if the colon is too severely inflamed. The epithelial and endothelial basement membrane (BM) is an abundant extracellular matrix (ECM) of the intestine. Type VIII collagen is directly associated with the BM and the C-terminus of this collagen contains the anti-angiogenic signalling molecule, vastatin. Due to the abundant vasculature in the intestine, we investigated if a serum biomarker that targets the vastatin site of type VIII collagen was associated with the degree of inflammation in UC.
Methods: Serum was collected from 61 UC Patients who were endoscopically recorded for extension of disease: remission, proctitis, left-sided, pancolitis, and unknown. Endoscopy could not be completed in patients with unknown extension of disease; however, five out of six unknown patients had at least left-sided colitis, but most possibly pancolitis. Rat serum from acute (n = 10) and chronic dextran sulphate sodium (DSS) colitis (n = 39) were included. A competitive ELISA for the C-terminus of type VIII collagen (PRO-C8) was used to estimate serum levels of type VIII collagen/vastatin.
Results: PRO-C8 serum levels were elevated in UC patients with proctitis (p = 0.003), left-sided (p = 0.008), pancolitis (p = 0.002), and unknown (p = 0.0003) extension of disease compared with patients in endoscopical remission. In addition, PRO-C8 serum levels were



Abstract P301 – Figure 1. Serum levels of PRO-C8 in UC patients grouped by extension of disease (A). Endoscopy was not completed for patients with unknown extension of disease. Five out of six unknowns have at least left-sided colitis, and possibly pancolitis. Serum levels of PRO-C8 in rats with acute (B) and chronic (D) DSS colitis. Unpaired t test and Mann–Whitney test were applied. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

elevated in unknown (p = 0.036) and pancolitis (p = 0.03) patients compared with proctitis. The levels were also elevated in unknowns (p = 0.04) compared with left-sided, for which pancolitis patients had a tendency (p = 0.065) of higher PRO-C8 levels (Figure 1A). Serum PRO-C8 was confirmed to be increased in both acute and chronic DSS colitis (Figure 1B and C).

Conclusions: PRO-C8, containing the anti-angiogenic signalling molecule vastatin, was associated with extension of disease in UC patients and was elevated in patients for which endoscopy could not be completed. Increased PRO-C8 was shown to originate from intestinal inflammation in DSS colitis in rats. Thus, PRO-C8 may be a serological biomarker that reflects intestinal tissue inflammation based on extension of disease. This also indicates that UC patients with broad tissue involvement may have an altered collagen signalling and that ECM signals are part of the disease pathology.

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Predictors of outcome in children with Crohn's disease

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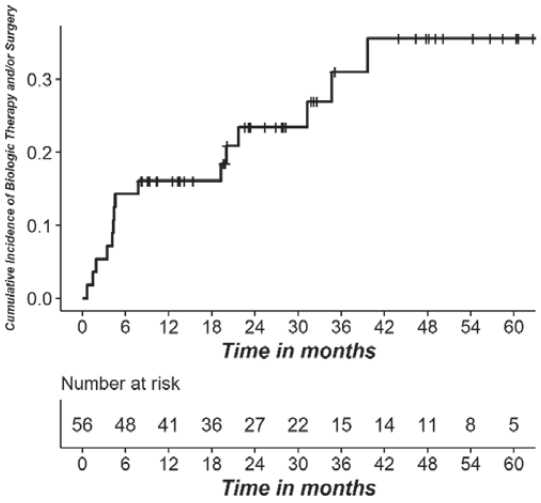
Background: Data regarding the incidence and the risk factors either for biologic therapy or for surgery in children with Crohn's disease (CD) are still lacking. The aims of this study were to determine the cumulative incidence of need for biologics and for surgery and to identify associated risk factors in a cohort of children with CD.

Methods: We conducted a retrospective chart review of 56 children diagnosed with CD from January 2013 through June 2017 with at least 12 months follow-up. Age at onset; gender; family history; anthropometric data; clinical, laboratory, endoscopic, and histological findings at diagnosis, timing of therapeutic regimens, and small bowel US were thoroughly investigated. Data regarding disease localisation according to Paris classification and disease activity indexes were also collected. The primary outcome was defined as need for biologic therapy and for intestinal surgery. Statistical significance was predetermined as $p < 0.05$. Percentages were rounded to the nearest whole numbers.

Results: The 56 enrolled patients [M/F: 31/25; median age: 12.8 years (range 6.7–16.8)] were divided into two groups: Group A, represented by 41 (73%) patients who did not receive biological treatment and/or surgery; Group B, represented by the remaining 15 (27%) patients subjected to biological treatment and/or surgery. Univariate Cox models showed that family history (hazard ratio [HR] 3.02, p = 0.04), C-reactive protein (CRP) (HR 1,016, p <0.001) and terminal ileal thickening (HR 1.14, p = 0.02) were associated with increased risk for intestinal surgery and/or use of biologics. Age, gender, anthropometrics, disease activity, disease behaviour and location, and extraintestinal manifestation were not associated with the need for more intensive therapy. Kaplan–Meier survival estimates of the cumulative incidence of surgery and biological therapy were 36.6% (95% CI = 17.2%–49.9%) at 5 years from the diagnosis of MC (Figure 1).



Conclusions: In children with CD, our preliminary data suggest that family history, CRP, and terminal ileal thickening evaluated by US at diagnosis are independent risk factors for biologic therapy and bowel surgery. In addition, in contrast with previous studies, we found a low cumulative rate of bowel surgery with a similar use of biologic therapy.

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Hyperbilirubinemia can be induced with azathioprin treatment in patients with inflammatory bowel disease: a hospital-based cohort study

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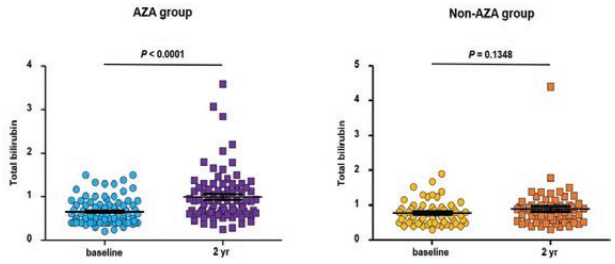
Background: Intestinal mucosal injury is supposed to cause liver disease and abnormal liver function tests are frequently observed in inflammatory bowel disease (IBD) patients. We investigated the hepatic biochemistry abnormality and change during the treatment in IBD patients.

Methods: IBD patients who were newly diagnosed and followed up in our hospital up to 2017 with the results of hepatic biochemistries at the both time points of diagnosis (before IBD treatment) and then at 2 years later (after IBD treatment) were enrolled. The biochemical profiles including aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TB), direct bilirubin (DB), alkaline phosphatase (ALP), Γ-glutamyltransferase (GGT) and the risk factors for the abnormal results were multi-variably analysed.

Results: One hundred forty-six (77 patients of Crohn's disease and 69 ulcerative colitis) patients were enrolled. HBs Ag positivity was found in 9 (6.2%) patients and anti-HCV antibody in 1 (0.7%). Radiologic diagnosis of fatty liver was found in 15 (10.2%) patients and gallbladder stone in 10 (6.8%). Within first year, 85 (58.2%) patients started and maintained azathioprine (AZA) therapy. At diagnosis, 45 (30.8%) patient revealed at least one abnormal hepatic biochemistry. AST was elevated than upper limit of normal (ULN) in 9 (6.2%) patients, ALT in 11 (7.5%), TB in 14 (9.5%), DB in 16 (11%), ALP in 21 (14.6%) and GGT in 15 (10.3%). At 2 years later, 59 (40.4%) patients showed at least one abnormal hepatic biochemistry. TB was elevated compared with baseline (p < 0.001) and

absolute abnormal elevation of TB (>0.5 mg/dl) was significantly related with AZA (p = 0.006). In the AZA therapy group, hyperbilirubinemia (>1.2 mg/dl) was found in 6 (7.1%) patients at initial diagnosis, but 19 (22.4%) patients at 2 years later. In this group, absolute TB abnormal elevation was found in 63 (64.1%) patients. Eighteen (21.2%) patients were within normal TB level at diagnosis and experienced newly developed hyperbilirubinemia after AZA therapy.



Levels of serum total bilirubin at the diagnosis and 2 years later in azathioprine-using group and non-azathioprine-using group.

Conclusions: Abnormal hepatic biochemistry profiles were observed in nearly one-third of IBD patients at diagnosis. AZA therapy is related with elevation change of TB during the treatment of inflammatory bowel disease.

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Predicting severity in Crohn's disease

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Background: Stratification of patients with Crohn's disease (CD) according to the risk of developing complications is essential to delineate therapeutic approach. A recent score (Siegel *et al*., Gut 2017) aims to assess disease severity, considering clinical and endoscopic activity, and complications during disease course, ranging from 0 to 100 values. Purpose: Evaluate the predictive capacity of this score at diagnosis (dx) for disease complications during the follow-up (surgery and hospitalisation).

Methods: Retrospective study, including incident patients with CD at our hospital between January 2012 and July 2017. The score was calculated at dx and at the end of follow-up, and information about disease course was collected.

Results: In total, 64 patients (32 women), with mean age at dx 33.4 ± 15.4 years. At dx 29 patients (45%) had L1 disease, 12 patients L2, 22 patients L3, and 1 patient L4. Forty-three patients (67%) had B1 phenotype, 7 patients B2, and 14 patients B3. At follow-up, 28 patients (44%) required surgery, 33 (52%) required hospitalisation, and 2 had phenotype progression. Median score at dx was 16 (4–50) and at follow-up was 9 (0–39). At dx score was higher in younger patients (22 A1 vs. 14 A3, p = 0.05), patients with penetrating phenotype (25 B3 vs. 11 B2, p = 0.005) and there was a tendency to a higher score in patients with upper GI disease (26 vs. 18, p = 0.07) and in those requiring surgery (21 vs. 18, p = 0.1). There was a positive correlation between score at dx and number of surgeries (r = 0.29, p = 0.002) and hospitalisations (r = 0.37, p = 0.018). There was a tendency for patients with a higher score at dx to have a shorter mean time to surgery (p log-rank=0.07). At follow-up, there was a score decrease in 46 patients (72%), with 11 having a score of 0, an increase in 16 patients, and the score remained the same in 2 patients. Patients in whom the score decreased below median (<16) were more frequently patients without hospitalisations (p = 0.03) or surgeries (p = 0.008) at follow-up. There was no difference in score at follow-up regarding different therapies.

Conclusions: The aforementioned severity score seems to be a promising instrument for stratification and prognosis of patients with CD, and its usefulness should be validated in prospective studies.

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Platelet parameters evaluation as a non-invasive marker of inflammation in Crohn's disease

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Background: Immunological disturbances play a crucial role in the pathogenesis of Crohn's disease (CD) by leading to inflammation of the intestinal mucosa. Blood clotting disorders accompany this inflammation and reinforce it by a positive feedback loop. Platelets (PLT) are important key regulators in inflammatory disorders beyond haemostasis and thrombosis. Aim of this study was to assess if platelet parameters, may be used as a non-invasive marker for monitoring disease activity in CD patients.

Methods: In total, 100 patients with diagnosed CD were enrolled in the study (W50/M50) at the mean age of 33.5 years hospitalised at Department of Gastroenterology, Medical University of Lodz with different clinical course, disease location and a heterogeneous therapy. The clinical state of each patient was classified according to Harvey–Bradshaw index (H-B). In all patients, venous blood samples were drawn for assessment of CRP, Fe, blood count and the stool sample was taken for faecal calprotectin evaluation. The results were analysed by dividing patients into two groups - exacerbation and remission considering the calprotectin level >200 or the H-B ratio ≥5.

Results: In the entire study group, positive correlation was found between calprotectin and platelet parameters: PLT, PCT, and negative correlation between calprotectin and MPV (Table 1).

Table 2. Correlation between calprotectin and:	Clinical activity of the disease according to Harvey-Bradshaw index				Clinical activity of the disease according to calprotectin <200 or ≥200µg/g			
	Exacerbetion		Remission		Exacerbation		Remission	
	R	p	R	p	R	p	R	p
CRP	0,335	0,0052	0,320	0,074	0,119	0,319	0,207	0,291
Hgb	-0,340	0,0045	-0,375	0,0343	-0,269	0,0221	-0,073	0,712
WBC	0,184	0,132	0,395	0,0251	-0,019	0,874	0,027	0,890
PLT	0,427	0,0003	0,237	0,191	0,234	0,0482	0,321	0,096
MPV	-0,366	0,0021	-0,345	0,078	-0,265	0,0292	-0,278	0,160
PCT	0,382	0,0013	0,161	0,424	0,184	0,133	0,275	0,164
Fe	-0,515	0,0000	-0,029	0,896	-0,339	0,0076	-0,028	0,895

Abbreviations: CRP- C reactive protein; Hgb- hemoglobin; WBC-white blood cells; PLT- platelets; MPV-mean platelet volume; PCT- plateletcrit; Fe- iron

Similarly, a positive correlation was found between H-B and PLT and PCT, and no correlation with MPV was found. Then, the correlation between the parameters and calprotectin was rated in two groups - exacerbation and remission. In the analysis of patients with exacerbation, statistically significant results with all platelet parameters were found in the group with H-B index above 5. Also CRP, Hgb, Fe correlated with H-B index, no correlation with WBC was found. In the group with calprotectin >200-PLT (p = 0.048) and MPV (p = 0.029) correlated with the calprotectin level, there was no correlation with PCT. Among patients in the period of exacerbation, the correlation of calprotectin with the most frequently determined

inflammatory parameters, CRP and WBC, has not been demonstrated. There were no correlations between platelet parameters in the group of patients in remission (Table 2).

Table1.	PLT		MPV		PCT	
	R	p	R	p	R	p
H-B index	0,376	0,0001	-0,152	0,141	0,319	0,0016
Calprotectin	0,405	0,0000	-0,346	0,0006	0,366	0,0003
CRP	0,486	0,0000	-0,337	0,0008	0,458	0,0000
WBC	0,486	0,0000	-0,206	0,0447	0,499	0,0000
Hgb	-0,360	0,0002	0,183	0,0760	-0,394	0,0001
Fe	-0,535	0,0000	0,399	0,0002	-0,543	0,0000

Abbreviations: PLT- platelets; MPV-mean platelet volume; PCT- plateletcrit; H-B index- Harvey Bradshaw index; CRP- C reactive protein; WBC-white blood cells; Hgb- hemoglobin; Fe- iron

Conclusions: Our study showed that level of platelets is a useful, non-invasive, inexpensive, and underestimated method for monitoring inflammation in CD.

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Double balloon enteroscopy in paediatric Crohn's disease and 10 years follow-up

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Background: Crohn's disease can occur throughout the entire gastrointestinal tract, often discontinuously, with the ileum and colon being the most common site. However, CD may involve any region of the small bowel (SB) other than the ileum and colon and isolated SB CD can present a diagnostic challenge. Double Balloon Enteroscopy (DBE) is an endoscopic modality for children that allow the diagnostic and therapeutic procedures of SB disease. Our aim was to evaluate the SB by DBE in children refractory to CD treatment
Methods: Between 2007 and 2010, 20 paediatric patients (age 2–17 years) with CD diagnosis, refractory to treatment were selected to undergo SB by DBE. The main objective was to evaluate SB inflammation-related, narrowing, malignancy or other diseases. Previously, all had performed radiological imaging to exclude stricturing. Only one experienced endoscopist performed all the DBE. In addition, 10 years follow-up with therapy was analysed
Results: The mean patient age was 12 years (range 2–17 years). Four patients (5%) had SB CD solely in jejunum, which was not detected by either colonoscopy or radiological examination (Table)

	CD patient at diagnosis	10-year follow-up
Patients (*n*)/median age (years)	20/12	14/22
Sex (%)	M65/ F35	M64/ F36
DBE lesions, %	90	
	Initial therapy (%)	Therapy at 10 years follow-up (%)
5-Aminosalicylic acid	25	7
Corticosteroid	60	28
Thiopurine/methotrexate	80	5
Infliximab, adalimumab	70	28
No treatment		21

Sociodemographic data.DBE lesions were: Active duodenojejunal ulcers, mucosal healing and/or pseudo polyps and mucosal granularity. General anaesthesia was performed in 6 children from 2 to 7 years and deep sedation with propofol in 14 patients. Mean length of SB examined was 220 cm beyond the ligament of Treitz (range 120 to 360 cm). Mean duration of the procedure: 48 min (range 30 to 60). No significant complications were related to the procedure. One patient had a malignancy diagnosis extra-intestinal; one had IL-10 and/or IL-10R gene mutation and one change the diagnosis to ulcerative colitis. Currently, 14 patients are in follow-up, 5 children in paediatric GI clinic and the other 9 at adult GI clinic. Curiously, the proportion of patients free of long-term therapy has decreased.
Conclusions: We conclude DBE is a safe and useful tool to clarify SB pathologies in paediatric patients like CD. DBE can provide additional information in patients who require therapeutic decision or to make differential diagnosis. In addition is allows biopsy sampling. General anaesthesia or sedation and should be considered

P307

The use of the patient safety form in patients with inflammatory bowel disease, can improve the low screening and starting HBV prophylaxis rates in real life

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Background: The rate of hepatitis B virus(HBV) screening and starting HBV prophylaxis is low in patients with immunosuppressive therapy in daily practice. While starting the biological therapies in the patients with inflammatory bowel disease (IBD), use the patient safety form is mandatory in Turkey but there is no such requirement for long-term high-dose steroids. The aim of this study was to determine how much HBV screening and rates of antiviral treatment applied in patients with IBD in daily practice and to evaluate the relationship between the patient safety form and rate of HBV screening and starting HBV prophylaxis.
Methods: This is a retrospective study. Between January 2010 and May 2018, patients who received biological agents (including adalimumab, certolizumab, infliximab, and vedolizumab) with/without steroids, 5-aminosalicylic acid and/or immunomodulators (Group 1; use the patient safety form mandatory) and long-term high-dose steroids with/without 5-aminosalicylic acid and/or immunomodulators (Group 2: use the patient safety form not mandatory) in Medical University of Mustafa Kemal were included in the study. HbsAg and Anti-HbcIg tests performed during the period up to 1 year before treatment of immunosuppressive agent were accepted as screening. Methylprednisolone or equivalent steroid of its use for at least 4 weeks and at least 10 mg/day were considered to be as long-term high-dose. HbsAg and/or HbcIg positivity was defined as a risky patients for starting antiviral prophylaxis.
Results: A total of 1012 patients were included in the study. The immunosuppressive treatment distributions of the patients were as follows; 183 biological agents(Group 1), 829 long-term high-dose steroids (Group 2). Seven hundred and sixteen (70.7%) of the patients had screened for HbsAg and/or anti-HBcIg. HbsAg and anti-HBcIgG screening were found in 40.2% (407/1012) patients and only HBsAg screening was found in 30.5 (309/1012) patients. HbsAg positivity was found in 5.4% (39/716) of patients and HbsAg negative and anti-HBcIg positivity in 30.7% (125/407) of patients. The rates of HBsAg and/or anti-HBcIg screening were 95.6% (175/183) in group

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1 and 65.2 (541/829) in group 2 ($p < 0.001$). Rates riskly patients for starting antiviral prophylaxis were found in % 21.7 (38/175) in Group 1 and %23.2 (126/541) in Group 2 ($p > 0.05$). Rates starting HBV prophylaxis were %100 (38/38) in Group 1 and %56.3 (71/126) in Group 2 ($p < 0.001$).

Conclusions: The scanning rates are low in patients with IBD receiving long-term high-dose steroids and it was found that only half of risky patients received antiviral treatment. We also believe that the use of the patient safety form application in patients with IBD receiving long-term high-dose steroids can improve the low screening and treatment rates in real life.

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Utility of bowel ultrasound in diagnosing disease activity in Crohn's disease: Indian experience

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Background: To assess the utility of bowel ultrasound (USG) in assessing Crohn's disease activity in correlation with the simple-endoscopic score-CD (SES-CD) and Harvey–Bradshaw Index (HBI).

Methods: Patients with Crohn's disease who underwent colonoscopy for assessment of disease activity also underwent a USG within a 2-week period without change in treatment. Colonoscopic disease activity was assessed by the SES-CD, SES-CD score of 3 and higher was defined as endoscopically active. Clinical disease activity was assessed by the HBI, and a HBI of 5 or more was defined as active disease. USG parameters assessed include bowel wall thickness (BWT), loss of bowel wall stratification (BWS), and Doppler activity. Doppler activity was evaluated semi-quantitatively by the Limberg score.

Results: Thirty-five patients were included in the study, 12 patients (34%) were in endoscopic remission, 7 patients (20%) had mild endoscopic activity, 6 patients (17%) had moderate endoscopic activity and 10 patients (29%) had severe endoscopic activity as per the SES-CD score. As per the HBI, 18 (51%) patients were in remission, 6 (17%) had mild, 8(23%) had moderate and 3 patients (9%) had severe disease. Sixteen (46%) patients had only small intestinal involvement, 13 (37%) ileocolonic and 6 (17%) colonic only. Median BWT was greater in patients with active disease when compared with those in endoscopic remission (6 mm vs. 2.45 mm, $p < 0.01$). BWT correlated with SES-CD ($r = 0.455$, $p = 0.007$) and HBI ($r = 0.506$, $p = 0.002$). BWS correlated with SES-CD ($r = 0.432$, p = 0.011) and HBI ($r = 0.483$, $p = 0.003$),Doppler correlated with SES-CD ($r = 0.494$, $p = 0.003$) and HBI ($r = 0.656$, $p = 0.001$). Combining all 3 features (BWT, BWS, Doppler) correlated to SES-CD for active disease ($r = 0.8$, $p = 0.009$) and to HBI ($r = 0.76$, $p = 0.04$).

Conclusions: USG is a useful modality in assessing disease activity in Crohn's disease. Bowel wall thickness, loss of stratification, and Doppler activity in the bowel wall correlate with endoscopic and clinical disease activity; and these features can be used in future studies assessing using USG to assess disease activity in Crohn's disease.

P309

Impact of co-morbidities on loss and lack of response to anti-TNFs in inflammatory bowel disease: VERNE study

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Background: Although anti-TNFα therapy is an effective approach for IBD, a great amount of patients does not respond to induction therapy and a significant proportion loses response over time, making it necessary to search for accurate prognostic markers to guide patient selection. This study aimed to evaluate the impact of the co-morbidities profile on the response to anti-TNFs in IBD patients treated in Spanish hospitals.

Methods: This was a retrospective, non-interventional, multi-centre (24 sites), observational study that included consecutive adult patients diagnosed with UC or CD who started treatment with biologics between June 2011 and June 2013. Data about patient characteristics, including comorbidities, were collected. Studied variables were analysed descriptively.

Results: Three hundred and ten patients with IBD were analysed, 194 with CD and 116 with ulcerative colitis. Average age was 44.9 years (SD: 13), 53.5% were male and most of them Caucasian (95.8%). CD locations were ileum and colon (44.6%), terminal ileum (37.3%), colon (15.5%) and upper gastrointestinal tract (2.6%); UC locations were extensive colitis (48.2%), left colitis (43.8%) and proctitis (8.0%). Most frequent comorbidities were: Chronic Obstructive Pulmonary Disease (COPD) (3.7%), connective tissue disease (3.0%), diabetes mellitus (2.3%), mild chronic hepatopathy (2.0%), myocardial infarction (1.7%), solid tumours (1.7%), congestive heart failure (1.3%) and cerebrovascular disease (1.3%).

Logistic regression models showed that COPD was an independent factor associated with lack of response (OR 2.67 CI 95%: 1.33–5.35; $p = 0.006$), and myocardial infarction of loss of response (OR 3.30; CI 95%: 1.48–7.35; $p = 0.003$) to anti-TNF therapy.

The concomitant use of corticosteroids was an additional independent factor associated with lack of response (OR 2.16; CI 95%: 1.25–3.73; $p = 0.006$) and loss of response (OR 2.45; CI 95%: 1.35–4.44; $p = 0.003$), and, in contrast, CD was a negative independent predictor of lack of response (OR 0.59; CI 95%: 0.37–0.93; $p = 0.024$) and loss of response (OR 0.58; CI 95%: 0.34–0.99; $p = 0.044$).

Conclusions: In this population of IBD patients who received first anti-TNF treatment, the most frequent comorbidities were COPD, connective tissue disease, diabetes and hepatopathies. Those associated with lack and loss of response were COPD and myocardial infarction, respectively. Results suggest that patients characteristics should be considered when selecting the optimal biological treatment for IBD patients.

P310

Diagnostic delay: assessment, improvement and outcome consequences in inflammatory bowel disease

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Background: Classically diagnostic delay has always been associated to Crohn's disease (CD), especially when only ileum is involved and to male sex and higher age. Moreover, some authors believe that diagnostic delay may worsen the outcome (higher surgery risk). The aim of the study was to assess diagnostic delay in inflammatory bowel diseases and to evaluate its consequences on the outcome.

Methods: We conducted an observational retrospective study. We included all patients that have been recruited in a previous study about adherence to the therapy. Diagnostic delay was defined as a diagnosis made later than 1 year after the beginning of the symptoms.

Results: 221 patients were affected by CD and 147 by ulcerative colitis (UC); 157 were female and 211 were male. The diagnostic time ranged from 6 months to 30 years ago (mean time 15 years ago). Our results confirmed that diagnostic delay is more common in CD patients (38% in CD vs. 18% in UC; $p = 0.001$); no significant difference was found between male and female group. In UC group diagnostic delay was significantly higher in patients who received diagnosis before 2010 (18.5% before 2010 vs. 3.3% after 2010; $p = 0.01$); no significant improvement resulted in CD patients. In patients with a delayed diagnosis a higher need of immunosuppressive or biological therapy (35.4% in diagnostic delay group vs. 20.5% in non-delay group; $p = 0.0045$) and major risk of surgery (41.6% in diagnostic delay group vs. 24.2% non-delay; $p = 0.0016$) resulted. On the other hand, no difference was found regarding intestinal and extra-intestinal complications.

Conclusions: Over time there has been a significant improvement in UC diagnosis, while CD diagnosis still remains a challenge for the physicians, suggesting that higher sensibility of new available diagnostic tests is not the only reason for IBD increasing diagnosis (especially in CD). Moreover, the need for immunosuppressive and/or biological therapies and of surgery may be consequences of diagnostic delay.

Clinical: Therapy and observation

P311

Pharmacokinetics and exposure–response relationships of intravenously administered ustekinumab during induction treatment in patients with ulcerative colitis: Results from the UNIFI induction study

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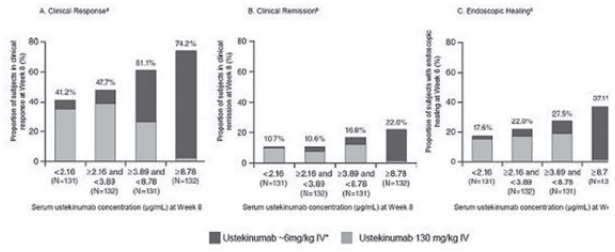
Background: Pharmacokinetic (PK) and exposure–response (ER) data for ustekinumab (UST) from the UNIFI study in ulcerative colitis (UC)[1] were evaluated.

Methods: PK, efficacy, and safety data were obtained from this Phase 3, double-blind, placebo-controlled induction trial which enrolled 961 patients with moderate–severe UC. Pts who previously failed biologics (1 or more TNF-blockers or vedolizumab) or conventional therapy (corticosteroid and/or 6-MP/AZA) were included. Pts were randomised 1:1:1 to receive an IV induction dose of UST 130 mg or a weight-range based dose of ~6 mg/kg, or placebo at Week 0. Serum UST concentrations and antibodies to UST were evaluated with validated assays. Clinical efficacy outcomes based on the Mayo score were assessed at Wk8; C-reactive protein (CRP) and faecal markers were evaluated as efficacy biomarkers. The relationships between serum UST concentrations and efficacy, as well as the incidence of infections, serious infection and serious adverse events (SAE) during induction were evaluated.

Results: Serum UST concentrations over time through Wk8 were dose proportional and similar between biofailure and non-biofailure patients, and patients receiving immunomodulators (IMM) at baseline and those not receiving IMM. Median peak serum UST concentrations for UST 130 mg and ~6 mg/kg dose groups were 43.2 μg/ml and 127.0 μg/ml, respectively; median Wk8 UST concentrations were 2.5 μg/ml and 8.6 μg/ml, respectively. The incidence of antibodies to UST through 8 weeks was 0.6% based on a drug-tolerant assay. Wk8 serum UST concentrations were positively associated with the proportions of patients achieving clinical response, clinical remission, and endoscopic healing (Figure 1), and inversely related to CRP and faecal calprotectin/lactoferrin levels. Greater proportions of patients in the ~6 mg/kg group achieved UST exposures in the upper quartiles of UST exposure associated with higher efficacy. Serum UST concentrations were not associated with the incidence of infections, serious infections or SAEs.



*Decrease from induction baseline in the Mayo score by ≥30% and ≥3 points, with either a decrease from induction baseline in the rectal bleeding subscore ≥1 or a rectal bleeding subscore = 0 or 1.
[b]Mayo score ≤2 points, with no individual subscore >1.
[c]Also described as endoscopic improvement in the appearance of the mucosa and defined as a Mayo endoscopy subscore = 0 or 1.
*Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55 kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight > 85 kg).

Figure 1. Relationship between serum ustekinumab concentrations at Week 8 and clinical efficacy outcomes at Week 8.

Conclusions: Serum UST concentrations were approximately dose-proportional and a positive E-R relationship for efficacy was observed during UST induction treatment in patients with UC. No associations were observed between systemic UST exposure and selected safety events at the IV doses evaluated. These results are consistent with those reported for patients with Crohn's disease.

Reference

1. Sands BE, Sandborn WJ, Panaccione P, *et al*. Safety and efficacy of ustekinumab induction therapy in patients with moderate to severe ulcerative colitis: results from the Phase 3 UNIFI Study. Oral Presentation at ACG 2018, Philadelphia, PA.

P312

Efficacy in biologic failure and non-biologic-failure populations in a Phase 3 study of ustekinumab in moderate–severe ulcerative colitis: UNIFI

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Background: Ustekinumab (UST), an IL12/23 blocker approved for Crohn's disease, was effective in Ph3 induction and maintenance of moderate–severe ulcerative colitis (UC). Efficacy in biologic-failure (BF) and non-biologic-failure (NBF) populations was evaluated.

Methods: Pts were randomised to a baseline IV induction UST dose (130 mg or weight-range based doses approximating 6 mg/kg (~6 mg/kg)), or PBO. Responders to UST IV induction entered maintenance and were randomised to SC 90 mg UST (q12wks or q8wks), or PBO. Primary endpoint for wk8 induction and wk44 maintenance was clinical remission. Major secondary endpoints for wk8 induction: endoscopic healing, clinical response, and change from baseline in total IBDQ score and wk44 maintenance: maintenance of clinical response, endoscopic healing, corticosteroid-free clinical remission, and maintenance of clinical remission in baseline remitters.

Results: Among patients with documented BF (51.1% of randomised patients), 98.8% had failed at least 1 anti-TNF, 32.6% had failed both anti-TNF and vedolizumab. NBF patients were predominantly bio-naïve (94.3%). In induction, for BF and NBF patients, proportions of patients who achieved clinical remission was significantly greater for UST ~6 mg/kg and 130 mg vs. PBO (BF patients-$p < 0.001$ for both doses; NBF patients-$p < 0.05$ for both doses, respectively, Table 1). For BF and NBF patients, major secondary endpoints of clinical response and endoscopic healing and change from baseline in IBDQ were significantly greater for UST ~6 mg/kg and 130 mg vs. PBO (Table 1). Though treatment differences were generally similar between BF and NBF patients, rates were consistently lower for BF patients in each treatment group. In maintenance, for BF and NBF patients, proportions of patients who achieved clinical remission was significantly greater for UST q8w and q12w vs. PBO (BF patients-$p < 0.001$, $p = 0.044$, respectively; NBF patients-$p = 0.024$, $p = 0.020$, respectively, Table 2). For BF and NBF patients, proportions of patients who achieved each major secondary endpoint was generally greater for UST q8wk and q12wk vs. PBO. In BF patients, the efficacy of UST q8wk was generally greater than UST q12wk (Table 2).

Conclusions: UST was effective for induction and maintenance treatment of moderate–severe UC patients with a history of biologic therapy failure (ie, TNF-antagonists and/or vedolizumab) as well as patients without a history of biologic therapy failure who were predominantly bio-naive.

Table 1. UNIFI Induction key endpoints at Week 8 by biologic failure vs. non-biologic failure.

Primary efficacy analysis N	PBO N=319	130 mg UST N=320	6 mg/kg* UST N=322
Pts who are biologic failures N	**161**	**164**	**166**
Pts in clinical remission[b]	2 (1.2%)	19 (11.6%) p<0.001	21 (12.7%) p<0.001
Clinical response[c]	44 (27.3%)	74 (45.1%) p<0.001	95 (57.2%) p<0.001
Endoscopic healing[d]	11 (6.8%)	30 (18.3%) p=0.002	35 (21.1%) p<0.001
IBDQ median change from BL N	**159**	**162**	**165**
Median (IQ range)	9.0 (-4.0, 28.0)	26.5 (7.0, 49.0)	27.0 (7.0, 52.0)
Range	(-58, 78)	(-45, 134)	(-36, 130)
P-value		p<0.001	p<0.001
Pts who are <u>not</u> biologic failures N	**158**	**156**	**156**
Pts in clinical remission[b]	15 (9.5%)	31 (19.9%) P=0.009	29 (18.6%) P=0.022
Clinical response[c]	56 (35.4%)	90 (57.7%) p<0.001	104 (66.7%) p<0.001
Endoscopic healing[d]	33 (20.9%)	54 (34.6%) p=0.006	52 (33.3%) p=0.014
IBDQ median change from BL N	**158**	**154**	**156**
Median (IQ range)	14.0 (-2.0, 44.0)	37.0 (9.0, 59.0)	33.5 (13.5, 61.0)
Range	(-58, 126)	(-28, 118)	(-30, 126)
P-value		p<0.001	p<0.001

[a]Weight-range based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55 kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight > 85 kg), [b]Clinical remission defined as Mayo score ≤ 2 points, with no individual subscore > 1; primary endpoint, [c]Clinical response defined as a decrease from induction baseline in the Mayo score ≥ 30% & ≥ 3 points with either a decrease in rectal bleeding subscore (RBS) ≥ 1 or a RBS of 0 or 1, [d]Endoscopic healing (also described as endoscopic improvement in the appearance of the mucosa) was defined as a Mayo endoscopy subscore of 0 or 1 point. IBDQ = Inflammatory Bowel Disease Questionnaire

Table 2. UNIFI Maintenance key endpoints at Week 44 by biologic failure vs. non-biologic failure.

	Placebo SC[a] N=175	90mg UST SC Q12 Wk N=172	90mg UST SC Q8 Wk N=176
Pts who are biologic failures N	**88**	**70**	**91**
Clinical remission at Week 44[b]	15 (17%)	16 (22.9%) P=0.044	36 (39.6%) P<0.001
Maintained clinical responsethrough Week 44[c]	34 (38.6%)	39 (55.7%) P=0.008	59 (64.8%) P<0.001
Endoscopic healing at Week 44[d]	20 (22.7%)	18 (25.7%) P=0.163	41 (45.1%) P<0.001
Corticosteroid-free clinical remission at Week 44[e]	14 (15.9%)	16 (22.9%) P=0.026	34 (37.4%) P<0.001
Maintenance of clinical remission through Week 44 among remitters at baseline[f]	8/20 (40.0%)	3/8 (37.5%) P=1.00	10/20 (50.0%) P=0.751
Pts who are <u>not</u> biologic failures N	**87**	**102**	**85**
Clinical remission at Week 44[b]	27 (31.0%)	50 (49.0%) P=0.020	41 (48.2%) P=0.024
Maintained clinical response at Week 44[c]	44 (50.6%)	78 (76.5%) P<0.001	66 (77.6%) P<0.001
Endoscopic healing at Week 44[d]	30 (34.5%)	57 (55.9%) P=0.007	49 (57.6%) P=0.002
Corticosteroid-free clinical remission at Week 44[e]	27 (31.0%)	49 (48.0%) P=0.028	40 (47.1%) P=0.034
Maintenance of clinical remission through Week 44 among remitters at baseline[f]	9/25 (36.0%)	23/32 (71.9%) P=0.008	12/18 (66.7%) P=0.067

[a]Patients who responded to ustekinumab IV induction dosing and were randomly assigned to placebo SC upon entry into the maintenance study.
[b]Clinical remission is defined as a Mayo score of ≤2 points, with no individual subscore >1
[c]Clinical response defined as a decrease from induction baseline in the Mayo score ≥30% & ≥3 points with either a decrease in rectal bleeding subscore (RBS) ≥ 1 or a RBS of 0 or 1
[d]Endoscopic healing (also described as endoscopic improvement in the appearance of the mucosa) was defined as a Mayo endoscopy subscore of 0 or 1 point.
[e]Corticosteroid-free clinical remission is defined as a Mayo score of ≤2 points, with no individual subscore >1 and not receiving corticosteroids at Week 44
[f]Pts who were in remission at the start of maintenance therapy and maintained remission through Week 44

P313

Impact of upadacitinib on the general clinical condition of patients with Crohn's disease (CD): data from the randomised CELEST study

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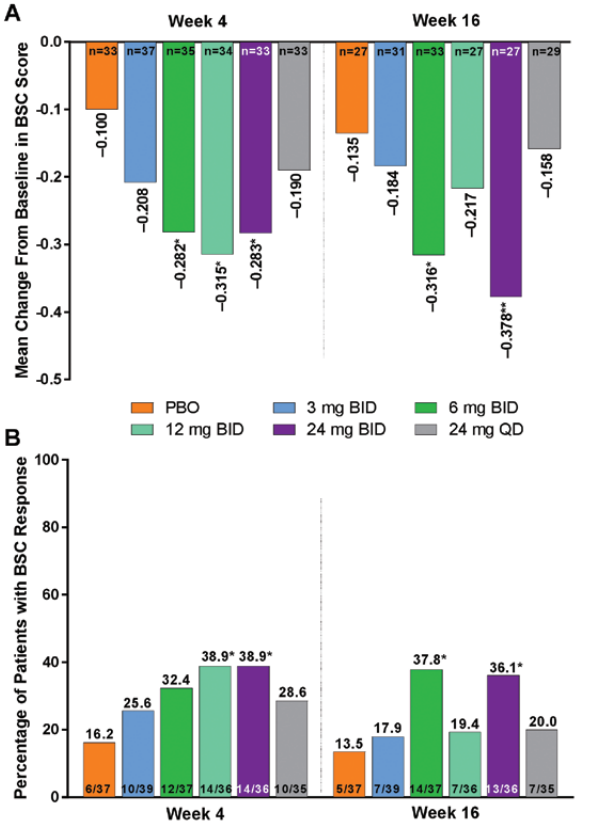
Background: This analysis assessed the impact of upadacitinib (UPA), an oral selective JAK1 inhibitor, on the general clinical condition of patients with CD. We assessed body weight and serum albumin levels, common measures used in clinical practice, as well as improvement in diarrhoea. Stool consistency was assessed via the Bristol Stool Chart (BSC), a patient-reported outcome measure used widely in patients with functional bowel disorders and favoured by regulatory agencies.
Methods: The placebo-controlled Phase 2 CELEST study (NCT02365649) enrolled adults with moderate to severe CD refractory or intolerant to immunosuppressants/biologics. During the induction period, patients were randomised to placebo (PBO) or UPA 3 mg, 6 mg, 12 mg, or 24 mg twice daily (BID) or 24 mg once daily (QD) for 16 weeks, followed by a 36-week double-blind extension phase. Changes over time from baseline (BL) in body weight and serum albumin levels were assessed (ANOVA). Stool consistency was assessed by change from BL to Weeks 4 and 16 in BSC score (proportion of days over the last week prior to the visit with BSC Type 6 [very soft] or 7 [liquid] stool; observed data) and proportion of patients who achieved BSC response at Weeks 4 or 16 (≥50% reduction in number of days over the last week with ≥1 BSC Type 6 or 7 stool vs. BL; non-responder imputation). UPA vs. PBO were evaluated at $p = 0.1$ level.
Results: Among 220 randomised patients, mean ± SD weight was 75.3 ± 20.1 kg, mean albumin levels were 38.6–39.7 g/l, and mean ± SD BSC score was 0.9 ± 0.3 at BL. Weight significantly improved from BL to Week 12 with UPA doses ≥6 mg (range: 1.2–1.6 kg) vs. PBO (–0.6 kg; $p < 0.05$); at Week 16, changes remained significantly improved from PBO (0.0 kg) with UPA 24 mg BID (2.1 kg; $p = 0.031$). Albumin level changes from BL were significant as early as Week 2 with all UPA doses (range: 0.2–1.9 g/l) vs. PBO (–1.0 g/l; $p < 0.05$) and were maintained through Week 16 with UPA doses ≥6 mg (range: 2.6–4.0 g/l) vs. PBO (0.4 g/l; $p < 0.05$). BSC scores significantly improved from BL by Week 4 with UPA 6 mg, 12 mg, and 24 mg BID vs. PBO and were maintained to Week 16 with 6 mg and 24 mg BID ($p \leq 0.05$; Figure A). A significantly greater proportion of patients receiving UPA 12 mg and 24 mg BID at Week 4 and 6 mg and 24 mg BID at Week 16 achieved BSC response vs. PBO ($p < .05$; Figure B).



BID, twice daily; BSC, Bristol Stool Chart; PBO, placebo; QD, once daily; SES-CD, Simplified Endoscopic Score for Crohn's Disease; UPA, upadacitinib.
Panel A: Mean BSC score defined as proportion of days over the last wk prior to the visit with BSC Type 6 (very soft) or 7 (liquid) stool (observed analysis); statistical comparison between each UPA dose group and PBO using analysis of covariance with treatment, baseline disease severity (SES-CD <15 and ≥15), and baseline value as covariate; *P<0.05, **P<0.01 vs PBO.
Panel B: BSC response defined as ≥50% reduction in the number of days over the last wk with ≥1 BSC Type 6 or 7 stool versus baseline (non-responder imputation); statistical comparison between each UPA dose group and PBO based on Cochran-Mantel-Haenszel test stratified by baseline SES-CD (SES-CD<15 and SES-CD≥15); *P<0.05 vs PBO.

Figure. Change from baseline to Weeks 4 and 16 in Bristol Stool Chart score (A) and proportion of patients with Bristol Stool chart response at Weeks 4 and 16 (B).

Conclusions: UPA induction treatment resulted in significant improvements in body weight, serum albumin levels, and stool consistency in patients with CD compared with PBO. Improvements in these parameters paralleled conventional outcomes such as CD activity index and mucosal healing.

P314

Long-term fate of the excluded rectum in Crohn's disease

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Background: Faecal diversion with ostomy construction is performed in nearly 10% of Crohn's disease (CD) patients, often for refractory perineal disease. The long-term fate of these retained rectums has not been extensively studied; hence, we undertook a retrospective review of the outcomes of a cohort of CD patients with excluded, retained rectums.
Methods: A data base of all CD patients followed at The Mount Sinai Hospital was searched for those who had undergone initial rectal exclusion surgery between 1990 and 2014, and who retained the excluded rectums for at least 6 months. We then retrieved electronic records to determine the last-recorded outcomes of these rectums, whether removed, reconnected, or still excluded.
Results: Among 910 CD patients in the Mount Sinai Hospital Data Warehouse, we identified 91 who met all criteria for rectums retained for at least 6 months following original stomal diversion. Follow-up data (mean 9 year, [range 3.4–13.9]) were available for 81 (89%). Forty-five (56%) of these patients were female. Perineal disease had been noted preoperatively in 44 (54%) cases. The median age at the time of faecal diversion was 34 year (26–44). Although some patients had multiple indications, the primary reasons for rectal exclusion were perineal disease in 32%, acute or refractory bowel disease in 32%, internal fistula in 15%, bowel stricture in 8.6%, colon cancer in 2.5%, and unclear in 9.9%. At the time of last follow-up, 37 patients (46%) had undergone excision of the rectum. Among the 37 patients who underwent total proctectomy, the principal indications were clinicians' concerns regarding inadequate surveillance (43%), worsening perineal fistulisation (32%), extensive soiling (19%), one case of anal cancer (2.7%), and one case of rectal dysplasia (2.7%). Among the 44 patients who still had retained rectums, 19 (54%) had been reconnected) and 12 of these (63%) were known free of symptoms. Of the 25 patients with retained excluded rectums, only 9 (36%) were symptom-free; the remainder had fistulae (24%), perianal irritation (20%), and one each (4%) stenosis, sexual difficulty, and anal cancer.
Conclusions: Among 81 CD patients with long-term excluded rectums, only 44 (54%) still had their rectums *in situ* after a mean 9-year follow-up. Of these, only 21 (48%) were symptom-free. Two patients among the 81 (2.5%) developed anal cancer.

P315

Systemic and tissue modulation of IL-23 pathway biomarkers in a Phase 2 study of risankizumab in patients with Crohn's disease

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Background: Risankizumab, a humanised monoclonal antibody that specifically targets the p19 subunit of interleukin (IL)-23, is currently under evaluation in Crohn's disease (CD) and other inflammatory diseases. This biomarker study aimed to provide mechanistic insights on risankizumab in patients with active CD.
Methods: We evaluated data from a randomised, double-blind, placebo (PBO)-controlled Phase 2b induction study in patients with moderate-to-severe CD (NCT02031276) who received intravenous risankizumab (200 or 600 mg), or PBO at Weeks 0, 4, and 8. At baseline (BL) and Week 12, IL-23 pathway biomarkers and other biomarkers of inflammation were measured as protein (from plasma) or by RNA sequencing (RNAseq) (from colon or ileum tissue biopsies). In addition, we assessed potential correlations between BL IL-22 or reduction in IL-22 from BL and Week 12 clinical response following risankizumab treatment.
Results: Plasma and colon RNA data were available for 22–35 patients in each of the three treatment groups (Table 1). At Week 12, statistically greater reductions (%) from BL in risankizumab-treated vs. PBO-treated patients were observed for plasma biomarkers (IL-17, IL-1b, IL-22, C-reactive protein, calprotectin, and lactoferrin) and colon RNA biomarkers (IL-17A, IL-1b and IL-23A). Comparisons between risankizumab and PBO treatments groups were significant for the majority of plasma and RNA endpoints; comparisons between risankizumab dose groups (200 vs. 600 mg) were not significant with the exception of calprotectin. KEGG (Kyoto Encyclopaedia of Genes and Genomes) pathway analysis of RNA signatures demonstrated perturbation of the IL-17 signalling pathway and other inflammation signatures by risankizumab 600 mg. Neither BL IL-22 levels nor IL-22 reduction from BL following risankizumab treatment was predictive of the clinical efficacy at Week 12.
Conclusions: Risankizumab treatment in patients with active CD led to greater reductions in IL-23 pathway and other inflammation biomarkers compared with PBO, as measured in both plasma and tissue biopsies. IL-22 plasma levels at BL or reduction in IL-22 following risankizumab treatment were not predictive of response to risankizumab.

Table 1. Plasma and RNAseq biomarker changes at Week 12.

Plasma Protein Biomarkers			
	Decrease from Baseline (%)		
	PBO (n=31)	Risa 200 mg (n=34)	Risa 600 mg (n=35)
IL-17A	17.7^{ns}	58.8****	41.6**
1L-1b	1.0^{ns}	38.4***	28.9*
IL-22	9.7^{ns}	43.2****	58.0****
CRP	13.7^{ns}	37.6**	58.8****
Calprotectin	13.6^{ns}	53.3***	78.7****
Lactoferrin	33.7^{ns}	65.0****	73.1****
RNAseq Biomarkers (colon biopsies)			
	Decrease from Baseline (%)		
	PBO (n=24)	Risa 200 mg (n=22)	Risa 600 mg (n=26)
IL-17A	21.3^{ns}	45.7**	64.5****
1L-1b	16.0^{ns}	72.9***	80.4****
IL-23A	11.4^{ns}	34.7**	41.9***

p-values: *, **, ***, ****, p≤0.05, 0.01, 0.001 and 0.0001, respectively; ns, non-significant.
Risa, risankizumab.

P316

Transanal minimal invasive proctectomy (TaMIP) for perineal Crohn's disease; a multi-centre prospective cohort study

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Background: Transanal minimally invasive proctectomy (TaMIP) has some advantages particularly in relation to access to the deep pelvis. Key challenges faced with the TaMIP approach for proctectomy in Crohn's disease are the diseased pelvis and inflamed, bulky mesorectum causing difficult planes. This study aims to assess the short-term outcomes and perineal wound complications following TaMIP for Crohn's disease.

Methods: All patients undergoing TaMIP proctectomy between 2014 and 2018, at 2 tertiary care referral centres were prospectively evaluated. Thirty-day morbidity, operative details and perineal wound complications were analysed.

Results: A total of 33 patients (M 42%, age 38.5 years; range 26 to 77) have undergone TaMIP for Crohn's disease. Surgeries were performed as double single port procedures with either complete mesorectal excision or close rectal dissection. The mean operative time was 120 min (range: 60–240) for the perineal procedure and 234 min (range: 140–279) for the total procedure. One case (3%) had to be converted to an open procedure due to difficult dissection and haemorrhage. Ninety per cent of the patients were ASA II and 54.5% underwent completion proctectomy while 45.5% had a panproctocolectomy as a single procedure. Four patients (12%; II 2, III 2) had complications which were Clavien-Dindo II and above. One patient had re-intervention for a pelvic collection while another patient had a ureteric injury. Vacuum dressing was used for primary wound closure in one patient. Major perineal wound dehiscence was seen in 6% (2 of 33) of the patients while one needed vacuum therapy. In long-term follow-up one patient developed an enterocutaneous fistula at the abdominal wound while 7 (21%) chronic perineal sinuses were reported.

Conclusions: Perineal Crohn's disease poses a challenge for transanal minimally invasive surgery due to the chronic inflammation and perineal sepsis. Transanal approach offers a safe and feasible option for perineal Crohn's disease. The commonest complication following TaMIP is the development of a chronic perineal sinus and evaluation with laparoscopic and open techniques would be useful to ascertain if this rate is different.

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Characterisation of patients with delayed response to ustekinumab for Crohn's disease

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Background: In UNITI-1 and 2, pivotal induction studies of ustekinumab (UST) in patients with CD, 467 non-responders to UST 130 mg or ~6 mg/kg IV received UST 90 mg SC at Week 8. Overall, 50.5% achieved response at Week 16 (delayed responders, DR).[1] We sought to characterise DR population induced with ~6 mg/kg IV and identify predictors for delayed response.

Methods: UNITI-1 and 2 patients who were induced with UST~6 mg/kg IV and had a UST SC dose at Week 8 were included in this post hoc analysis and classified as Week 8-responders (ER), DR (no response at Week 8/response at Week 16) or non-responders (NR, no response at Weeks 8 and 16). Levels of UST and CRP at Weeks 8 and 16 and FeCal at Weeks 6 and 16 were described. Pearson and Spearman correlations between drug exposure, changes in FeCal and CRP and change from baseline (BL) in CDAI at Weeks 6, 8, and 16 were analysed. Univariate logistic regression modelling was performed on BL variables, including concomitant medications, UST, FeCal, and CRP levels and changes from BL. Factors from the univariate model with $p < 0.15$ were included in a multivariate logistic regression model and significant predictors ($p < 0.15$) were selected by backward method.

Results: Among 387 patients induced with UST~6 mg/kg IV, 38.7% were ER, 23.8% were DR, 37.5% were NR. Serum UST, CRP and FeCal levels, correlation results, and multi-variate logistic regression are in Table 1. Drug levels were similar in ER and DR and slightly lower in NR. UST levels weakly correlated with CDAI changes from Wk0–16 in ER, but not in delayed responders. Among DR, Wk16 response rates were equally distributed in different quartiles from Wk8 exposure. No or weak correlation was found between changes from BL in FeCal CRP and CDAI at the same visit. Univariate logistic regression model identified age, BMI, corticosteroid (CS), active fistula (AF) at BL and history (hx) of extra intestinal manifestation (EIM) and colonic disease as potential predictors for delayed response vs. Wk8 response. The final model identified patients with younger age, non-CS at BL, hx of EIM, pure ileal disease hx and AF as more likely to have delayed response vs. Wk8 response.

Table 1. Main results

Serum UST levels, CRP and FeCal by response groups			
	Wk8 responders (ER)	Delayed responder (DR)	Non-responder (NR)
Wk 8 Ustekinumab serum levels (mcg/ml) n=354; median, IQR	6.44 (3.57-10.06)	6.83 (3.38-9.93)	5.84 (3.12-9.12)
W16 Ustekinumab serum levels (mcg/ml) n=335; median, IQR	2.80 (1.19-4.43)	2.63 (1.17-4.32)	2.10 (1.06-3.35)
CRP at week 8 (Mean, SD) n=387	8.86 ± 10.35	10.19 ± 13.73	17.85 ± 30.02
CRP at week 16 (Mean, SD) n=387	10.18 ± 16.27	8.62 ± 11.63	20.01 ± 31.53
FeCal at week 6 (Mean, SD) n=383	562.25 ± 717.87	441.11 ± 738.63	833.97 ± 1698.93
FeCal at week 16 Mean, SD) n=385	473.64 ± 661.31	448.42 ± 658.02	933.76 ± 1756.49
Pearson correlation			
CRP vs CDAI change at week 8	0.17	0.15	0.07
CRP vs CDAI change at week 16	0.15	-0.04	0.05
Spearman correlation			
Wk8 UST levels vs CDAI change at week 8	-0.02	-0.05	-0.01
Wk16 UST levels vs CDAI change at week 16	-0.19	-0.06	-0.02
FeCal vs CDAI change at week 6	0.003	-0.12	-0.04
FeCal vs CDAI change at week 16	0.003	-0.20	0.03
Predictors of delayed response (vs early response) identified by Multivariate Logistic regression model			
Variable	**OR**	**95% Confidence Limits**	
Older age	0.98	0.96- 1.00	
No CS at baseline	1.56	0.87-2.80	
Medical history of EIM	1.60	0.92-2.77	
Non-colonic disease	2.17	1.09-4.32	
Active fistula at BL	2.98	1.24-7.14	

CRP:C reactive protein; FeCal: fecal calprotectin; CS: corticosteroid; EIM: extra intestinal manifestation; BL: baseline; IQR: interquartile range

Conclusions: Delayed response to UST induction is observed in about 24% of patients with CD induced with the ~6 mg/kg IV dose and one additional dose SC at Wk8. Among tested variables, neither Wk8

drug levels nor biomarker response or previous anti-TNF failure was predictive of delayed response. Younger age, no CS or active fistula at BL, hx of extra intestinal manifestation and pure ileal disease were associated with increased risk for delayed response vs. Wk8 response.

References

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Ustekinumab: early experience and medium-term outcomes from a UK multi-centre real-world cohort

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Background: Ustekinumab is effective in inducing and maintaining remission of Crohn's disease (CD) in clinical trials. We present the first UK real-world, multi-centre study of effectiveness.

Methods: Data were collected for patients started on ustekinumab for CD from September 2015 to May 2018 at 3 tertiary London centres. Clinical endpoints were (i) remission (Harvey–Bradshaw Index (HBI) ≤4 points) and (ii) response (reduction in HBI of ≥3 points or sustained HBI ≤ 4 points) at Week 8 and 32. Biological endpoints were (i) remission (CRP < 5 mg/l in patients with a baseline CRP >5 mg/l) and (ii) response (50% reduction in CRP) at Weeks 8 and 32.

Results: Baseline characteristics of the 149 patients analysed are shown in Table 1.

Table 1. Baseline characteristics of patients treated with ustekinumab between 2015 and 2018

Characteristic		N (total =149)
Gender:	Male	76 (51%)
	Female	73 (49%)
Tertiary Centre	Guys & St Thomas'	46 (31%)
	Royal London Hospital	37 (25%)
	University College London Hospital	66 (44%)
Median age (IQR), years		21 (14-84)
Median disease duration (IQR), years		13.2 (1-38)
Smoking Status:	Current	21 (15%)
	Never/Former	119 (85%)
	Unknown	9
Montreal Classification:		
Age at diagnosis, years:	A1 (< 16)	65 (44%)
	A2 (16-40)	70 (47%)
	A3 (>40)	14 (9%)
Disease location:	L1 (Ileal)	29 (20%)
	L2 (Colonic)	32 (22%)
	L3 (Ileocolonic)	87 (58%)
	L4(Isolated Upper GI)	1 (1%)
Disease behaviour:	B1 (Inflammatory)	41 (28%)
	B2 (Stricturing)	51 (34%)
	B3 (Penetrating)	57 (38%)
Perianal involvement		65 (44%)
Prior biologic therapy:	Anti-TNF only	91(61%)
	Anti-TNF & Vedolizumab	52 (35%)
	Vedolizumab only	3 (2%)
	Biologic naïve	3 (2%)
Previous surgical intervention		85 (57%)
Concomitant medications (n=147):	Azathioprine/6MP/Methotrexate	65 (44%)
	Steroids	27 (18%)
Clinical data at baseline:	Mean HBI (n= 127)	6.24 (s.d. 4.88)
	Mean CRP (n=144)	18.1 (s.d. 21.94)
	Mean Faecal Calprotectin (n=36)	773 (s.d. 1557)

The majority (146 (98%)) had failed anti TNF therapy. All patients received i.v. induction and 147 (99%) received a s.c. dose at Week 8. At Week 32, 91 (75.8%) patients were on 8 weekly dosing. Discontinuation occurred in 24 (16.1%) patients due to: primary non-response (14 (9.4%)), drug reactions (2 (1.3%)), side effects (2 (1.3%)), and other causes (6 (4.0%)). Follow-up to Week 32 was available for 125 (83.8%) patients. Clinical and biological outcomes at Week 8 and 32 are shown in Figure 1.

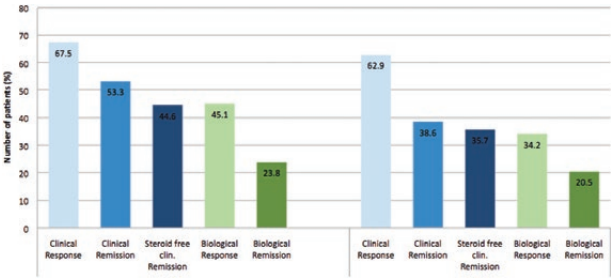

Figure 1. Clinical and biological outcomes at Weeks 8 and 32.

Clinical and biological outcomes at Weeks 8 and 32.

Adverse events occurred in 16 (10.7%) patients. Dosing schedule did not impact clinical and biological outcome at Week 32. Where paired data were available, mean (SD) HBI decreased significantly from baseline (6.2(4.9)) to Week 8 (4.6 (4.4), $n = 99$, $p = 0.016$) and was sustained at Week 32 (4.7 (4.1), $n = 56$, $p < 0.001$). Mean (SD) CRP decreased significantly from baseline (18.1 mg/l (21.9)) to Week 8 (11.9 mg/l (17.2), $n = 122$, $p = 0.002$), but did not sustain significant improvement at Week 32 (12.9 mg/l (17.4), $n = 93$, $p = 0.158$). Clinical remission at Week 8 was significantly associated with remission at Week 32: clinical remission ($n = 34$, $p = 0.013$, RR 3.16, 95% CI 1.23–8.13), and biological remission ($n = 56$, $p = 0.027$, RR 1.95, 95% CI 1.21–3.13). Biological remission at Week 8 was significantly associated with outcome at Week 32: biological response ($n = 62$, $p = 0.003$, RR 4.72, 95% CI 0.65–13.51), and biological remission ($n = 62$, $p = 0.003$, RR 4.41, 95% CI 1.78–10.87).

Conclusions: Ustekinumab is effective in a real-world cohort with response sustained at 6 months. Clinical and biological remission at Week 8 predicted both clinical and biological outcomes at Week 32.

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Trough levels of adalimumab better correlate with combined mucosal and transmural healing than clinical remission in Korean patients with Crohn's disease on adalimumab maintenance therapy

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Background: Studies on correlations between trough levels of adalimumab (TLAs) and levels of antibody to adalimumab (ATA levels) with combined mucosal and transmural healing as well as clinical remission in Crohn's disease (CD) in non-Caucasians are still lacking.

Methods: TLAs and ATA levels were measured using prospectively collected serum samples drawn from CD patients on adalimumab (ADL) maintenance therapy for more than 1 year at Asan Medical Center, South Korea, from August 2017 to July 2018. We analysed correlations between TLA/ATA levels and combined mucosal and

transmural healing as well as clinical remission. TLAs/ATA levels according to concomitant immunomodulator use were also evaluated.

Results: This study included 189 serum samples drawn from 149 patients. Ninety-eight patients were males (65.8%). The median age at diagnosis of CD and at starting ADL was 21.0 years (interquartile range [IQR], 18.0–28.0) and 31.0 years (IQR, 23.0–37.5), respectively. Fifty patients (33.6%) have been previously exposed to infliximab. Clinical remission (Crohn's disease activity index [CDAI] < 150) was observed in 77.8% (147/189 samples) and combined mucosal and transmural healing was observed in 16.2% (18/111 samples). TLAs differed significantly between two groups divided by a cut-off value of ATA as 4 μg/ml-eq (7.051 μg/ml [IQR 5.185–10.191] in ATI-negative samples [n = 182 {96.3%}] vs. 0.001 μg/ml [IQR 0.001–0.677] in ATI-positive samples [n = 39 {6.2%}], p < 0.001). TLAs showed significant differences between groups with or without combined mucosal and transmural healing (9.817 μg/ml [IQR 7.665–12.488] vs. 7.051 μg/ml [IQR 5.185–10.191], p = 0.010) but not between groups with or without clinical remission (7.891 μg/ml [IQR 5.477–10.835] vs. 6.786 μg/ml [IQR 4.080–11.031], p = 0.171). There was no difference in TLAs and ATA levels without/with concomitant immunomodulator use at the time of measuring TLAs/ATA levels, during induction period and continuously from induction period to the time of measuring TLAs/ATA levels (Table 1).

Conclusions: TLAs better correlated with combined mucosal and transmural healing than clinical remission in Korean CD patients on ADL maintenance therapy. There was no difference in TLAs/ATA levels according to concomitant immunomodulator use.

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High Cytomegalovirus DNA load in mucosal biopsies predicts steroid failure as well as colectomy in acute severe ulcerative colitis

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Background: Cytomegalovirus (CMV) reactivation may be responsible for steroid refractory acute severe colitis (ASC), which requires rescue therapy in form of surgery or advanced immunosuppression. The optimum technique for diagnosing CMV colitis in this setting remains unclear. We investigated the role of CMV Quantitative PCR for diagnosing CMV colitis and for predicting of steroid-failure in ASC.

Methods: Consecutive patients with ASC satisfying Truelove and Witts' criteria, hospitalised at a single-centre from May 2016 to November 2017, were included. The primary outcome measure was steroid-failure defined as colectomy and/or rescue therapy with cyclosporine or infliximab during admission. Oxford criteria, ulcerative colitis index of severity (UCEIS) at Day 1 and faecal calprotectin (FCP) at Day 3 were used to predict steroid response. Immunohistochemistry (IHC) and quantitative PCR for CMV was done on mucosal biopsies and the results were compared between steroid responders and non-responders.

Results: Of 37 patients (Mean age: 35 ± 12 years, 70% males), 14(38%) failed iv corticosteroids and 8(25%) required surgery. Although IHC for CMV was not different between steroid failures and responders (29% vs 17%, p = 0.40), patients with steroid failure had a significantly higher median level of mucosal CMV DNA [7840 (0–2 700 000) vs. 112 (0–34 459) copies/mg, p = 0.03]. Significantly greater number of patients with steroid failure had CMV DNA count >1000 copies/mg (71% vs. 26%, p = 0.007). CMV DNA count >1000 copies/mg (odds ratio 6.5 (95% confidence interval 1.3–33, p = 0.03)) and positive oxford criterion on Day 3 of iv corticosteroids (OR 6 (95% CI 1.2–30, p = 0.03)) were independent predictors of steroid-failure and need for rescue therapy/colectomy.

Conclusions: CMV DNA quantification in mucosal biopsy can detect CMV colitis and predict steroid failure in acute severe colitis with reasonable accuracy.

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On effectiveness, safety, and TDM of thioguanine in a cohort of 274 patients with IBD, intolerant for conventional thiopurines

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	TLAs (μg/ml)		ATA levels (μg/ml-eq)	
	Non-use	Use	Non-use	Use
At the time of measuring TLAs/ATA levels	8.176 (6.009–10.845)	7.291 (5.219–10.926)	0.001 (0.001–0.001)	0.001 (0.001–0.001)
	p = 0.599		p = 0.743	
During induction period	7.891 (5.337–10.947)	7.626 (5.347–10.861)	0.001 (0.001–0.001)	0.001 (0.001–0.001)
	p = 0.903		p = 0.453	
Continuously from induction period to the time of measuring TLAs/ATA levels	8.007 (5.526–10.945)	7.291 (5.266–10.668)	0.001 (0.001–0.001)	0.001 (0.001–0.001)
	p = 0.833		p = 0.172	

*Median (interquartile range)

TLAs/ATA levels according to concomitant immunomodulator use.

TLAs above 11.79, 12.00 and 14.76 μg/ml (area under the receiver-operating characteristic curve = 0.695) identified patients on deep healing with specificities of 85%, 90% and 95%, respectively.

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Background: Thioguanine (TG) has been considered as an alternative drug in patients with inflammatory bowel disease (IBD) who failed prior conventional immunomodulating therapy. In this study, we report on effectiveness, safety and therapeutic drug monitoring (TDM) data of an intercept cohort of patients with prolonged TG maintenance therapy.
Methods: In this nationwide, multi-centre study, medical records of TG using IBD patients were retrospectively reviewed. Both patient and drug characteristics as well as effectiveness and safety profile of TG therapy were assessed. Beneficial effect of therapy was defined as clinical remission, without (re)initiation of corticosteroids, concurrent biological therapy or surgical intervention. All adverse events (AE) which occurred during follow-up were listed and graded according to the common terminology criteria (CTCAE).
Results: In total, 274 patients (female 63% and Crohn's disease in 68%) were included with a median daily dosage of 20 mg (range 8–40 mg), median treatment duration of 51 months (IQR 36–89) and 1567 patient-years of follow-up. The beneficial therapeutic response to TG therapy was documented in 66% of patients within 6 months. A sustained clinical benefit of more than 1 year was observed in 51% of patients and 72% continued TG until end of follow-up. About 40% of patients developed AE during TG therapy of which 5% were graded as severe according to the CTCAE. Twenty-nine patients (11%) discontinued TG due to intolerance or severe AE. Infections requiring hospitalisation occurred in three (1.1%), non-melanoma skin cancer in six (2.2%) and melanoma in two patients (0.7%). Portal hypertension was found in three (1.1%) and NRH in two patients (0.7%). None of the patients developed pancreatitis including 43 patients (16%) with prior azathioprine or mercaptopurine-induced pancreatitis. Beneficial therapeutic response was correlated with 6-thioguanine-nucleotide (6-TGN) threshold levels of > 682 pmol/8 × 10^8 RBC ($p < 0.05$).
Conclusions: Long-term TG therapy was effective and well-tolerated as a maintenance treatment for IBD in about 70% of patients, continuing TG during a median treatment time of more than 4 years. Adverse events were not uncommon, but were mainly tolerable and of limited severity. An approximate 6-TGN threshold level of ≥ 700 pmol/8 × 10^8 RBC was associated with beneficial therapeutic response.

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Disease-related worries and concerns in patients with ulcerative colitis: 1-year data from ICONIC

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Background: ICONIC is the largest ongoing, prospective, multi-country observational study assessing cumulative disease-associated burden in adults with ulcerative colitis (UC) under routine care. This analysis evaluated patient worries and concerns up to 1 year using the Rating Form of inflammatory bowel disease (IBD) Patient Concerns (RFIPC) questionnaire.
Methods: Adults with early UC (diagnosed ≤36 months) were enrolled irrespective of treatment regimen or disease severity. Patients completed RFIPC, a 25-item questionnaire comprising frequently reported worries/concerns of IBD patients, at each visit (6-month intervals). Responses are scored on a 10-cm visual analogue scale for each individual question from 0 (no concerns) to 10 (a great deal). The mean of all 25 items represents the total score (lower scores indicate less worries/concerns). In this analysis, data are reported as observed using descriptive statistics at baseline (visit 1 [V1]), month 6 (V2), and month 12 (V3). Patients were stratified by physician-assessed disease severity (mild, moderate, severe, or in remission) at baseline, gender, and geographic location.
Results: Mean ± SD total RFIPC scores for all patients were 3.4 ± 2.2 (n = 1767) at V1, 3.0 ± 2.3 (n = 1562) at V2, and 3.0 ± 2.3 (n = 1412) at V3. At V1, mean RFIPC total scores were significantly higher in patients with severe disease vs. patients with mild ($p < 0.0001$) or moderate ($p = 0.0174$) disease or those in remission ($p < 0.0001$). Significant differences in changes from V1 to V3 in mean RFIPC total scores were observed between all disease severity groups ($p < 0.05$) except mild vs. in remission; the greatest changes from V1 to V3 were observed in patients with moderate and severe disease at baseline. The disease-related specific concerns with the highest mean total RFIPC scores (ie, scores ≥4.5) for all patients at V1 were 'having an ostomy bag', 'effects of medication', 'uncertain nature of disease', and 'energy level'. Mean total RFIPC scores for these specific concerns decreased over time for all patients. Mean RFIPC total scores at V1 were significantly higher in patients living in Latin America vs. other regions ($p < 0.05$) and in males vs. females ($p < 0.0001$). However, no significant differences were observed between geographic regions or genders for change from V1 to V3 in total RFIPC scores.
Conclusions: Data from ICONIC demonstrated that patients with early UC are highly concerned with the treatment and complications of their disease at all severities of disease, with higher impact among patients with more severe disease. However, these worries decrease over time. Regional and gender differences in UC-related worries/concerns were observed.

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Prognostic factors for long-term adalimumab treatment

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Background: Adalimumab is widely used in the treatment of patients with Crohn's disease (CD), either as first- and second-line therapy. However, data concerning the treatment persistence of adalimumab in patients with CD are scarce. Aims of the present study were (1) to evaluate the rate of primary non-response to adalimumab (PNR, defined by a withdrawal of adalimumab before the fourth month of treatment), (2) to evaluate the treatment persistence rates of

adalimumab during the follow-up, and (3) to identify factors associated with PNR and adalimumab persistence in CD patients.

Methods: We performed a retrospective study in from January 2012 to December 2017 in the three tertiary centres of Amiens, Caen, and Lille in France. All consecutive CD patients treated with adalimumab were analysed. Only patients who received a full adalimumab induction treatment were considered. Survival analyses were performed using the Kaplan–Meier method. Patient- and disease-related factors were used to identify independent predictors of PNR and of adalimumab failure-free survival using Cox proportional hazards regression.

Results: Between January 2012 to December 2017, 405 patients with CD received a full induction of adalimumab treatment. At adalimumab introduction, 41% were female, median age was 31[IQR: 24–44] years, median disease duration was 6 [IQR: 1–14] years and 30% of patients had a BMI ≥ 25 kg/m^2 (overweight and obese patients). 136 (34%) patients previously received infliximab treatment: 12% stopped infliximab for PNR, 49% for secondary loss of response (LOR), and 37% for intolerance, and 2% for other reasons. Median time on adalimumab was 1.7 [IQR: 0.7–3.6] years, and 226 (55%) patients experienced adalimumab failure. Seventy-five (16%) underwent major abdominal surgery and 102 (26%) were hospitalised during the follow-up. Thirty-eight (9%) patients had a PNR to adalimumab and 367 (91%) patients maintained scheduled adalimumab treatment. Adalimumab failure-free survival rates were 76% at 12 months, 59% at 24 months and 51% at 36 months. Multivariate Cox regression identified disease duration ≥ 2 years [HR 3.16 (95% CI 1.15–1.85), p = 0.02] and previous infliximab treatment [HR 2.38 (1.09–2.57), p = 0.017] as independent predictors of adalimumab failure survival.

Conclusions: In this large study of CD patients, more than half of the patients maintained adalimumab at 3 years. Patients with early CD, naive of anti-TNF treatments exhibited the best profile to response to adalimumab treatment. Awaiting results from disease modifications trials, these results suggest the clear benefit of introducing biologics early in the disease history.

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Tuberculosis infection under anti-TNF therapy – should we be looking for it?

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Background: Anti-tumour necrosis factor (TNF) therapy has revolutionised the treatment of inflammatory bowel disease. However, a major concern is the increased risk of developing tuberculosis (TB), which requires diagnosis and treatment of latent TB infection (LTBI) before initiation of anti-TNF agents. Currently, no recommendations exist regarding the need to regularly re-test patients for latent TB during treatment. We aimed to assess the incidence and to identify risk factors for newly acquired TB infection in patients under anti-TNF agents.

Methods: Adult patients under anti-TNF therapy for at least 12 months were retrospectively assessed. Patients with a negative pre-treatment interferon-γ releasing assay (IGRA) that repeated IGRA during anti-TNF treatment were reviewed. Patients with a pre-treatment positive IGRA were excluded.

Results: Out of 244 patients under anti-TNF agents (124 infliximab, 120 adalimumab), 87 patients were included. Patients had a mean age of 40 ± 14 years, 64.4% were females, 93.1% were under infliximab and 64.4% had Crohn's disease. Subsequent positive IGRA was identified in 9 patients (10.3% of our sample, 3.7% of all patients under anti-TNF therapy in our centre), of which 3 had active TB and 6 had LTBI.

When comparing patients with and without subsequent positive IGRA, no differences were found regarding age (39.6 vs. 36.7 years, $p = 0.991$) or gender (66.7% vs. 64.1% females, $p = 0.999$). Patients with subsequent positive IGRA have had close contact with patients with TB more frequently (22.2% vs. 0.0%, $p = 0.010$), however no differences were found regarding travels to TB-endemic areas (11.1% vs. 7.7%, $p = 0.548$), professional risk for TB infection (11.1% vs. 9.0%, $p = 0.999$), concomitant treatment with immunosuppressants (77.7% vs. 71.8%, $p = 0.999$), use of systemic steroids during anti-TNF treatment (33.3% vs. 35.9%, $p = 0.999$), diabetes mellitus (11.1% vs. 5.1%, $p = 0.429$) or active smoking (22.2% vs. 20.5%, $p = 0.999$). Furthermore, no differences were found in the duration of treatment at the time of subsequent IGRA (30.2 ± 26.7 vs. 42.5 ± 30.1 months, $p = 0.640$).

Conclusions: In patients under anti-TNF therapy, at least 3.7% of patients have a subsequent positive IGRA after treatment beginning. In our sample, only close contact with patients with TB was associated with a subsequent positive IGRA. Therefore, considering that infection during treatment is present in a non-negligible percentage of patients, and most of the classical risk factors cannot be used to identify at-risk patients, physicians may consider to routinely repeat IGRA in patients under anti-TNF therapy.

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Integrating efficacy and safety of vedolizumab and other advanced therapies for the treatment of ulcerative colitis: Results from a network meta-analysis

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Background: Direct head-to-head comparisons of the efficacy and safety of advanced therapies for ulcerative colitis (UC) are limited. We performed a systematic literature review and indirect treatment comparison of randomised controlled trials (RCTs) of biologics and tofacitinib (TOFA) for UC.

Methods: Medline, Embase, and Cochrane Library databases were searched from 1997 to July 2018 to identify RCTs of vedolizumab (VDZ), adalimumab (ADA), infliximab (IFX), golimumab (GOL) and TOFA. Efficacy outcomes were sustained response and remission at 1 y. Safety outcomes were overall adverse events (AEs), serious AEs (SAEs), overall infections, serious infections, and AEs leading to discontinuation as reported at 1 year. Odds ratios (OR) with 95% credible intervals (CrI) were estimated using network meta-analyses (NMA) and were transformed into number-needed-to-treat (NNT)

and number-needed-to-harm (NNH) using the pooled placebo (PBO) estimates across all trials. Results are reported for the overall population and among bio-naïve patients. Data for sustained response and remission with TOFA for bio-naïve patients were not available.

Results: Six RCTs were included in the NMA. Overall, VDZ 300 mg Q8W had statistically significantly higher chances of sustained response and remission (OR: 2.20 [1.07–4.64] and 2.57 [1.09–6.13], respectively) compared with ADA. In bio-naïve patients, VDZ 300 mg q8w had numerically higher OR of both sustained response and remission compared with all other therapies; however, the results were not statistically significant (data not shown). Compared with PBO, the OR of SR was statistically significantly higher for all the interventions (Table 1). The lowest NNT for sustained remission was with TOFA in the overall population and with VDZ in bio-naïve patients. Similar trends were observed for SR. The risk of all the AEs (including SAEs) was numerically the lowest with VDZ, with NNH values closest to PBO (Table 2).

Conclusions: Indirect treatment comparisons from this NMA suggested VDZ may achieve higher rates of both sustained response and sustained remission than comparator therapies in the overall study populations and was associated with lowest risk of AEs. These findings support the favourable benefit-risk profile of VDZ in UC, especially in bio-naïve patients. Head-head trials are required to confirm the findings.

Table 1. Odds ratios and number-needed-to-treat for sustained remission with vedolizumab and other treatments for ulcerative colitis.

	Overall Population		Biologic Naïve Cohort	
	Odds Ratio (95% CrI)	NNT (95% CrI)	Odds Ratio (95% CrI)	NNT (95% CrI)
Placebo (Reference Group)				
Adalimumab 160/80/40 mg[1]	2.81 (1.58, 4.86)	29.77 (14.77, 85.57)	2.37 (1.23, 4.49)	23.01 (9.93, 113.1)
Infliximab 5 mg/kg[1]	5.8 (2.86, 11.37)	11.89 (6.34, 27.42)	4.96 (2.54, 9.45)	8.69 (4.93, 19.23)
Infliximab 10 mg/kg[1]	5.52 (2.72, 10.79)	12.55 (6.64, 29.72)	4.73 (2.42, 9.03)	9.18 (5.01, 20.97)
Tofacitinib 10 mg/ 5 mg[1,2]	8.2 (4.9, 13.77)	8.14 (5.31, 13.18)	NA	NA
Tofacitinib 10 mg/ 10 mg[1,2]	10.79 (6.5, 17.98)	6.27 (4.28, 9.61)	NA	NA
Golimumab 200/100/50 mg[1,2]	3.4 (1.93, 5.93)	22.53 (12.61, 52.54)	2.98 (1.75, 5.04)	16.5 (9.37, 38.33)
Golimumab 200/100/100 mg[1,2]	3.86 (2.26, 6.56)	18.96 (11.47, 36.55)	3.34 (2.02, 5.57)	14.1 (8.71, 27.75)
Vedolizumab 300 mg Q4W[1,2]	6.69 (3.42, 13.7)	9.92 (5.5, 21.2)	5.91 (2.54, 13.8)	7.27 (3.78, 18.12)
Vedolizumab 300 mg Q8W[1,2]	7.2 (3.62, 14.3)	9.22 (5.24, 19.15)	6.38 (2.82, 14.9)	6.7 (3.61, 15.85)

CrI: Credible Intervals; NA: [Data] not available; NNT, number needed to treat; Q4W: every 4 weeks; Q8W: every 8 weeks.
[1]Data from ACT-1, PURSUIT-J, PURSUIT-M, OCTAVE SUSTAIN, ULTRA-2, and GEMINI 1 were included in the analysis.
[2]Due to re-randomization designs used for both VDZ, GOL and TOFA, study outcomes were recalibrated to ensure valid comparisons.
Interpretation of NNT and odds ratio (compared to placebo): A positive NNT or an odds ratio >1 indicates that a given treatment is **more efficacious** than placebo. An NNT value represents the average number of patients that would have to receive a given treatment in order to achieve one additional outcome of sustained remission.

Table 2. Odds ratios and number-needed-to-harm for safety outcomes with vedolizumab and other treatments for ulcerative colitis.

	Overall AEs		Overall Infections		Serious AEs		Serious Infections		AEs Leading to Discontinuation	
	Odds Ratio (95% CrI)	NNH (95% CrI)	Odds Ratio (95% CrI)	NNH (95% CrI)	Odds Ratio (95% CrI)	NNH (95% CrI)	Odds Ratio (95% CrI)	NNH (95% CrI)	Odds Ratio (95% CrI)	NNH (95% CrI)
Placebo (Reference Group)										
Adalimumab[1]	0.93 (0.57, 1.48)	−76.9 (−9.4, 17.2)	1.26 (0.88, 1.78)	18.2 (−35.7, 7.1)	0.97 (0.57, 1.68)	−333.33 (−18.5, 14.3)	0.81 (0.18, 3.14)	−250 (−45.4, 20.4)	0.65 (0.36, 1.13)	−31.3 (−13.9, 83.3)
Golimumab[1]	1.46 (0.75, 2.80)	18.18 (−20, 7.6)	1.37 (0.88, 2.14)	13.2 (−34.5, 5.5)	0.85 (0.52, 1.42)	58.8 (15.9, 22.7)	1.13 (0.40, 3.97)	333.3 (−66.7, 15.6)	0.96 (0.47, 2.12)	−333.3 (−18.2, 10.8)
Infliximab[1]	1.03 (0.69, 1.52)	200 (−14.1, 15.9)	1.9 (1.29, 2.78)	6.4 (4.1, 16.1)	0.81 (0.40, 1.66)	−47.6 (−12.5, 13.7)	0.83 (0.11, 7.27)	−250 (−41.7, 7.6)	0.45 (0.27, 0.74)	−19.2 (−45.5, −11.2)
Tofacitinib[1]	1.39 (0.97, 1.96)	20.4 (−200, 10.5)	1.61 (1.16, 2.24)	8.7 (5.1, 28.6)	1.24 (0.72, 2.13)	40 (−30.3, 8.6)	2.58 (0.89, 9.29)	28.6 (−333.3, 6.1)	0.96 (0.51, 1.81)	−333.3 (−19.6, 13.7)
Vedolizumab[1]	**0.82 (0.44, 1.45)**	**−28.6 (−5.9, 18.2)**	**1.04 (0.66, 1.68)**	**90.91 (−10.8, 7.8)**	**0.49 (0.26, 0.96)**	**−16.9 (−9.3, −200)**	**0.64 (0.17, 2.83)**	**−125 (−43.5, 24.4)**	**0.28 (0.05, 1.17)**	**−14.9 (−8.1, 66.7)**

AE: adverse event; NNH, number needed to harm.
[1]Data from ACT-1, PURSUIT-J, PURSUIT-M, OCTAVE SUSTAIN, ULTRA-2, and GEMINI 1 were included in the analysis. Due to small event rates, safety outcomes were pooled for each treatment with a multiple dosing regimen.
Interpretation of NNH relative to placebo:
- A positive NNH (> 0) indicates treatment is **less safe** than placebo. A high NNH indicates a relatively similar, but not better, rate of safety with treatment than with placebo.
- A negative NNH (< 0) indicates treatment is **safer** than placebo. A least negative (or close to zero) NNH indicates a better safety with treatment than with placebo.
- The bolded estimates in the table show the best safety profile.

Interpretation of Odds Ratio (compared to placebo):
- An odds ratio >1 indicates a higher rate of adverse events with the treatment evaluated.
- An odds ratio <1 indicates a lower rate of adverse events with the treatment evaluated.

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Audit and review of infliximab therapeutic drug monitoring and prescribing practices in paediatric inflammatory bowel disease (IBD) patients

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Background: Infliximab (IFX) is a monoclonal antibody against TNF-α which is implicated in the inflammatory response of IBD. Despite its success a large proportion of patients experience loss of response (LOR). This is a big concern, especially in children where treatment options are more limited. Therapeutic drug monitoring (TDM) has been proposed as a way of identifying patients at risk of LOR, as it is associated with sub-therapeutic IFX levels and the presence of antibodies to IFX (ATIs). IFX TDM was introduced to optimise IBD outcomes.

The objectives of this study were to audit whether all IBD patients on IFX had proactive TDM at the end of IFX induction (ie, fourth infusion), evaluate the IFX TDM results and examine how these influenced prescribing.

Methods: Sixty-three IBD patients were initiated on IFX in 2016 and 2017. Forty-five patients were included. Excluded were patient's still undergoing induction or had a delay, dose increase or discontinued IFX during induction. Recorded were IFX levels, ATI levels, IBD disease type, IFX induction regimen and changes to therapy in response to TDM.

Results: IFX TDM was performed in 39/45 (86%) patients at the fourth IFX infusion.

The majority of patients 31/45 (69%) had standard induction (5 mg/kg at Weeks 0,2,6,14), 9/45 (20%) had escalated induction (5 mg/kg at Weeks 0, 2, 6, 12) and 5/45 (11%) had rapid induction (5 mg/kg at weeks 0,1,4,8/12). The review demonstrated that 30/39 (77%) patients had suboptimal IFX levels (<4 mg/l), 5/39 (13%) patients achieved therapeutic IFX levels (4–8 mg/l), and 4/39 (10%) patients had high IFX levels (>8 mg/l). Patients were more likely to achieve therapeutic IFX levels with escalated induction compared with standard induction, 37% compared with 8%. ATI's were detected in 10/39 (26%) patients. All of these patients also had low or undetectable IFX levels suggesting that low IFX levels are a primary driving factor for the development of ATIs. In response to TDM results 32/39 (82%) patients required a change in therapy. Of these 29/32 (90%) required IFX optimisation which is defined as an increase in dose to 10 mg/kg (44%), decrease in dosage interval to 6 weekly (38%) or both (8%). Two patients switched therapy (6%) and 1 discontinued IFX and had a colectomy (3%).

Conclusions: Our results demonstrate that TDM is helping to identify patients at risk of LOR. A high proportion of patients have sub-therapeutic IFX levels and the presence of ATI's after IFX induction. These results strongly suggest that standard induction is unsuitable for paediatric IBD patients. Further work is needed to explore an optimum induction regimen.

Clinicians are optimising IFX therapy in response to TDM. Further work is necessary to explore the impact of IFX dose optimisation on disease outcomes.

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Segmental colectomy for ulcerative colitis: a new paradigm? A multi-centric study in 72 patients

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Background: The gold standard of surgery for ulcerative colitis (UC) is total coloproctectomy (TCP) with J-pouch. The only alternative is total colectomy (TC) with ileorectal anastomosis. There is no place for segmental colectomy (SC) due to the supposed high risk of postoperative colitis in the remnant colon. The aim of this study was to report a multi-centric experience of SC in UC patients to assess if SC can represent an alternative to TCP or TC.
Methods: This was a retrospective multi-centric study from expert centres in Europe and US. All UC patients undergoing SC were included. Postoperative complications according to Clavien-Dindo's classification, long-term results and risk factors for postoperative colitis and reoperation for colitis on the remnant colon were assessed.
Results: 72 patients (50 men (70%), with a mean age at diagnosis of UC of 46 ± 18 years and mean age at SC of 57 ± 17 years were included: sigmoidectomy (n = 28), right colectomy (n = 24), proctectomy (n = 11) and left colectomy (n = 9). Indications for surgery were: colonic cancer (n = 27), sigmoid 'diverticulitis' (n = 17), colonic stenosis (n = 5), colonic dysplasia or polyps (n = 8), and miscellaneous (n = 15). Postoperative complications were observed in 17/72 patients (24%): classified Clavien-Dindo I-II in 7 (10%) and III or more in 10 (14%). Three patients died postoperatively (4%) due to respiratory (n = 2) or hepatic (n = 1) failure.
5/69 patients (7%) developed early flare of UC before 3 months postoperatively: 2 treated initially medically of whom 1 required completion TC and 3 with refractory colitis requiring either completion SC (n = 1), completion TC (n = 1) or TCP with definitive end ileostomy (n = 1); 29/64 other patients (45%) developed flare of UC more than 3 months after SC after a median delay of 26 months. Among them, 12/29 (41%) underwent surgery (1 SC, 3TC and 8 TCP), after a median delay of 26 months after SC. After a median follow-up of 40 months, 24/69 patients (35%) were reoperated after a median delay after SC of 19 months: 22/24 (92%) underwent TC (n = 9) or TCP (n = 13) and 2/24 (8%) an additional SC. Reasons for redosurgery were: colitis (n = 14; 20%), cancer (n = 3) or dysplasia (n = 3), colonic stenosis (n = 1), and unknown reason (n = 3). Endoscopic score before SC was Mayo II-III in 5/5 (100%) patients with early flare vs. 16/44 without (36%; p = 0.01) and in 9/12 (75%) patients with reoperation for colitis vs. 11/35 without (31%; p = 0.02).
Conclusions: After segmental colectomy in UC patients, postoperative early colitis is rare (7%) with only 20% requiring reoperation for colitis during follow-up. Thus, in selected UC patients with no active colitis, segmental colectomy could represent a reasonable alternative to total coloproctectomy or total colectomy.

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Low vitamin K, vitamin D and calcium dietary intake in IBD patients represents a potentially reversible risk factor for osteoporosis

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Background: Patients with inflammatory bowel diseases (IBD) are at increased risk of osteoporosis due to chronic inflammation, corticosteroids, surgery and deficiency of micronutrients. Inadequate intake of calcium and vitamin D (VitD) are frequent and represent easily reversible risk factors. More recently attention has been focussed on the role of vitamin K (VitK) in the alterations of bone metabolism, but few data are available on the dietary intake of VitK in IBD. The aim of the study was to assess the dietary intake of VitK, VitD and Calcium in IBD and seek correlations with demographics and disease characteristics.
Methods: A food frequency questionnaire, validated for calcium intake, integrated with questions on the main dietary sources of VitD and VitK, was administered to 208 IBD patients (90 Crohn's disease (CD) and 118 ulcerative colitis (UC), 112 males and 96 females, mean age 50 years) and 195 controls. Data were compared with Institute of Medicine's Dietary reference intakes: Recommended Dietary Allowance (RDA) for Calcium and VitD and Adequate Intake (AI) for VitK.
Results: The dietary intake of VitK, VitD and calcium expressed as per cent of RDA/AI was significantly lower (p < 0.01) in IBD than in controls. The risk of inadequate VitD and VitK intake was higher in IBD than in controls: 91.8% vs. 84.1% and 55.8% vs. 30.3% (OR 2.1, 95% CI 1.1–4, p = 0.0186 and OR 2.9, 1.9–4.4, p < 0.001, respectively).
IBD males had reduced intake of all micronutrients compared with controls, while in females the difference was significant only for VitK. The difference vs. controls was significant in all age groups for VitK (p < 0.01) and in patients ageing > 40 years for calcium. VitD intake showed a no significant trend. No differences between Crohn's disease and Ulcerative colitis were observed.The difference of VitD dietary intakes between active and inactive IBD was significant (46.5% vs. 57.2%, p = 0.015). The intake of VitD was lower in IBD patients ageing >60 years, compared with other age groups. Conversely, the calcium and VitK intakes were similar.
Conclusions: Dietary calcium, VitK and VitD intakes were significantly reduced in IBD vs. controls. IBD patients with active IBD had lower VitD intake than those in remission. The correction of dietary habits may reverse some risk factors for osteoporosis in a large proportion of IBD patients. Focussing attention on micronutrients may help identifying those patients who may profit from calcium, VitD and VitK supplementation, and prompt effective dietary counselling.

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Adalimumab therapeutic drug monitoring test validated for measuring ABP 501 biosimilar

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Background: Promonitor®-ADL test is routinely used to monitor IBD patients treated with adalimumab (ADL). ABP 501 [adalimumab biosimilar; EU: AMGEVITA® (adalimumab); US: AMJEVITAT (adalimumab-atto), Amgen] was authorised throughout the European Union in March 2017 and has been recently launched in several countries. Therapeutic drug monitoring (TDM) is broadly used as an aid for patient management. However, all TDM tests available should be properly validated against each new approved biosimilar to ensure safe application for patient monitoring as these may guide dose adjustments. Here we validate the suitability and performance of Promonitor-ADL CE-marked test for quantification of AMGEVITA in comparison to the reference HUMIRA®.

Methods: The validation study was in accordance with the design requirements established in the Clinical and Laboratory Standards Institute (CLSI) guideline EP17-A2 (Lower Limit of Quantification, LLOQ) and EP10-A3 (imprecision and bias). CLSI guidelines set a standard for the diagnostic industry accepted by all regulatory agencies. LLOQ was determined with four independent human serum sample matrices per each of three low level ADL concentrations, replicated three times per two lots of Promonitor-ADL (Progenika, Spain) kits for each drug HUMIRA and AMGEVITA over 3 days by one operator. Imprecision was evaluated using three replicates of five human serum sample matrices representative of clinically relevant ADL concentrations and spanning the measurement range of Promonitor-ADL, run on one instrument with one kit lot by one operator over six non-consecutive operating days and one run per testing day, with an acceptance criteria of CV%≤20%.
Results: The LLOQ of Promonitor-ADL for AMGEVITA and HUMIRA were 0.34 µg/ml and 0.36 µg/ml, respectively. LLOQ values met accuracy goal proposed based on total error ≤25% and precision. The imprecision of Promonitor-ADL calculated by estimating the components of variance due to within-run and between-day factors meet the accuracy goals proposed at all concentration levels of AMGEVITA vs. HUMIRA (CV% between 5% and 10%). The bias study showed that Promonitor-ADL can equally measure the active moiety ADL either in the reference biologic ADL or in the biosimilar AMGEVITA. The test is able to quantify AMGEVITA in the measurement range of 0.9 to 10.9 µg/ml with a bias estimate of –0.089 to 0.306 µg/ml and an overall imprecision of 6% to 9%. The measurement range includes the recommended clinical decision points.
Conclusions: Promonitor-ADL test can equivalently measure either the reference ADL or the approved biosimilar AMGEVITA with the same sensitivity, precision and accuracy.

P330

A national survey on therapeutic education in inflammatory bowel disease by an association of caregivers and expert patients: French Association for Therapeutic Education in inflammatory bowel disease (AFEMI)

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Background: Nowadays, many stakeholders are convinced of the essential role that therapeutic patient education (TPE) plays in the management of inflammatory bowel disease (IBD) and in the improvement of patients' quality of life. This led to the creation, in 2018, of AFEMI (French Association for Therapeutic Education in IBD). The purpose of this national survey was to determine the current situation of TPE in IBD in France.
Methods: Questionnaires were developed by a committee of physicians, TPE specialists and patients, and were emailed to 73 centres involved in the care of patients with IBD. Questionnaires have been completed by gastroenterologists, nurse coordinators or by the entire TPE team.
Results: Of the 73 centres contacted, 37 responded, including 33 public (university and non-university hospital) and four private centres. Of the responding centres, 70% reported having an accredited IBD TPE Programme. One was being created in 16% of the centres. Seventy per cent of the centres had a transversal TPE structure. The number of educators ranged from 1 to 5, with a mean of 2.5. Six people (on average) were involved in TPE programmes, with considerable variety between centres. Finally, TPE was defined as a priority action for the centre in only 26% of the responding centres. Less than half of the centres had a room dedicated to TPE and/or a transversal platform for patients. Among the topics addressed in individual sessions or in workshops, knowledge of the disease (95%), diet (91%), fatigue (77%) were almost always routinely proposed, while pain (18%), physical activity (27%) or work (50%) were not always covered. Sixty-eight per cent of responding centres did not have a tool for evaluation or planning of their TPE program. Twenty-four per cent of respondents used digital media (applications, websites, telemedicine) for the daily practice of TPE. Fifty per cent of the patients enrolled in a TPE program in the responding centres had been referred by the French Crohn's and colitis association (AFA, Association François Aupetit). Twenty-nine per cent of the centres routinely offered TPE sessions to all patients and 24% of the centres held them during consultations. Fifty-two per cent of the centres involved an expert patient in their program. An educational diagnosis was only made for 33% of the patients and an evaluation of the benefits of the TPE at the end of the program was only carried out in 28% of the centres.
Conclusions: TPE in IBD has started to develop and is becoming more organised in France, even if there is still a heterogeneity of practices. AFEMI's key missions are to promote the development of TPE in IBD and to harmonise practices (specific training of IBD educators, development of better tools, healthcare professionals support through structured programmes).
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Real-world assessment of biological treatment of inflammatory bowel disease at an Austrian Referral Centre: the ULTIMATE study

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Background: Inflammatory bowel diseases (IBD) are characterised by a chronic or relapsing inflammation of affected gut segments leading to progressive gut damage and intestinal complications. Biologics are considered to be the most effective treatment options nowadays. However, primary nonresponse, loss of response and side effects may occur in a clinically-relevant number of patients. We analysed treatment duration and dose escalations with biologics as well as hospitalisation rates during treatment periods.
Methods: This was a retrospective single-centre cohort study at an Austrian referral IBD centre. All consecutive patients with Crohn's

disease (CD) (n = 93) or ulcerative colitis (UC) (n = 53) who initiated a biologic treatment such as TNF-α-inhibitors and vedolizumab between January 2006 October 2016 were included. Medical characteristics including details of treatment with biologics were captured from chart review. The study outcomes were treatment duration, the need for dose escalation with biologics and hospitalisation rates. We performed a descriptive analysis.

Results: The number of patients who received each treatment lines (n = 268) are presented in the table. Median duration of first, second, and 3rd line biologic treatments in CD patients were 32.2, 34.9, and 11.8 months, respectively, compared with 21.8, 19.9, and 16.6 months in UC patients. Dose escalation was required in 39.6% of all therapy lines (n = 106). This was required in 34.9% of all first-line treatments and increased numerically in subsequent lines. The dose was increased by 37.1% compared with the standard dose in all treatment lines. In patients who received over two lines, the dose increase for TNF-α-inhibitors was numerically higher compared with vedolizumab (42.3% vs. 33.9%); vedolizumab was primarily used as second and third line treatment. The hospitalisation rate rose numerically with the number of treatment lines.

Treatment lines	Adalimumab	Infliximab	Vedolizumab	Golimumab	Other	Total
First line	73 (59/14)	61 (32/29)	6 (1/5)	6 (1/5)		146 (93/53)
Second line	26 (18/8)	20 (14/6)	26 (12/14)	3 (1/2)	3 (2/1)	78 (47/31)
Third line	1 (0/1)	6 (4/2)	16 (9/7)	2 (2/0)	2 (1/1)	27 (16/11)
Fourth line		3 (3/0)	3 (3/0)	5 (3/2)	3 (2/1)	14 (11/3)
Fifth line				1 (1/0)	2 (2/0)	3 (3/0)
Total	100 (77/23)	90 (53/37)	51 (25/26)	17 (8/9)	10 (7/3)	268 (170/98)

Description of analysed treatment lines after conventional treatment of CED patients (CD/UC).

Conclusions: The duration of first and second biologic treatment lines were both nearly 3 years for CD and nearly 2 years for UC, respectively, and decreased with subsequent treatment lines. Overall, approximately 40% of all IBD patients needed dose escalation of their biologic treatment. The hospitalisation rate increased with the number of treatment lines.

P332

Multinational comparisons of practices in overseas travel in Crohn's disease and ulcerative colitis

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Background: Travelling overseas with inflammatory bowel disease (IBD) has increases in morbidity, however few studies have examined these risks. The aims of this multinational study were to identify global travel-preparation and travel practices in IBD patients, predicting who will experience barriers when travelling overseas.

Methods: Patients from gastroenterology clinics in Australia, England, and Israel were invited to participate in the study. Surveyed topics included disease type and management, pre-travel advice, use of travel insurance, amount of overseas travel, and flare-ups during travel. Participants who answered questions assessing difficulties travelling overseas were defined as experiencing a barrier. Binary logistic regression was used to examine predictors of experiencing barriers.

Results: Survey respondents (n = 1887) from England (n = 1507), Israel (n = 42) and Australia (n = 338) had a mean age range of 30–49 years, 75.6% female (n = 1657), and 60.2% had Crohn's disease. Pre-travel advice was obtained mostly from IBD specialists (32.7%) and GPs (27.6%), and pertinent pre-travel advice patients requested related to travel insurance (39.6%), care of IBD during travel (28.4%) and drug infusions and transportation (28%). Vaccination rates pre-travel was only 16%. Multi-variate logistic regression indicate significant predictors of experiencing a barrier during overseas travel were sex ($p < 0.05$, β = 1.39), appropriate travel preparation (β = 3.96, 95% CI 1.07–1.80), IBD severity (β = 1.35, 95% CI 1.70–9.19), and education (β = 1.57, 95% CI 1.23–2.00).

Conclusions: This study is the first to examine international travel practices in the IBD population with a multi-national cohort. As such the results of this study will help inform current IBD specialists how best to prepare IBD patients for international travel.

P333

Associations between multiple immunosuppressive treatments before surgery and surgical morbidity in patients with ulcerative colitis during the era of biologics

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Background: Immunomodulators or biologics, with the exception of corticosteroids, do not appear to be risk factors for postoperative infectious complications of ulcerative colitis (UC). Recently, many immunosuppressive therapies including some biologics are used mainly to treat UC, and many patients are on multi-agent immunosuppressive therapy at the time of surgery. Therefore, we evaluated the influence of preoperative multiple immunosuppressive agents on the occurrence of surgical site infection (SSI) in UC during the era of biologics.

Methods: We reviewed surveillance data from 301 patients who underwent restorative proctocolectomy between January 2015 and April 2018. The incidences of SSI and possible risk factors among patients receiving different immunosuppressive therapies were compared and analysed.

Results: The incidence of incisional SSI (wound infection) was 6.6%, and that of organ/space SSI (abdominal/pelvic sepsis) was 7.0%. Prednisolone (PSL), carcineurin inhibitors (CNIs), and anti-TNF-α antibodies were administered to 117/301 (38.9%), 119/301 (39.5%), and 146/301 (48.5%) patients, respectively. Doses of PSL were significantly decreased because of the recent shift towards the

use of biologics. The median total amount of PSL administered and preoperative PSL dose were 3,000 mg and 10 mg, respectively. Numbers of patients who are treated with none agents or thiopurine alone, with one agent, with two agents, and with three agents were 66(21.9%), 107(35.5%), 111(36.9%), and 17(5.6%), respectively. Age at initial surgery was significantly lower in patients with three agents, including PSL, CNIs, and anti-TNF-α antibody ($p < 0.01$). Urgent/emergent surgery was significantly less common in patients with no or one agent(s) ($p = 0.04$). Patients with no agents or AZA/6-MP administration alone had many more surgical indications of cancer/dysplasia ($p < 0.01$). Severe or fulminant disease was significantly lower in patients with no agents or thiopurine alone than in other groups ($p < 0.01$). The kinds and numbers of immunosuppressive agents did not significantly correlate with each incidence. Preoperative serum albumin <3.4 g/dl (odds ratio: OR, 5.0), surgical indication of cancer/dysplasia (OR, 8.4), and perioperative blood transfusion (OR, 4.6) were shown to be independent risk factors for incisional SSI, whereas only perioperative blood transfusion (OR, 3.4) was identified as an independent risk factor for organ/space SSI.

Conclusions: Although no correlation between preoperative immunosuppressive therapies was found, we should mention selection bias for treatment before surgery. However, biologics, calcineurin inhibitors, and thiopurines did not affect surgical morbidity in UC.

P334

Chromoendoscopy is superior to white light endoscopy for the detection of advanced colonic neoplasia in patients with inflammatory bowel disease

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Background: Although recent guidelines recommend chromoendoscopy (CE) as a method of choice for neoplasia surveillance in inflammatory bowel disease (IBD), there is still controversy regarding the utility of this technique in clinical practice. The aims of this study were to compare the accuracy of CE and white light endoscopy (WLE) for the detection of overall neoplasia and advanced neoplasia in patients with IBD.

Methods: Patients who underwent surveillance colonoscopy were identified from a single institution IBD database from 1999 to 2017. Patients with prior history of colon cancer or total colectomy were excluded. CE procedures were compared with their respective WLE controls in a paired comparison and the frequency of all neoplasia, advanced neoplasia and serrated neoplasia was assessed for both targeted and random biopsies. Demographic and clinical data were obtained from review of medical records

Results: Total 315 procedure performed in 106 individuals were identified over a median follow-up 3 years (median 3 colonoscopy/patients). Among them, 290 procedures performed in 98 individuals were finally included in the analysis. The median age was 56 years (20–87), 55.1% were male, 69.4% had UC and 11.2% had PSC. CE and WLE were performed in 159 and 131 episodes, respectively. CE detected neoplasia in 40.9% of colonoscopies vs. 23.7% with WLE ($p = 0.02$). In addition, CE detected more advanced neoplasia (18.2% vs. 6.1%, $p = 0.002$) and more serrated lesions (14.5% vs. 6.1%, $p = 0.02$). Significantly fewer samples were obtained per procedure with CE (14.9 ± 9.7 vs. 20.9 ± 11.1, $p < 0.01$). Cancer was diagnosed in 2 cases, one detected by CE and the other one after colectomy.

	Chromoendoscopy ($n = 159$)	White light endoscopy ($n = 131$)	p
Neoplasia per procedure	65 (40.9%)	31 (23.6%)	0.020
Advanced neoplasia per procedure	29 (18.2%)	8 (6.1%)	0.002
Serrated neoplasia per procedure	23 (14.5%)	8 (6.1%)	0.022
Targeted biopsy (mean ±SD)	213 (1.3 ± 1.2)	89 (0.7 ± 1.0)	<0.001
Neoplasia per targeted biopsy	88	38	0.819
Random biopsy (mean ± SD)	2143 (13.7 ± 9.3)	2630 (20.2 ± 10.6)	<0.001
Neoplasia per random biopsy	4	5	0.490

Characteristics of neoplastic lesions detected by chromoendoscopy and white light endoscopy

Conclusions: CE has a higher detection rate than WLE for conventional neoplasia, advanced neoplasia and serrated neoplasia in patients with IBD under surveillance. Considering that significantly fewer biopsies are required, CE may be both more accurate and more cost-effective compared with WLE.

P335

Long-term follow-up of switching from original infliximab to infliximab biosimilar: real-world data

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Background: Infliximab original has changed the natural history of inflammatory bowel diseases (IBD) over the past two decades. However, the recent expiration of its patent has allowed the entry of the first Infliximab biosimilar into the European and Spanish markets. Currently, switching drugs data in IBD are limited. Our aim was to assess the long-term data of effectiveness, loss of response, safety and immunogenicity of switching to CT-P13 from infliximab reference product (RP) in patients with inflammatory bowel disease.

Methods: This was a prospective single-centre observational study in patients with moderate to severe Crohn's disease (CD) and ulcerative colitis (UC). All patients were switched from infliximab RP

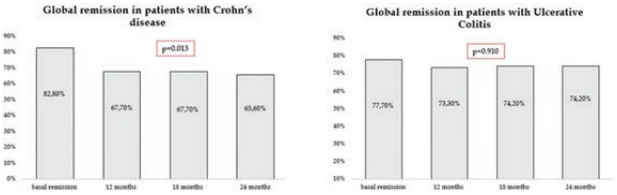
(Remicade®) to CT-P13 treatment and followed up to 24 months. The efficacy endpoint was the change in clinical response according to the Harvey–Bradshaw (HB) score and partial Mayo score for patients with CD and UC, respectively. C-reactive protein (CRP) and IFX-drug level were also measured. Adverse events and ADAs were monitored and recorded throughout the study.

Results: A total of 100 patients with inflammatory bowel disease (64 CD/36 UC) were included. Seventy-two per cent of them remained on CTP-13 and 28% patients discontinued the therapy due to loss of response (15%), adverse events (4%) or remission/mucosa healing (8%). Baseline demographics and phenotypic characteristics of patients with CD and UC according to the Montreal Classification are shown in Table 1.

Characteristic		n (%)	CI (95%)
Sex	Men	51 (51)	40.7; 61.3
	Women	49 (49)	38.7; 59.3
Age	Crohn Disease	40.5 (18 – 77)	
	Ulcerosa Colitis	44.0 (37- 53)	
Smoking status			58.4; 77.6
Never		68 (68)	9.9; 26.0
Previous		18 (18)	5.9; 20.1
Current		13 (13)	
CD patients n= 64			
Age at diagnosis	A1 (< 16)	8 (12.5)	3.6; 21.4
	A2 (17- 40)	46 (71.9)	60.1; 83.7
	A3 (>41)	10 (25.6)	5.9; 25,3
Location at diagnosis			
	L1 (ileal)	16 (25)	13.6; 36.4
	L2 (colonic)	27 (42.2)	29.3; 55.1
	L3 (ileocolonic)	18 (28.2)	16.3; 39.9
	L3+L4 (upper gastrointesinal tract)	3 (4.7)	0.9; 13.1
Disease behavior			
	B1 (nonstricturing, nonpenetrating)	39 (60.9)	48.2; 73.7
	B2 (stricturing)	12 (18.8)	8.4; 29.1
	B3 (penetrating)	13 (20.3)	9.7; 30.9
Perianal disease	yes	28 (43.8)	30.8; 56.7
UC patients N=36			
Extent (UC)	E1 (proctitis)	13 (36.1)	19.9; 53,2
	E2 (left-sided colitis)	11 (30.6)	14.1; 46.9
	E3 (pancolitis)	12 (33.3)	15.5; 50.1
Severity	S1 (mild)	13 (36)	19.9; 53,2
	S2 (moderate)	17 (47.2)	29.5; 64.9
	S3 (severe)	6 (16.7)	3.1; 30.2
Extraintestinal manifestations	Yes	10 (27.7)	11.8; 43.8
Concomitant medications use			
Thiopurines	CD	27 (42.2)	29.3; 55.1
	UC	13 (36.1)	19.0; 53,2
Methotrexate	CD	14 (21.8)	10.9; 32.8
	UC	3 (8.3)	1.8; 22.5
Steroids	CD	10 (15.6)	5.9; 25.3
	UC	5 (13.9)	4,7; 29.5
Time using Remicade	(months), median (IQR)	58 (37-80)	
Time global using IFX	(months), median (IQR)	81 (63-107)	

Baseline demographics and phenotypic characteristics according to the Montreal Classification.

Global Remision: 75.8% (75/99), 69.6% (64/92), 69.9% (65/93), and 68.5% (63/92) of patients were in remission at 6, 12, 18 and 24 months, respectively. Twenty-two per cent of patients increased the dose, reaching remission in 60%.



CD and UC remission.

HB score, partial Mayo Score, CRP and IFX-drug levels did not show clinical significant changes.

Conclusions: Most of the patients switching from infliximab original maintained CT-P13 at 2 years of follow-up with a good profile of effectiveness and safety.

P336

Behavioural treatment options for psychological comorbidities in patients with inflammatory bowel disease: a systematic literature review

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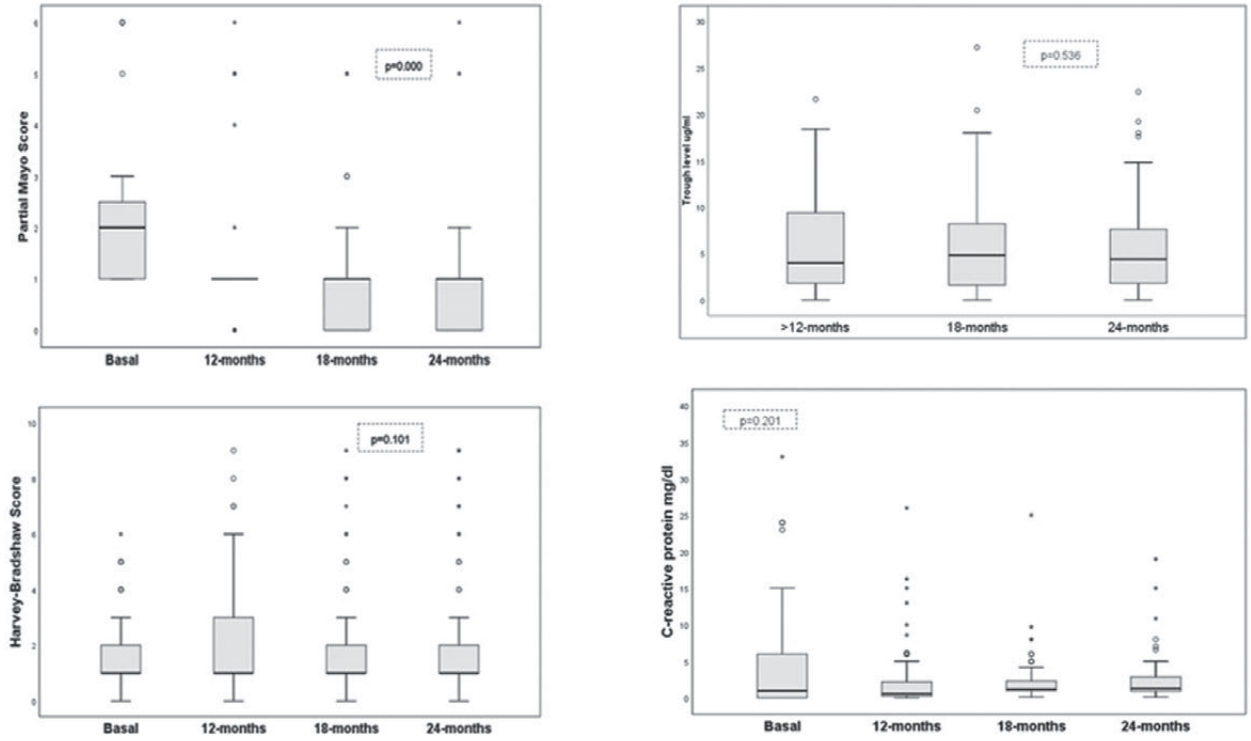
Background: Many patients with inflammatory bowel disease (IBD) have psychological comorbidities, such as anxiety and depression. We report results from a systematic literature review (SLR) conducted to explore the burden, behavioural treatment options, and unmet needs associated with psychological comorbidities in patients with IBD.

Methods: MEDLINE® and Embase® were searched (via ProQuest®) for articles and conference abstracts (published January 2003–August 2018) on psychological comorbidities in IBD (ie, anxiety and depression). Studies in adult and adolescent populations were included. Outcomes including epidemiology, behavioural treatments, and unmet needs were reviewed.

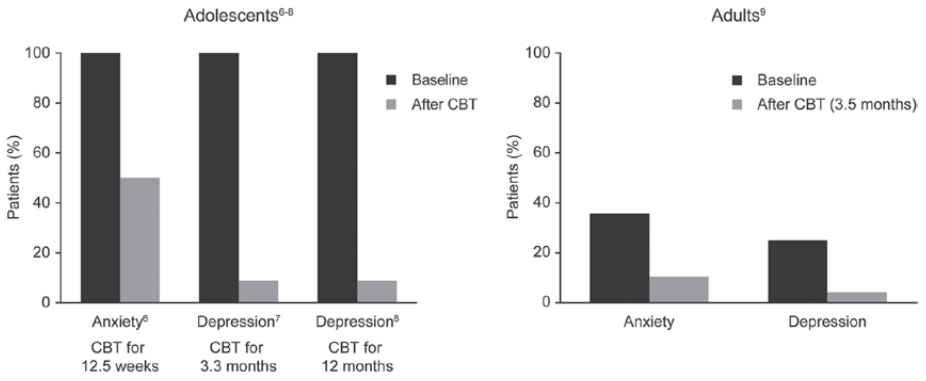
Results: Of 1,551 publications identified, 69 on clinical burden/unmet needs were included (31 articles; 38 conference abstracts). In patients with IBD, prevalence of depression ranged from 2.2%[1] to 62.3%[2] and anxiety ranged from 7.6%[3] to 41.8%.[4] Cognitive behavioural therapy (CBT), which is effective in the treatment of anxiety and depression,[5] reduces the rate of comorbid anxiety and depression when present in adolescents and adults with IBD (Figure).[6–9] Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version scores significantly improved after CBT (baseline 5.64; endpoint assessment 1.09, $p < 0.001$).[8] In adults, IBDQ total symptom score improved from 144.7 at baseline to 168.12 after CBT therapy; individual domains (systemic, emotional, and social) also improved.[9] In a separate study, group therapy significantly decreased Beck Depression Inventory scores from 13.9 to 6.88 ($p \leq 0.05$).[10] However, up to half of depressed patients with IBD were not consulting a mental health professional.[11] Screening for depression was inconsistent, with it not being documented or addressed in 67.6% of patients with IBD.[12] Additionally, over the past 12 months, 41.1% of IBD patients with (vs. 22.4% of those without) depression felt that they did not receive health care when needed.[11] One barrier to psychological care is reimbursement for mental health providers, for example, one study found that 52.5% of claims for psychiatric services for IBD patients were not reimbursed.[13]

Abstract P335



Scores UC and CD.

Serious adverse events related to medication were reported in 14 (14%) patients, two patients developed low levels of ADAs during the follow-up.



Note: Szigethy 2006[8] was an extension of Szigethy 2004[7]; improvement was sustained in the extension part of the study.

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Conclusions: This SLR shows behavioural interventions, such as CBT and group therapy, were effective at reducing anxiety and depression in patients with IBD. However, there are gaps in patient care and access to these treatments where healthcare professionals could intervene to improve outcomes in this patient population.

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Switching from originator infliximab to CT-P13: single-centre experience from the UK

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Background: The infliximab biosimilar (CT-P13) received market authorisation for inflammatory bowel disease in late 2016 with the aim of reducing cost and increasing access to therapy. The prospect of 'switching' patients from originator to CT-P13 has concerned clinicians. #8232;We present an experience of 'switching' from originator infliximab (IFX-O) to CT-P13 and present efficacy, safety, and immunogenicity data from our cohort.

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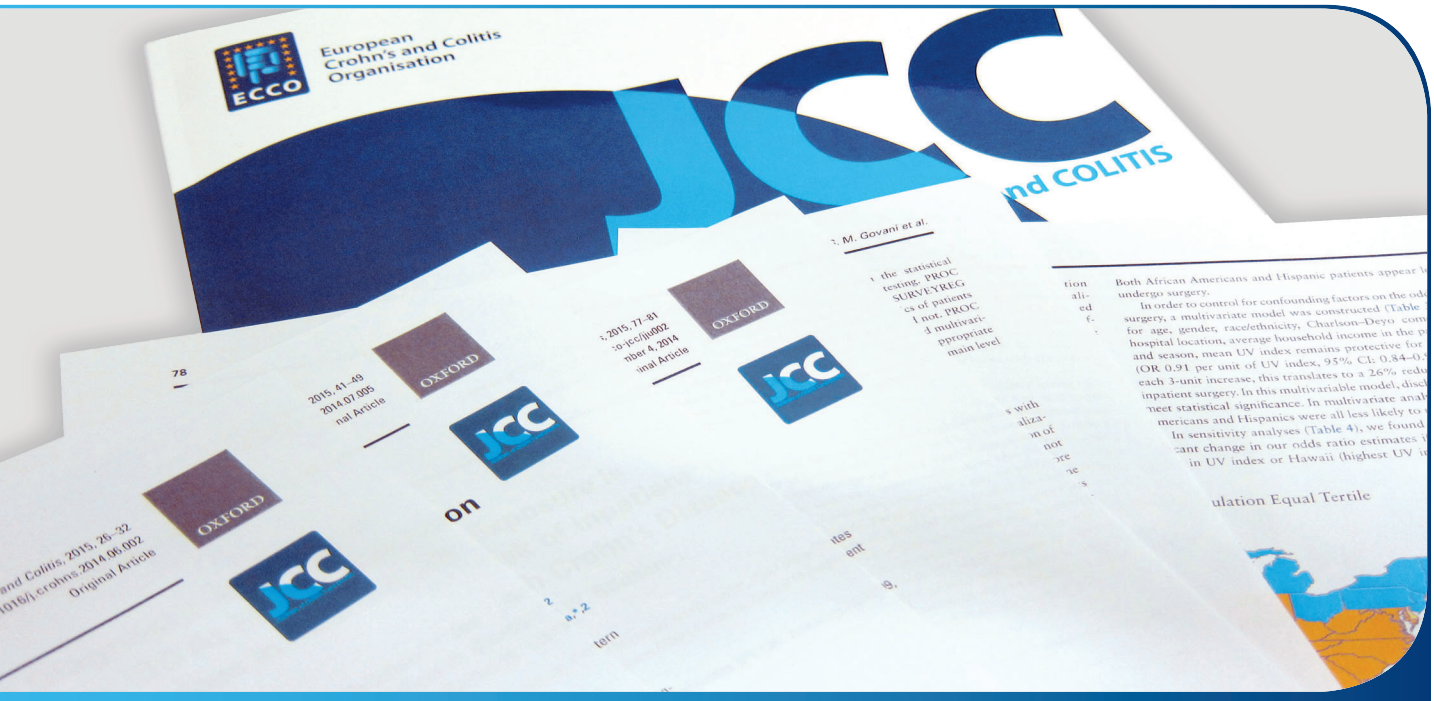

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Methods: We performed a retrospective review of patients switched from IFX-O to CT-P13. Disease demographics, clinical course and outcomes were analysed from electronic case records at a median of 8 months and at last follow-up at 13 months.
Results: Ninety-six patients (35 females) were 'switched' from IFX-O to CT-P13. Of these 44 had Ulcerative colitis (UC) and 52 had Crohn's disease (CD) with a mean age at diagnosis of 34.7 years (median = 33, IQR = 24.5). Montreal phenotype for UC was E1 = 1, E2 = 16, E3 = 27 and for CD (L1 = 10, L2 = 12 , L3 = 29, L4 = 1) and (B1 = 27, #8232;B2 = 14 , B3 = 11), 9 patients had perianal disease. Mean duration of IFX-O treatment was 49. 8 months (median = 44, IQR = 52) and on CT-P13 11.5 months (median 13). At switch, 76 patients had a normal CRP (UC = 33, CD = 43), and in 15 patients it was elevated (UC = 10, CD = 5). At 8 months, 80 patients remained in biochemical remission (UC = 35, CD = 45) and in 14 patients (UC = 8, CD = 6) CRP increased. Seventy-two patients (UC = 34, CD = 38) were in clinical remission (pMayo < 2 and HBI < 5). Of 51 patients (UC = 21, CD = 30) undergoing endoscopic assessment, 31 achieved mucosal healing (UC = 13, CD = 18). At 13 months, 69 patients remained on CT-P13. Twenty-seven discontinued the drug due to immunogenicity (*n* = 10), loss of response (*n* = 5), surgery (*n* = 5), remission (*n* = 5) , side effects (*n* = 2), and 1 patient died of hospital acquired pneumonia. 39 out of 96 patients had therapeutic drug levels checked within 13 months of switch, of whom 27 had sub-therapeutic levels (below 4 μg/ml). Antibodies to Infliximab were seen in 15 of 39 patients (38.5%), of whom 8 were switched to an alternative biologic, 2 had dose escalation (10 mg/kg IFX), 4 patients stopped IFX with no other intervention, and 1 person continued treatment at same dose with low antibody titre of 6.
Conclusions: Biosimilar IFX (CT-P13) was well tolerated. Clinical efficacy and loss of response rates with CT-P13 appears to be similar to IFX-O. This holds promise for a wider adoption of 'switching' to fulfil the purported aims of wider access to treatment at a lower cost.

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Long-term complications in patients with fistulising Crohn's disease

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Background: Fistulisng Crohn's disease is most severe form of disease behaviour in patients with Crohn's disease (CD) and is associated with high morbidity. Long-term follow-up data on disease course are lacking from Asian countries. We retrospectively analysed CD patients with fistulising behaviour for long-term complications under inflammatory bowel disease (IBD) clinic follow-up from a single centre.
Methods: Medical records of 807 CD patients diagnosed between 2005 and 2018 were screened for fistulising behaviour, including perianal and non-perianal fistulas as identified by clinical or radiological methods. Total of 100 patients with fistulising CD were included in analysis
Results: Among all patients (mean age 30.3 ± 13.25 years, males: 71%, mean duration of follow-up: 3.5 years), perianal fistula was the commonest (57%), followed by entero–enteric fistula (20%), entero-vaginal (6%), entero-vesical (3%) and entero-cutaneous (8%) fistula. More than 2 types of fistulas were seen in 10% patients. Majority had complex perianal fistula and 46% of them had perianal collections. Diarrhoea was the most common presenting symptom (49%) followed by abdominal pain (24%) and perianal symptoms (13%). Colonic involvement was seen in 81% patients (L2 = 44%, L3 = 37%). Perianal fistula without involvement of rectal mucosa (rectal sparing) was observed in 8% cases. Extra intestinal manifestations were seen in 21% of patients. Most of the patients received multiple courses of antibiotics and none of the patient had complete response. Fifty per cent of patients were on immunomodulatory therapy including azathioprine/6-mercaptopurine and methotrexate. Thirty-six per cent patients were treated with biologicals (infliximab 22, adalimumab 6, both 8). Clinical response was achieved in 72% of patients. Four patients responded to addition of second biological. Interestingly, high percentage (42%) of patients had history of antitubercular therapy. Five patients underwent VAAFT (Video Assisted Anal Fistula Treatment) surgery. Twelve per cent patients required diversion procedure in view of non-response to medical or surgical therapies. Long-term complications like anal canal strictures were seen in 8% cases. One patients developed colorectal malignancy in perianal fistula and one patient developed adenocarcinoma from the site of entero-enteric fistula. Four patients expired during follow-up.
Conclusions: Patients with fistulising CD have a complicated disease course, characterised by increased risk of anal strictures, malignancy, mortality and surgery. Biologics are associated with moderate response rates in patients with fistulising CD.

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Application of Bayesian modelling with infliximab to determine optimal patient-specific regimens

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Background: Infliximab (IFX), a chimeric monoclonal IgG1 anti-TNF-α antibody, is often used to treat inflammatory bowel disease (IBD), particularly if non-biologic treatments have failed. IFX is usually administered intravenously at the approved standard dose of 5 mg/kg initially at Weeks 0, 2, and 6, then in standard dose intervals of every 8 weeks. Individualisation of IFX dosing to optimise clinical response is considered desirable with an accepted target trough serum concentration of ≥5 μg/ml, yet application of therapeutic drug monitoring (TDM) is often difficult due to significant patient variability. To assist clinicians with individualised IFX dosing, a Bayesian pharmacokinetic dosing strategy was developed.
Methods: The electronic medical records of adult IBD patients treated with IFX at gastroenterology physician office infusion centres were retrospectively reviewed. All patients receiving IFX with a minimum of two serum concentration measurements and 3 infliximab doses prior to serum levels were identified. Data collected from these records included patient demographics, pertinent laboratory, IFX dosing history, serum IFX concentrations, timing of TDM relative to dosing, type of IFX assay employed, and presence of IFX antibodies. The predictive performances of a previously published model (Ternant et al.) were evaluated on this external patient cohort.

Further protocol assessment and clinical validation of this dosing tool are currently underway.

Results: We identified 87 patients who met our inclusion criteria. The mean age was 42 (range 18–76), mean weight was 79.5 kg (range 47–141.5), and 47% male. 174 serum samples were assayed, with each patient assigned to one of the two commercially available assay types. A robust Bayesian pharmacokinetic dosing platform was implemented satisfactorily, providing accurate individual concentration predictions (bias –0.28 mg/l; RMSE 4.7); however, the bias and precision of forecasted trough concentrations varied significantly based on assay method.

Conclusions: We developed a unique decision support dosing tool for use with IFX. This platform provides clinical guidance for IFX dosing based on patient characteristics and pharmacokinetic principles and supports individualisation of both IFX dose and interval.

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Vedolizumab in the treatment of chronic refractory pouchitis: a systematic review

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Background: Approximately 50% of patients with ileal pouch anal anastomosis (IPAA) develop pouchitis, with 10–15% of acute pouchitis developing chronic pouchitis (CP). Whilst the majority responds to antibiotic therapy, treatment options for chronic antibiotic-refractory pouchitis (CARP) include combination antibiotic therapy, budesonide, immunomodulators (IM) or anti-tumour necrosis factor (TNF) antibodies. There is limited data on the role of vedolizumab (VZB), an a4b7 integrin antagonist, in the treatment of CP. We performed a systematic review of the literature to explore the efficacy of VZB in CP.

Methods: A systematic literature search in MEDLINE (1966–November 2018), Cochrane Central Register of Clinical Trials, and abstracts from recent major gastroenterology meetings (Digestive Disease Week, United European Gastroenterology Week and Congress of European Crohn's and Colitis Organisation) was performed using the following terms: 'integrin', 'vedolizumab', 'pouchitis'. Only English language publications and abstracts on the efficacy of VZB for CP in ulcerative colitis patients with IPAA were included; Crohn's disease of the pouch was excluded. Additional trials were identified through review of reference list of included articles

Results: Six case reports (n = 6)[1–6] and 3 retrospective case series[8–10] (2 in abstract form, n = 51) were included; 1 case series (Philpott J 2017)[7] was excluded (duplicate). Only 1 ongoing randomised-controlled phase IV study (NCT02790138) was found whose data has yet to be reported. All patients (n = 57) had chronic antibiotic-refractory/dependent pouchitis and received VZB after failing prior therapy, including IM and anti-TNF. In the case reports,[1–6] six patients (mean age 36 years, M:F 1:1) with CARP received induction/maintenance VZB; symptom improvement was seen as early as 6 weeks and pouchoscopy at 14–33 weeks reported near/complete resolution of pouchitis. In the 3 retrospective case series, 64–75% achieved improvement/clinical remission (CR) at 12–14 weeks, with 58.3% still in CR at 46 weeks: (a) 14 of 19 (73.7%) with CARP who received at least 1 dose of VZB had improvement of modified Pouchitis Disease Activity Index (mPDAI) at 12 weeks (median decrease 2 units, p = 0.031)[9]; (b) 9 of 12 (75%) who received induction/maintenance VZB achieved CR (mPDAI< 5 + decrease of ≥2) at 14 weeks, with 7 (58.3%) still in CR at median 46(14–105) weeks[10]; (c) after 3–4 doses of VZB, 64% with CARP/antibiotic-dependent pouchitis achieved CR (PDAI<7)[8] at 14 weeks. Minor adverse events were reported in 10–16%.[8–10]

Conclusions: From uncontrolled studies and case reports, VZB appears to be efficacious and safe for the treatment of CP refractory to antibiotics and other therapy including anti-TNF. Controlled data are needed to confirm its efficacy in this group of patients.

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Identification and management of psychological distress after stoma surgery: a qualitative study of patients and healthcare professionals

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Background: Evidence suggests that psychological distress is common among people with inflammatory bowel disease (IBD) following stoma surgery and is associated with adverse clinical and quality of life outcomes. Despite this, psychological problems are often under-detected and under-treated. The aim of this qualitative study was to identify the barriers and facilitators affecting access to psychological

care among young adults with IBD following stoma surgery, from the perspective of both patients and relevant healthcare professionals (HCPs). This study was undertaken within the context of the National Health Service (NHS) in the UK (UK).

Methods: Semi-structured interviews were conducted with 13 young adults with IBD and a stoma (aged 18–29), and 16 HCPs (including general practitioners, consultant gastroenterologists, colorectal surgeons, IBD nurses and stoma care nurses). Data were analysed using a grounded theory approach. Ethics approval was obtained from the NHS West Midlands Research Ethics Committee (REF: 17/WM/0236).

Results: Psychological distress was commonly reported by young adults, particularly in the immediate period before and after stoma surgery, which in some cases persisted. Not all described having this distress recognised by their healthcare team and/or received psychological support. Various barriers and facilitators to accessing care were identified at patient, professional and healthcare system levels. Patients' attitudinal factors such as stigma on mental health and reluctance to seek help, as well as knowledge about available services influenced their decision to consult, or not, about psychological distress. HCP barriers included a lack of time during consultations to address psychological issues, as well as the perception that mental health problems go beyond their professional remit. System barriers included the complexity of care pathways which resulted in a lack of role clarity and coordination between primary and secondary care professionals, and funding constraints which limited the provision of specialised psychological services. HCPs emphasised the importance of developing a good-quality therapeutic relationship to facilitate disclosure of distress, as well as receiving appropriate training to further their skills and confidence in better addressing psychological problems.

Conclusions: This study indicates the need for clinicians to support disclosure of psychological symptoms among young adults with IBD after undergoing stoma surgery. The development of more effective care pathways, which include psychological services for patients with an identified need, are required. Although this is an NHS-based study, these findings may nevertheless have broader applicability.

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A population pharmacokinetic model to support therapeutic drug monitoring during vedolizumab therapy

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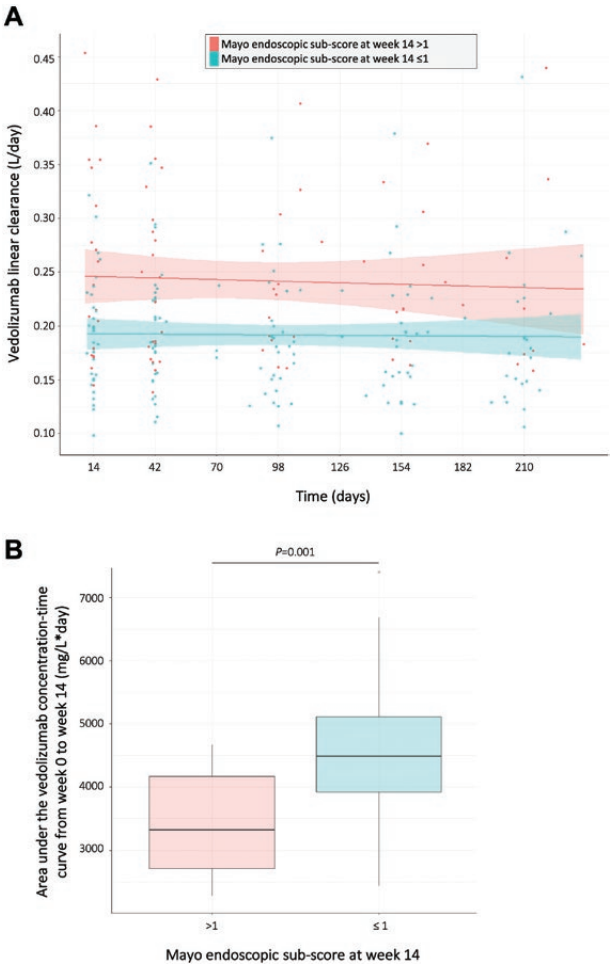
Background: Patients with ulcerative colitis (UC) and Crohn's disease (CD) starting vedolizumab (VDZ) therapy can benefit from therapeutic drug monitoring (TDM).[1] A population pharmacokinetic (popPK) model may support dose optimisation to improve attainment of the predefined trough concentration (TC) targets.

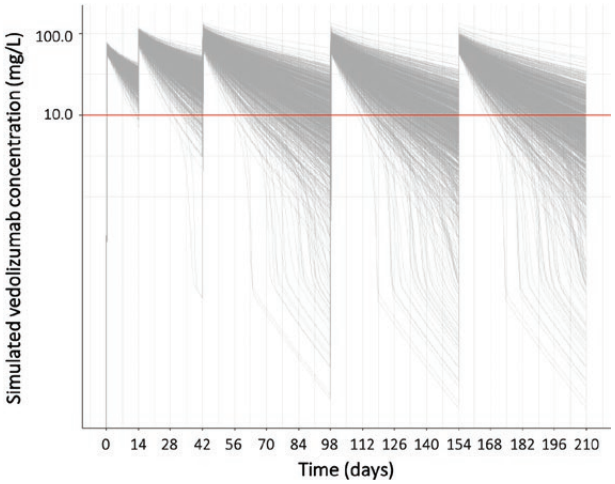
Methods: A total of 939 trough samples (from week (w) 2 to w30) of 178 patients (66 UC, 112 CD; excluding one patient with antibodies to VDZ) was used to develop a popPK model. Data were analysed under a known two-compartment model with parallel linear and nonlinear clearance by using prior distributions from the GEMINI popPK model to support estimation of PK parameters that were poorly informed by the current data (NONMEM 7.4 with $PRIOR).[1] Simulations were performed using Berkeley-Madonna 8.3.

Results: Our model with fully data-driven estimation of the linear clearance (CL_L; 0.207 L/day [3%], typical value [relative standard error]) and volume of distribution in the central compartment (V_c; 4.62 L [9%]) showed good predictive capacity. Linear terminal elimination half-life of VDZ was 15.5 days. Lower albumin, mean platelet volume and haemoglobin, and higher C-reactive protein and fat-free mass were associated with higher CL_L, thus predicting lower VDZ exposure. Prior anti-TNF therapy did not impact CL_L. Furthermore, CL_L was not different between patients with UC and CD. Still, 28% and 40% of the interindividual variability (IIV) on CL_L and V_c, respectively, remained unexplained. Patients with Mayo endoscopic sub-score (MES) ≤1 at w14 had a lower VDZ CL_L already at w2 (p = 0.009) (Figure 1A). VDZ CL_L slightly decreased with time (p = 0.028). In addition, the cumulative area under the VDZ concentration-time curve (AUC) from w0 to w14 was higher in patients with MES ≤1 at w14 (p = 0.001) (Figure 1B). Although VDZ is characterised by nonlinear CL, this only appeared to be relevant in the sub-therapeutic concentration range (<10.0 mg/l), providing additional motivation to target patients above the predefined ~14.0 mg/l TC threshold during maintenance therapy (Figure 2).[1]

Conclusions: Our model demonstrates good predictive capacity and may be implemented in a TDM software tool to improve attainment of the exposure targets (TC and AUC) in individual patients with inflammatory bowel diseases.



(A) The estimated vedolizumab linear clearance (linear mixed effects model) and (B) the area under the vedolizumab concentration-time curve from week 0 to Week 14 (Wilcoxon Rank-Sum test) of patients with Mayo endoscopic sub-score at Week 14 >/≤1.



Simulated profiles from the vedolizumab popPK model (n = 1,000; median covariate values). The red line indicates the critical 10.0 mg/l concentration below which concentrations drop more rapidly due to an increasing contribution of nonlinear clearance.

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Efficacy of ustekinumab in Crohn's disease at maintenance Week 56: IM-UNITI study

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Background: Ustekinumab (UST), a human IgG1κ monoclonal antibody that binds to the p40 protein subunit of IL-12 and IL-23 cytokines, is approved for moderate–severe Crohn's disease (CD). Primary endpoint data (Wk44) from the pivotal Phase 3 study, IM-UNITI, have been previously reported. We examined efficacy of UST after 1 year of maintenance therapy (Wk56).

Methods: The Phase 3 program of UST in CD includes 2 multicentre, double-blind, placebo (PBO) controlled 8-week induction studies, UNITI-1 (anti-TNF therapy failures) and UNITI-2 (conventional therapy failures) comprised of 1281 patients. Pts in clinical response(reduction in CDAI ≥100 points or in clinical remission) at Wk8 to IV UST induction in UNITI-1 and 2 were randomised 1:1:1 to SC UST 90 mg q8w or q12w or PBO in IM-UNITI. Pts completing Wk44 of IM UNITI qualified to participate in the IM-UNITI extension study. The study was unblinded when Wk44 analyses were completed. Due to the durable biologic effect of a single IV induction, 36% of the randomised withdrawal population on SC PBO in maintenance were in remission at Wk44. At Wk56, 84.6% of patients remained blinded; unblinded patients were conservatively assumed to have same remission status as Wk44. Wk56 remission data were assessed in this post-hoc analysis of the primary randomised population of 388 patients who initially responded to UST IV induction and were subsequently randomised to UST 90 mg q8w (n = 128), 90 mg q12w (n = 129), or PBO (n = 131) in the maintenance study. Wk56 is the first long-term extension visit 12 weeks after Wk44 of IM-UNITI.

Results: Compared with Wk44, patients on UST at Wk56 maintained remission (50.8% for UST q8w, 49.6% for UST q12w; p < 0.001), while there was a noteworthy reduction in remission rates (27.5%) in PBO patients (Table 1). The proportion of patients in clinical remission not receiving corticosteroids at Wk56 was significantly greater with UST vs. PBO (46.1% UST q8w, 43.4% UST q12w, 22.1% PBO; p < 0.001). In a subgroup analysis of conventional therapy failure patients (UNITI-2), a greater proportion of patients treated with UST achieved clinical remission that was maintained at Week 56 from Wk44 (Table 1) compared with PBO. Safety at Wk56 was similar to previous safety results reported for Wk44; no new safety events were observed.

Table 1. Efficacy at Week 44 and 56 for primary randomised population and patients who failed conventional therapy efficacy.

	PBO	UST 90mg SC q8w	UST 90mg SC q12w
Primary Randomised Population, N	131	128	129
Wk 44 Remission, n (%)	47 (35.9)	68 (53.1) p=0.005	63 (48.8) p=0.040
Wk 56 Remission, n (%)	36 (27.5)	65 (50.8) p<0.001	64 (49.6) p<0.001
Wk 56 Remission and not receiving corticosteroids n (%)	29 (22.1)	59 (46.1) p<0.001	56 (43.4) p<0.001
Subgroup of Patients who Failed Conventional Therapy (UNITI 2 Population), N	70	72	72
Week 44 Remission, n (%)	31 (44.3)	45 (62.5) p=0.02	41 (56.9) p=0.146
Week 56 Remission, n (%)	24 (34.3)	45 (62.5) p<0.001	44 (61.1) p=0.002
PBO=placebo; q8w=every 8 weeks; q12w=every 12 weeks; SC=subcutaneous; UST=ustekinumab; Wk=Week			

Conclusions: In patients with moderate–severe CD who responded to UST induction, SC UST is significantly better at maintaining clinical remission vs. PBO. Remission rates among UST patients were maintained from Wk44 to Wk56; yet, durable biologic effect from one IV induction dose seemed to diminish more rapidly from Wk44 to Wk56.

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Real-world effectiveness of tofacitinib in ulcerative colitis: a multi-centre study

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Background: We aimed to describe the real-world effectiveness of tofacitinib in ulcerative colitis (UC).
Methods: We analysed a retrospective, multi-centre cohort from six centres in the USA. UC patients started on tofacitinib (10 mg BID) for active disease were included. Primary outcome was clinical response (>50% reduction in symptoms) at Week 8 as determined by physician global assessment. Secondary outcomes included clinical remission (no symptoms) at Week 8, clinical response/remission at Week 16 and endoscopic healing (defined as Mayo endoscopic score ≤1 or absence of erosions/ulcerations) within 6 months of initiating tofacitinib. Descriptive statistics and Fisher exact tests were performed. Logistic regression assessed predictors of Week 8 response. A multi-variable model was created using backward elimination.
Results: A total of 123 UC patients were included with a median age of 38 years (IQR 27–46) and 5 years disease duration (IQR 2–9). 56.1% were men and 60.2% had pancolitis. 28.5% were bio-naïve while 40.7% had been exposed to both anti-tumour necrosis factor (anti-TNF) biologics and vedolizumab (VDZ). Ninety-six patients completed 8 weeks of tofacitinib. 60.8% had clinical response and 13.5% clinical remission at Week 8. At Week 16 (total n = 74), 55.4% had clinical response and 48.6% clinical remission. 64.9% (total n = 57) had endoscopic healing. A larger proportion of bio-naïve patients achieved clinical response with no difference between those exposed to both anti-TNF and VDZ or either alone (Table 1). Patients with prior exposure to 2 biologic classes (anti-TNF and VDZ) had lower rates of endoscopic healing compared with bio-naïve and 1 biologic class exposure (Table 1). Bio-naïve status and higher albumin were associated with greater chance of Week 8 response while pancolitis, baseline endoscopic Mayo score 3, concomitant steroids at start of tofacitinib, and male gender were associated with lower chance of response (Table 2). In multi-variable analysis, bio-naïve status (aOR 5.50, 95% CI 1.71–17.65), concomitant steroids (aOR 0.25, 95% CI 0.07–0.83), and male gender (aHR 0.25, 95% CI 0.08–0.83) were associated with Week 8 response.
Conclusions: Tofacitinib is effective at inducing clinical response in a real-world clinical setting. Prior exposure to biologics is associated with reduced chance of clinical response and endoscopic healing.

Table 1. Tofacitinib response rates by prior biologic exposure. (*p = 0.007, **p < 0.001, *** p < 0.001. Patients who discontinued tofacitinib before Week 8 or 16 were considered non-responders.)

Prior biologic exposure status	Clinical response Week 8*	Clinical response Week 16**	Endoscopic healing by 6 months***
Bio-Naïve	81.8% (total n = 33)	81.3% (total n = 32)	87.1% (total n = 31)
Prior exposure to 1 class (Anti-TNF or VDZ)	44% (total n = 25)	36.4% (total n = 22)	57.1% (total n = 14)
Prior exposure to 2 classes (Anti-TNF and VDZ)	55.3% (total n = 38)	35% (total n = 20)	16.7% (total n = 12)

Table 2. Baseline variables significantly associated with tofacitinib clinical response at Week 8 OR: odds ratio; CI: confidence interval.

Univariable logistic regression variable	OR (95% CI)	p-value
Bio-Naïve	4.50 (1.64–12.37)	0.004
Pancolitis (ref = limited colitis)	0.34 (0.14–0.86)	0.02
Albumin (g/dl)	2.63 (1.02–6.80)	0.046
Mayo endoscopic score 3 (ref=score 2)	0.27 (0.10–0.72)	0.01
Male (ref=female)	0.28 (0.11–0.70)	0.007
Concurrent steroids at start of tofacitinib	0.22 (0.08–0.58)	0.002

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Risk of long-term post-operative recurrence (POR) in Crohn's disease patients with a first postoperative normal endoscopic assessment under thiopurine prevention

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Background: Endoscopic post-operative recurrence (PORe) in Crohn's disease (CD) occurs between 30 and 50% after intestinal resection with anastomosis under preventive treatment within the first 6–12 months after surgery. The natural history of those patients who do not present PORe in the first endoscopy is not known and no recommendations about PORe monitoring beyond the first year after surgery in this population are available. Objective: To evaluate the natural history of the PORe in those patients who do not present PORe in the first endoscopic assessment.
Methods: From a specific database including all patients with CD who underwent resection with anastomosis at our institution since 1998 were prospectively included and followed, we identified those who initiated AZA within the first month after surgery and who underwent a first endoscopic assessment showing no PORe (Rutgeerts score i1) and who had at least a further endoscopic assessment. PORe was defined by Rutgeerts score i2, clinical POR (PORc) as the appearance of symptoms requiring changes in CD treatment, and surgical recurrence (PORs) as the need for a new resection. We defined a combined outcome (CO) as the occurrence of any of the following events: need for biological agents, PORc, or PORs during the follow-up.
Results: From 291 patients undergoing ileocolic resection and anastomosis, 94 patients (29%) had a first post-surgery endoscopy with Rutgeerts score i1. Regarding PORe risk factors: 52% penetrating pattern, 48% smokers at surgery, 12% previous resections and 22% perianal disease. Twenty-one per cent of patients received metronidazole in the first 3 months postop. The median follow-up was 84 (IQR 49–156) months. Thirty-seven per cent developed PORe (median 45 [IQR 30–60] months), of whom 65% were i2 and 35% were i3-i4, whereas only 14% PORc and 3.6% PORs. The accumulated probability of developing PORe during the follow-up was 0%, 16%, 40% and 50% at 1, 3, 5, and 10 years from the first postop endoscopic assessment, while the cumulative probability of CO was 1%, 2.5% 12%, and 19% at 1, 3, 5, and 10 years. No factors were associated with PORe.
Conclusions: The risk of PORe in patients without significant lesions in a first endoscopic assessment under thiopurine prevention is relatively low but steady over time, suggesting that monitoring remains necessary. In these patients PORs is very low in the long-term.

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Small bowel permeability improves with nutritional therapy in mild-to-moderate active paediatric Crohn's disease

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Background: Intestinal permeability (IP) is increased in Crohn's disease (CD) patients and their first degree relatives. The causes of barrier disruption remain unclear but likely relate to inflammation with possible effects of nutrients and microbes. Infliximab has been shown to improve IP in CD but the impact of nutritional therapy on IP is unknown. We prospectively assessed the effects of nutritional therapy on IP in a randomised controlled trial, comparing the Crohn's disease exclusion diet (CDED) to the gold standard exclusive enteral nutrition (EEN) in children with CD. Mannitol is an easily absorbed small sugar that reflects the small bowel (SB) surface area, whereas the disaccharide lactulose is only absorbed through larger pores and reflects permeability; therefore, the ratio of lactulose/mannitol (L/M) represents SB relative permeability.

Methods: The CDED study was a 12-week prospective, international, multi-centre, randomised controlled trial in children with mild-to-moderate active luminal CD, comparing CDED to EEN. During the first 6 weeks of the study patients in the CDED group received CDED Stage 1 diet + 50% calories from liquid formula (Modulen, Nestle) whereas the EEN group were fed exclusively with Modulen. A L/M test for intestinal permeability was performed at weeks 0 and 3 by administering a sugar solution containing lactulose (5 g) and mannitol (1 g) and then collecting urine for LC-MS/MS analysis. A cut-off L/M ratio of 0.015 was chosen, based on published literature (McOmber et al. JPGN 2010).

Results: L/M ratios were available at both time points for 39 patients (23 CDED and 16 EEN). At baseline, 9/23 (39%) CDED and 8/16 (50%) EEN patients had a normal L/M ratio, whereas at 3 weeks of treatment this increased to 15/23 (65%) and 9/16 (56%), respectively. Using generalised estimating equation analysis there was no difference in change of L/M between groups (p = 0.193). In both groups, 50% of those with abnormal L/M ratio at baseline (ratio > 0.015) normalised at Week 3 (7/14 for CDED; 4/8 with EEN). Interestingly, 1/14 (7%) CDED cases with normal L/M ratio became abnormal at 3 weeks, vs. 3/16 (19%) in the EEN group (NS). These findings indicate an improvement in IP with 3 weeks of nutritional therapy; however, there was no correlation between change in IP status and failure to respond to therapy or poor compliance to the diet at 3 weeks.

Conclusions: Although both EEN and CDED are associated with improved IP, this was not observed in all patients, despite clinical improvement. This suggests that small bowel IP alone may not be a primary mechanism for early clinical response; the effect of IP on sustaining remission following dietary therapy will require further study.

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New-onset autoimmune disorders, primarily psoriasis, in anti-TNF biologic exposed paediatric patients: the DEVELOP experience

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Background: DEVELOP is a multi-centre, prospective, observational registry of the long-term safety and clinical outcomes of 6070 paediatric patients with inflammatory bowel disease (IBD) treated with anti-tumour necrosis factor biologics (aTNF) and/or other medical therapies for IBD as part of routine clinical care. DEVELOP has sites in the USA, Canada and the European Union. Our aim was to characterise the incidence of new autoimmune disorders (AD) in a paediatric IBD population exposed to aTNF compared with a population exposed only to non-biologics (NB).

Methods: Physicians participating in the registry prescribe IBD treatments based on their usual clinical practice and standards of care. Pts are categorised into cohorts according to their prevalent or incident medication exposure, including patients receiving therapy prior to enrolment and/or during registry follow-up. The most recent available data cut (June 30 2018) includes 21083 patient-years (PY) of follow-up in the aTNF cohort and 11277 PY in the NB cohort. Investigators record all new AD in the study database during biannual visits.

Results: Among all IBD patients, the incidence of all new AD was statistically significantly greater in the aTNF cohort (0.99 events/100 PY) than the NB cohort (0.27 events/100 PY) (Table 1). These results were driven by new-onset psoriasis (0.58 events/100 PY), the most frequently reported new AD in the aTNF cohort compared with 0.02 new psoriasis events/100 PY in the NB cohort.

The incidence of serious new AD was low in both the aTNF cohort (0.20 events/100 PY) and the NB cohort (0.07 events/100 PY). In the aTNF cohort, serious new AD that occurred more than once included the following: psoriasis (0.06 events/100 PY, n = 12 events); sclerosing cholangitis (0.02 events/100 PY, n = 4); lupus-like syndrome (0.02 events/100 PY, n = 4); optic neuritis (0.01 events/100 PY, n = 3); autoimmune hepatitis (0.01 events/100 PY, n = 3). In the NB cohort, there were no reports of serious adverse events of psoriasis, optic neuritis, or lupus-like syndrome, and one report (0.01 events/100 PY) each of autoimmune hepatitis and juvenile idiopathic arthritis and two cases of sclerosing cholangitis (0.02 events/100 PY).

Conclusions: New AD were noted approximately once every 100 PY in the aTNF cohort and were significantly more common compared with the NB cohort. New serious AD in the aTNF cohort were uncommon, with only 0.20 events per 100 PY. New AD do arise in aTNF treated paediatric IBD patients but overall are uncommon and not serious.

Table 1. Summary of all and serious new autoimmune disorders

	All New Autoimmune Disorders		All New Serious Autoimmune Disorders	
All IBD Patients	aTNF	Nonbiologics	aTNF	Nonbiologics
Number of patients	3840	1661	3840	1661
Total PY of follow-up	21082.8	11276.9	21082.8	11276.9
Patients with events/100 PY [No. of patients] 95% confidence interval	0.95 [201] [0.83, 1.09]	0.27 [30] [0.18, 0.38]	0.19 [41] [0.14, 0.26]	0.07 [8] [0.03, 0.14]
Events/100 PY [No. of events] 95% confidence interval	0.99 [209] [0.86, 1.14]	0.27 [31] [0.19, 0.39]	0.20 [43] [0.15, 0.27]	0.07 [8] [0.03, 0.14]
New autoimmune disorders that occurred more than once in the aTNF cohort; events/100 PY [No. of events]				
Psoriasis	0.58 [123]	0.02 [2]	0.06 [12]	0.00 [0]
Lupus-like syndrome	0.04 [8]	0.00 [0]	0.02 [4]	0.00 [0]
Juvenile idiopathic arthritis	0.04 [8]	0.02 [2]	0.00 [1]	0.01 [1]
Dermatitis psoriasiform	0.03 [6]	0.00 [0]	0.00 [0]	0.00 [0]
Sclerosing Cholangitis	0.03 [6]	0.04 [5]	0.02 [4]	0.02 [2]
Autoimmune hepatitis	0.02 [5]	0.04 [5]	0.01 [3]	0.01 [1]
Coeliac disease	0.02 [5]	0.02 [2]	0.01 [1]	0.00 [0]
Optic neuritis	0.02 [4]	0.00 [0]	0.01 [3]	0.00 [0]
Henoch-Schonlein purpura	0.02 [4]	0.01 [1]	0.01 [2]	0.01 [1]
IgA nephropathy	0.02 [4]	0.00 [0]	0.00 [1]	0.00 [0]
Episcleritis	0.01 [3]	0.00 [0]	0.00 [1]	0.00 [1]
Raynaud's phenomenon	0.01 [3]	0.00 [0]	0.00 [0]	0.00 [0]
Takayasu's Arteritis	0.01 [2]	0.00[0]	0.01 [2]	0.00 [0]

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Correlation between Mayo endoscopic score and validated histological score in ulcerative colitis

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Background: Mayo Endoscopic Score (MES) remains the most commonly used index in routine practice and various clinical trials. Recently two histological indices (Nancy and Robert Histological Index) have been developed in UC. Correlation between MES and these two validated histological scores has not been established. We aim to correlate MES with two validated histological indices in patients with UC.

Methods: It was a prospective single-centre study. Ninety-six patients with UC with different levels of severity were included. MES was documented from the most affected area. Biopsy was taken from the same area and reported by single gastrointestinal histopathologist who was blinded to the endoscopic score. Histological activity was reported using Nancy Index (NI) and Roberts Histological index (RHI). Statistical analysis was performed using Spearman's correlation coefficient and kappa coefficient.

Results: In total, 96 patients with UC, with median age of 36 years were enrolled. Seventeen patients were in endoscopic remission (MES 0/1). Correlation coefficient between MES and NI was $r = 0.389$ ($p < 0.001$) and correlation coefficient between MES and RHI was $r = 0.442$ ($p < 0.001$). There was an excellent correlation between NI and RHI $r = 0.872$ ($p < 0.001$). In patient with endoscopic mucosal healing ($n = 17$), agreement coefficient between MES and RHI was k = 0.336 ($p = 0.001$) and agreement coefficient between MES and NI was k = 0.053 ($p = 0.573$).

Conclusions: Mayo endoscopic score only moderately correlate with NI and RHI. Endoscopic mucosal healing is not strongly correlated with histological healing. Histological examination should be performed even in patients with mucosal healing to detect ongoing histological activity

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Cyclosporine has no clinically meaningful effect on pharmacokinetics (PK) of BMS-986165, an oral selective tyrosine kinase 2 (TYK2) inhibitor, in healthy subjects

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Background: Cyclosporine is a dual breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp) inhibitor. Current treatment guidelines for inflammatory bowel disease include cyclosporine for steroid-refractory ulcerative colitis.[1,2] BMS-986165, an oral selective TYK2 inhibitor, has demonstrated efficacy and acceptable safety in patients with moderate to severe plaque psoriasis,[3] and is under investigation in moderate to severe Crohn's disease (LATTICE; NCT03599622) among other chronic autoimmune diseases. The current study assessed the effect of cyclosporine co-administration on the PK and safety/tolerability of BMS-986165.

Methods: In this Phase 1, open-label, single-sequence drug–drug interaction study (NCT03419910), healthy male subjects aged 18–50 years with a body mass index (BMI) of 18–32 kg/m^2 received a once-daily, pharmacologically relevant, oral (po) dose of BMS-986165 on Days (D) 1–5, followed by a single dose of BMS-986165 + cyclosporine 500 mg po on D6. On PK sampling days, doses were administered after an overnight fast of ≥10 h. Blood samples were collected on D5 and D6 to determine the PK of BMS-986165 and cyclosporine.

Results: Overall, 20 subjects (mean [standard deviation] age 30.3 [7.0] years, BMI 26.0 [3.2] kg/m^2) were treated and evaluable for safety; 2 (10%) withdrew due to adverse events (AEs; pyrexia) before D5 PK sampling. Cyclosporine co-administration with BMS-986165 had no clinically meaningful effect on peak and total BMS-986165 exposures (16% increase in maximum concentration and 29% increase in area under the curve over 24 h; Table) or its key metabolites. Median (min, max) time to maximum concentration for BMS-986165 was 2.5 (1, 4) h on D5 and 2.5 (2, 8) h on D6. There were no serious AEs or deaths. All treatment-emergent AEs were considered mild and resolved by study end.

Table. Effect of concomitant cyclosporine administration on BMS-986165 PK in PK-evaluable subjects ($n = 18$).

	PK parameter	Day 5 BMS-986165 alone	Day 6 BMS-986165 + cyclosporine	Geometric LS mean ratio estimate (Day 6/Day 5)	90% CI for geometric LS mean ratio
Drug: BMS-986165	C_{max} (ng/mL)	41.7	48.2	1.156	(1.079, 1.239)
	AUC_{TAU} (h*ng/mL)	359	463	1.291	(1.244, 1.339)

Data are geometric LS means unless otherwise stated. AUC_{TAU}=area under the curve over 24 hours; CI=confidence interval; C_{max}=maximum concentration; LS=least-squares; PK=pharmacokinetic.

Conclusions: Cyclosporine, a dual BCRP and P-gp inhibitor, has no clinically meaningful effect on the PK of BMS-986165. Therefore, drugs inhibiting P-gp or BCRP (eg, cyclosporine, among others), are not expected to meaningfully impact the PK of BMS-986165. BMS-986165 alone or in combination with cyclosporine was well tolerated in healthy subjects in this study.

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Real-world data regarding treatment of ulcerative colitis patients with golimumab in Switzerland

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Background: Tumour necrosis factor (TNF)-inhibitors have markedly improved treatment of ulcerative colitis (UC), but loss of response in the long-term remains a frequent problem. A novel anti-TNF agent, golimumab, has been introduced in Switzerland for UC in 2014.
Methods: We aimed for real-word data from 1536 UC patients from the Swiss IBD cohort study (SIBDC). UC patients treated with golimumab from 2014 to 2018 were compared with the remaining SIBDC patients with UC. We also performed a chart review of a subgroup of patients to assess response to golimumab.
Results: Among 90 patients (5.9% of all SIBDCS patients with UC) treated with golimumab, extensive disease (E3) was more frequent compared with the non-golimumab group (n = 1409); (E3: 61% vs. 54%, E2: 37% vs. 33% and E1: 2% vs. 12%, p = 0.005). They had more active disease (average modified Truelove and Witts activity index [MTWAI] 8 [IQR: 4–10] vs. 4 [IQR: 2–8], $p < 0.001$) and more extraintestinal manifestations (56/90 [62%] vs. 615/1446 [43%], $p < 0.001$). In the golimumab group, previous treatment with infliximab, adalimumab, certolizumab or vedolizumab was common (26 patients [~29%] with 0 biologics, 44 patients [~49%] with 1, 17 [~19%] with 2, 3 [3%] with 3 biologics) and the rate of prior anti-TNF failure was higher than in the non-golimumab group ($p \leq 0.001$ for each biologic). Chart review for 57 patients showed a drop of MTWAI from 7 (IQR: 4–11) at baseline to 3 (IQR: 2–6.5) at 6 months (p = 0.0006) and to 2 (IQR: 1–5) at 12 months ($p < 0.0001$) upon golimumab therapy (Figure). Similarly, the partial Mayo score decreased from 3 (IQR: 1.75–5.25) to 0.5 (IQR: 0–4, p = 0.0002) and 1 (IQR: 0–3.5, p = 0.001) at 6 and 12 months, respectively. The partial Mayo score was normal for 17/35 patients (30% of original cohort) at 6 months and for 14/28 patients (25% of original cohort) at 12 months, respectively. Golimumab was continued in 23/57 patients beyond 12 months. The most frequent reason for stopping was golimumab failure (21 patients).

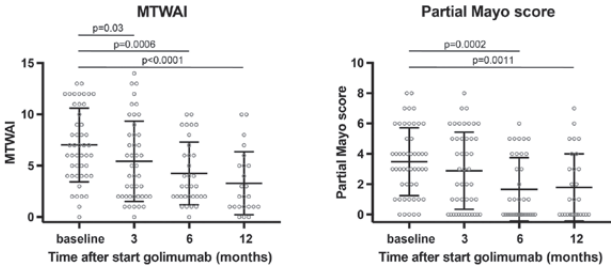

Figure. Time course for decrease in disease activity scores upon golimumab therapy. Statistics: Mann–Whitney *U* test. MTWAI, Modified Truelove and Witts activity index.

Conclusions: Golimumab has been used in Switzerland mainly for UC patients with severe and extensive disease and failure of prior biologic therapy. A quarter of this difficult to treat (70% with ≥ 1 biological treatment failure) patient population could be successfully treated with normalisation of the partial Mayo score at 12 months.

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MRI outcomes in perianal fistulising Crohn's disease following anti-TNF-α therapy: a systematic review and meta-analysis

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Background: Management of perianal fistulising Crohn's disease (pfCD) remains a significant challenge. Advent of biological agents has led to improved clinical outcomes. However, their effect on radiological findings is less well-established, despite MRI being a more accurate measure of disease activity, given the persistence of underlying tracts despite healing of the external opening.[1]
Methods: We performed a systematic review to assess disease activity on MRI pelvis following biological therapy, in adults. Online databases were searched in February 2018. Eight papers met this criterion, all of which administered an anti-TNF-α. All papers examined clinical outcomes, with 'remission' defined as closure of all baseline draining fistulas. Radiologically, 'healing' was defined as disappearance of tracts on T2-weighted sequences. Degree of radiological improvement was assessed in 4 papers, defined as decrease in T2-hyperintensity (2 papers), decrease in number of tracts/collections (1 paper), or decrease in number or volume (≥10%) of tracts/collections (1 paper). Endpoints ≤ 12 weeks post treatment commencement were considered short-term, and those >12 weeks long-term.
Results: Of 208 unique papers identified, 8 met inclusion criteria, with a total sample size of 233. Of 67 patients who received a post-treatment MRI at ≤12 weeks, 6/67 (9%) achieved radiological healing of the underlying fistula tract, 11/22 (50%) had improvement and 9/22 (41%) no improvement. Of 146 patients who underwent a post-treatment MRI at >12 weeks, 33/146 (23%) achieved healing, 20/45 (44%) had improvement and 15/45 (33%) no improvement. The odds ratios of MRI healing compared with clinical was

0.14 (95% CI, 0.03–0.54) in the short-term and 0.34 (95% CI, 0.21- 0.58) in the long-term, demonstrating a relative infrequency of radiological healing. Van Assche score findings varied, with some reporting significant differences between clinical responders and non-responders, and pre- and post-treatment,[2] and others no significant difference.[3]

Study	Number of pfCD	Induction with anti-TNFα	Maintenance with anti-TNFα	Short term clinical remission	Long term clinical remission	Short term MRI healing	Long term MRI healing	Short term Odds Ratio	Long term Odds Ratio
Bell et al	7	7	-	4/7 (57%)	-	2/7 (29%)	-	0.3 (0.03 – 2.76)	-
Van Assche et al (two part study)	8	8	-	4/8 (50%)	-	0/8 (0%)	-	0.06 (0.00 – 1.36)	-
	7	7	7	4/7 (57%)	-	0/7 (0%)	2/6 (33%)	-	-
Tougeron et al	26	26	16	13/26 (50%)	11/16 (69%)	-	2/14 (14%)	-	0.08 (0.01-0.47)
Savoye-Collet et al	20	20	20	-	7/20 (35%)	-	2/20 (10%)	-	0.21 (0.04-1.16)
Karmiris et al	59	59	-	-	24/59 (41%)	3/29 (10%)	5/38 (12%)	-	0.22 (0.08-0.65)
Horsthius et al	16	16	-	6/16 (38%)	-	1/16 (6%)	-	0.11 (0.01 – 1.07)	-
Tozer et al	41	41	41	-	4/19 (21%)	-	6/19 (32%)	-	1.73 (0.40 – 7.51)
Thomassin et al	49	-	49	-	26/49 (53%)	-	16/49 (33%)	-	0.43 (0.19-0.97)
Totals	233	184	192	31/64 (48%)	72/163 (44%)	6/67 (9%)	33/146 (23%)	0.14 (0.03 – 0.54)	0.34 (0.21-0.58)

Clinical and radiological outcomes following biological therapy.

Conclusions: Discrepancies exist between clinical and MRI outcomes in pfCD following biological therapy. Lack of consensus on the definition of MRI improvement, or a universally accepted grading system, has led to variability of endpoints assessed and heterogeneity in reported improvement. Further studies assessing recurrence rates in patients who do achieve healing, and variables which prognosticate for radiological healing, will aid management of pfCD.

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TDM of infliximab in IBD-patients: which pharmacokinetic marker to use?

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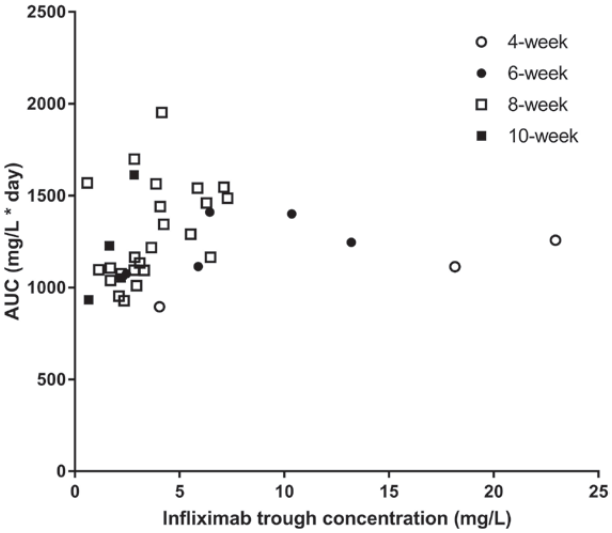
Background: According to the registered label of infliximab (IFX), patients with inflammatory bowel disease (IBD) receive 5 mg/kg IFX every 8 weeks during maintenance treatment. In clinical practice, the efficacy of IFX is often optimised by 'therapeutic drug monitoring' (TDM), that is, adjustment of doses and dosing intervals of IFX based on IFX serum trough levels (TL) (before an infusion). The TL is used as a pharmacokinetic (PK) surrogate reflecting the 'total' drug exposure or area under the concentration vs. time curve (AUC) after administration. With TDM gaining interest, we evaluated the correlation between IFX TLs and AUC in IBD patients during maintenance therapy.

Methods: We performed an analysis of a prospective cohort of 36 IBD patients treated with IFX maintenance therapy. IFX serum concentrations were measured at trough, peak (10 min after the end of infusion) and at mid-infusion (in between doses). Patients were divided into 4 groups according to their dosing interval of 4, 6, 8, or 10 weeks. TLs were measured by an enzyme-linked immunosorbent assay (ELISA) (Sanquin Laboratories, the Netherlands). AUC was calculated using Bayesian analysis (NONMEM®) and correlated to the corresponding IFX TL.

Results: Thirty-six IBD patients (Crohn's disease: 26, ulcerative colitis: 10) were included. Median [interquartile range (IQR)] age was 30 years [43–51] and disease duration 13 years [6–26]. A total of 19 patients used a concomitant immunomodulator (thiopurine: 17, methotrexate: 2). Correlations between AUCs and IFX trough concentrations were poor for the 6- and 8-week dosing interval (Table 1). In the 8-week interval, for patients with a IFX trough concentration between 3 and 5 mg/l the AUC ranged from 1094–1953 mg/l*day (Figure 1).

	4-week interval	6-week interval	8-week interval	10-week interval
N patients	3	5	24	4
AUC (mg/l * day) (min–max)	895–1257	1076–1410	928–1953	934–1614
Trough concentration (mg/l) (min–max)	4.0 – 22.9	2.5–13.2	0.6–7.3	0.7–2.8
Dose IFX (mg) (min–max)	350 – 400	350 – 450	250 – 600	300 – 500
Dose IFX (mg/kg) (min–max)	5.1–6.3	4.4–5.8	4.3–8.0	4.2–6.6
CRP (mg/l) (median [IQR])	0.15 [0.3–0.6]	1.2 [0.7–5.9]	1.1 [0.3–3.0]	9.8 [2.3–12.3]
Albumin (g/l) (median [IQR])	42 [45–47]	42 [45–47]	41 [43–45]	40 [43–48]
Correlation AUC-trough	0.99 (p = 0.1)	0.52 (p = 0.38)	0.42 (p = 0.04)	0.81 (p = 0.19)



Conclusions: Currently, IFX TLs are used as a pharmacokinetic marker for exposure in IBD patients. However, IFX TLs correlate poorly to AUCs of IFX. This raises the question if a TL is the best pharmacokinetic marker for optimising the clinical efficacy of IFX in IBD patients.

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Aberrant brain structural large-scale connectome in Crohn's disease

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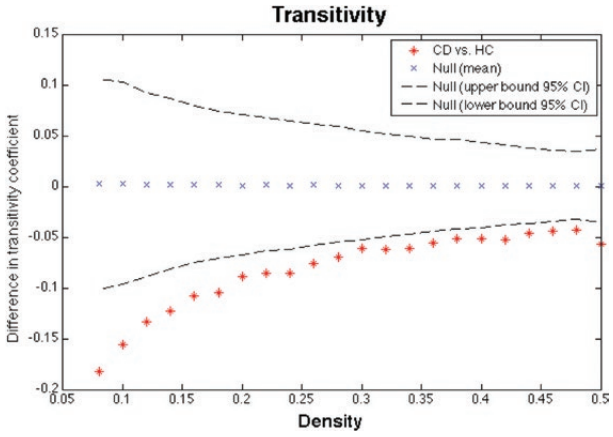
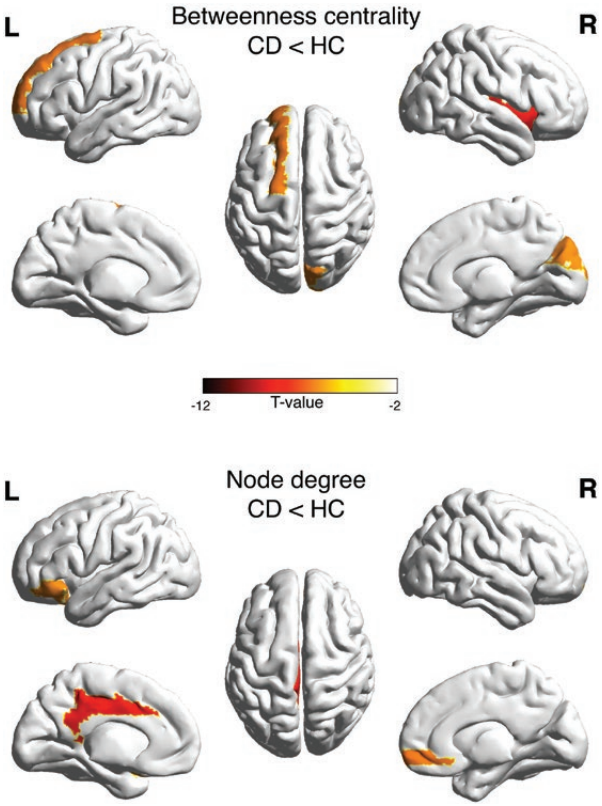
Background: Altered brain-gut-interactions and a bidirectional relationship between inflammation and psychiatric symptoms such as anxiety and depression are being discussed in patients with inflammatory bowel diseases (IBD). Alterations of brain structure and function in IBD have been reported by previous magnetic resonance imaging (MRI) studies with heterogeneous and partly conflicting results, hindering the establishment of a „neural phenotype' of IBD. Whether brain structural changes reflect independent localised deficits or rather a systematic disruption in the anatomical organisation of large-scale brain networks remains unclear. The present study therefore investigated the gray matter structural connectome in patients with Crohn's disease (CD).
Methods: Sixty participants (30 with quiescent CD and 30 matched healthy controls (HC)) underwent high-resolution brain MRI at 3 Tesla. Using graph theoretical analysis, well-established graph metrics were analysed at the global and regional network level and compared between groups.
Results: The networks in both groups followed a small-world organisation, i.e. an architecture that is simultaneously highly segregated and integrated. However, transitivity (a measure of global network segregation) was significantly reduced in patients with CD ($p = 0.003$)



Regionally, CD patients showed reduced nodal betweenness centrality (a measure of information flow) in the right insula and cuneus and the left superior frontal cortex as well as reduced nodal degree within the left-hemispheric cingulum and the left lateral and right medial orbitofrontal cortex



Conclusions: These findings advance our understanding of aberrant brain morphology in CD and lend support to the hypothesis that the disorder is accompanied by alterations in both global network organisation and regional connectivity. Future studies should investigate these factors in different disease states to determine the influence of inflammation on neural networks and shed light on possible neural correlates of disrupted brain-gut-interactions in IBD. A deeper understanding of neural networks in IBD may eventually help to develop complementary strategies in the personalised treatment of patients with 'extraintestinal' issues like anxiety, depression, or maladaptive coping.

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Perceived Quality of Care is associated to quality of life, work productivity and gender but not disease phenotype: a prospective study in a high-volume IBD centre

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Background: Measuring the quality of care (QoC) in IBD has become increasingly important, yet complex assessment of quality indicators and perceived quality of care is rare. In this prospective study, we evaluated patients' satisfaction on the QoC using the QUOTE-IBD questionnaire in the context of health related quality of life (HRQoL) and work productivity loss in a tertiary care IBD centre.
Methods: Consecutive patients attending McGill University Health Centre (MUHC)-IBD Centre completed the QUOTE-IBD, SIBDQ, IBD-Control and WPAI questionnaires. The QUOTE-IBD comprises 23 items (8 domains) rated for importance (I) and performance (P), then a quality impact (QI) score was calculated (QI = 10-[I*P]) reflecting the overall satisfaction with each item. QI scores were calculated for the evaluation of GP, IBD-specialist and hospital care in each patient. Results of the QUOTE-IBD were compared with demographic data, disease phenotype, SIBDQ, IBD-Control and WPAI questionnaires. Patient clinical data were captured upon completion of the questionnaires.
Results: 525 patients (47.1% male, mean age: 41 years, CD: 71.2% [L3: 54.6%, B2/B3: 50.3%], UC: 28.8% [extensive colitis: 55.6%], biological therapy: 55.6%) completed the questionnaire. Total QI scores were similar for GP, IBD-specialists and hospital care (8.57, 8.70 and 8.33, respectively). Lower satisfaction was found regarding accessibility and information on nutrition. In multi-variate analyses, there was no overall difference between the QoC domains provided by the GP and IBD-specialists in either CD or UC ($p = 0.231$ and $p = 0.061$), with the exception of specialised information provided ($p < 0.05$). Female gender, poor HRQoL (SIBDQ ≤ 50) and poor disease control (IBD-Control < 13) were associated with significantly lower mean QI scores in multiple domains assessing both GP and IBD-specialists ($p < 0.001$ for all). Work productivity loss assessed by WPAI was significantly higher in patients with extensive UC, biological therapy and active disease (each $p < 0.05$). There was a clear inverse correlation between QI scores and work productivity loss (GP: $p = 0.004$; IBD-specialist: $p < 0.001$).
Conclusions: Overall satisfaction with QoC was good and not different in GP and IBD-specialist provided care in this large referral IBD cohort. Female gender, poor HRQoL and work productivity loss was strongly correlated with patient satisfaction, highlighting that perceived QoC is subjective to disease control and quality of life.

P355

Diagnostic accuracy and usability of home calprotectin testing

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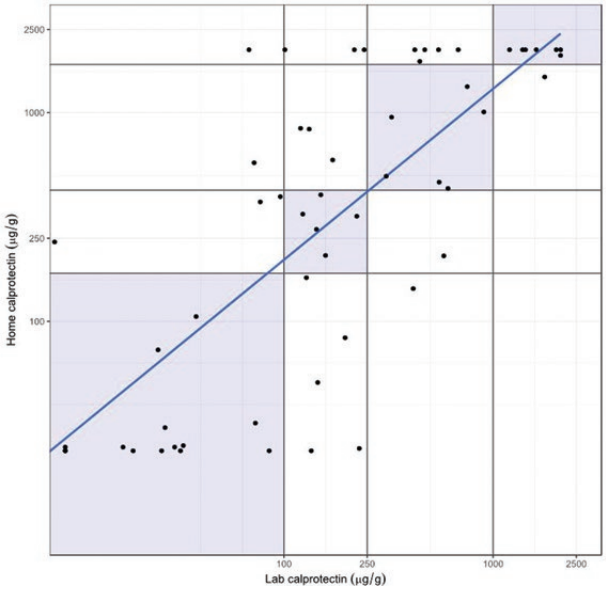
Background: Faecal calprotectin (FC) is a reliable and non-invasive stool biomarker that is useful in monitoring inflammation in patients with IBD. Testing is routinely performed in a laboratory by enzyme-linked immunosorbent assay (ELISA) which is time consuming and costly. QuantonCal (QC) is an immunologic rapid test that can measure calprotectin via a lateral flow device to a smart phone. It is designed to be used by the patient in their home and can deliver a result within 15 min. We sought to compare the accuracy and usability of QC against ELISA.
Methods: We approached patients attending IBD outpatient clinic at the Royal Devon and Exeter Hospital, UK. Inclusion criteria were owning a smartphone and need for measuring calprotectin to assess disease activity/inflammation. Patients collected a stool sample to perform QC and submitted a sample for ELISA analysis to assess correlation. Patients were invited to complete a questionnaire.
Results: Of 59 patients 32 had Crohn's disease, 23 ulcerative colitis and 4 IBDU. Thirty-eight (64.4%) submitted at least one sample for analysis, 26 (44.1%) submitted two samples, and 24 (42.3%) completed a satisfaction survey. 3 QC samples were excluded for invalid readings.
The QC and lab calprotectin readings were significantly correlated; Spearman's rank correlation coefficient = 0.737, $p < 0.005$, however the QC overestimated the lab calprotectin value by 74% (Figure 1). Median QC was 385 µg/g [IQR 31–1850], median lab 148 [IQR 46–529]).



Correlation betwen QuantonCal (home calprotectin) and laboratory calprotectin.

Using 27 lab calprotectin readings >250 µg/g as gold standard against QC readings, test performance was: area under the curve (AUC) = 0.870 (95% confidence interval (CI) = 0.779–0.961), sensitivity 90%, specificity 78%, positive predictive value 70%, and negative predictive value 94%. 24 patients completed the questionnaire. Acceptability was high: 15 (62.5%) thought QC was 'very easy', 7 (29.2%) 'easy,' no patients reported the application was 'difficult' or 'very difficult' to use. There was a preference towards QC compared with lab test: equal preference 9 (37.5%), slight preference 7(29.2%) and strong preference 4 (16.7%). Patients cited real-time results and feeling 'in control' of their disease as reasons for this.
Conclusions: The QC overestimated the lab calprotectin reading by 74%, with only moderate specificity and positive predictive value, rendering the diagnostic accuracy of QC poor. Inaccurate QC results could lead to false reassurance, delayed treatment, or inappropriate escalation of therapy. Despite patients reporting good usability, QC should not replace ELISA.
Reference
1. Fitzgerald D, Sugrue K, McCarthy J, *et al.* An evaluation of patient satisfaction with IBDoc calprotectin home test system. *J Crohn's Colitis* 2017;11;S493.

P356

Safety and effectiveness of granulocyte and monocyte adsorptive apheresis in paediatric patients with inflammatory bowel disease: a multi-centre cohort study

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Background: The usefulness of granulocyte and monocyte adsorptive apheresis (GMA) in paediatric patients with inflammatory bowel disease (IBD) has not been studied in depth. We investigated the safety and effectiveness of GMA in paediatric patients with IBD who participated in a post-marketing surveillance study referred to as the PARTICULAR study.
Methods: The PARTICULAR study was a retrospective, multi-centre cohort study that included patients with ulcerative colitis (UC) or Crohn's disease (CD) who received GMA between November 2013 and March 2017. The study enrolled patients with at least one special situation, including paediatric, being elderly, with anaemia and concomitant treatment with multiple immunosuppressants. Patients aged >18 years were excluded from this study. The GMA was performed using Adacolumn® (JIMRO, Takasaki, Japan). Each patient underwent up to 11 GMA sessions. All adverse events (AEs) were recorded during the observation time interval. Any AE, for which the causality of the GMA could not be ruled out was classified as an adverse device effect (ADE). In addition, feasibility problems (FPs) during the operation of the GMA column were recorded. The effectiveness of GMA was assessed in UC patients with a partial Mayo (pMayo) score of ≥3. Remission was defined as a pMayo score of ≤2. Patients receiving concomitant treatment with infliximab, adalimumab or calcineurin inhibitors were excluded from the effectiveness assessment.
Results: A total of 53 paediatric patients (40 UC, 13 CD) from 27 institutions, with a mean age of 15.0 years, were included. The incidence of AEs, ADEs and FPs were 18.9%, 5.7% and 20.8%, respectively. The ADEs included abdominal discomfort in 2 (3.8%) patients and one patient each with fever, nausea/vomiting and headache (1.9% each). The FPs included blood access failure in 10 patients (18.9%), venous pressure elevation in 4 (7.5%), clot formation in the apheresis lines in 2 (3.8%) and venous access difficulty in 1 patient (1.9%). A total of 17 patients (32.1%) discontinued GMA therapy ahead of the planned treatment schedule. Among these patients, the GMA therapy was discontinued for the following reasons: (1) decision by the physician (n = 12), (2) withdrawal due to AE (n = 4) and (3) withdrawal by own wish (n = 1); none were discontinued due to ADE and FP. The effectiveness of the GMA was assessed in 29 UC patients. The remission rate of the paediatric UC patients was 43.5%.
Conclusions: There were AEs and FPs in approximately 20% of paediatric patients with IBD treated by GMA, but none of these discontinued the GMA treatment due to ADE or FP. Remission was achieved by GMA in 44% of the paediatric UC patients. This study showed that GMA was well tolerated treatment option for the paediatric IBD patients.

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Serological biomarkers of interstitial matrix and basement membrane remodelling correlate to disease activity in Crohn's disease

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Background: There is an increased deposition of collagen type III and type IV in the intestinal wall of patients with Crohn's disease (CD) reflecting an altered remodelling in the interstitial matrix and the basement membrane in the gut. Propeptide of collagen type III (Pro-C3) and MMP-9 degraded collagen type III (C3M) and type IV (C4M) are serological biomarkers reflecting collagen III formation and collagen type III and IV degradation, respectively.
The aim of this study was to evaluate the correlation of Pro-C3, C3M, collagen III turnover ratio (C3M/Pro-C3) and C4M to clinical and endoscopic disease activity in CD.
Methods: 63 CD patients were included in a prospective biomarker evaluating study. Seventeen of the 63 CD patients underwent colonoscopy and Simple Endoscopic Score for Crohn's disease (SES-CD) were recorded. Thirty-five per cent (n = 24) of the patients had active disease defined by Harvey–Bradshaw Index (HBI) > 4. Pro-C3, C3M, and C4M were assessed by competitive enzyme linked immunosorbent assays (ELISAs). Collagen III turnover ratio were calculated and C-reactive protein (CRP) and faecal calprotectin (FC) were measured.
Results: Tables 1 and 2 show the correlations between the biomarkers and the activity scores. C3M was significantly correlated to SES-CD and Collagen III turnover ratio was significantly correlated to HBI and SES-CD. C4M2 was significantly correlated to SES-CD and had a non-significant correlation to HBI. Pro-C3 did not correlate to HBI and SES-CD.
Compared with current biomarkers of disease activity in CD collagen III turnover ratio correlated just as well to HBI as CRP and FC. Collagen III turnover ratio and C3M had a higher correlation to SES-CD than CRP, but FC had the best correlation to SES-CD.

	Correlation coefficient	p-value	Spearman's rho	Pearson's r
Pro-C3	–0.35	0.06	–0.30	–0.24
C3M	0.15	0.12	0.23	0.19
Collagen III turnover ratio	0.04	0.013	0.36	0.31
C4M2	0.36	0.065	0.28	0.23
CRP	0.79	0.013	0.39	0.31
FC	78	0.004	0.34	0.37

Correlation between the biomarkers and HBI

	Correlation coefficient	*p*-value	Spearman's rho	Pearson's r
Pro-C3	–0.20	0.11	–0.43	–0.41
C3M	0.16	0.02	0.37	0.58
Collagen III turnover ratio	0.05	0.004	0.46	0.67
C4M2	0.47	<0.001	0.65	0.81
CRP	0.03	0.88	0.47	0.04
FC	127	<0.001	0.71	0.90

Correlation between the biomarkers and SES-CD.

Conclusions: The data indicate that the collagen III turnover and part of the collagen IV turnover alters with increasing disease activity in CD and that C3M, collagen III turnover ratio and C4M2 might serve as biomarkers of disease activity in CD.

P358

Ustekinumab is effective for the treatment of chronic antibiotic-refractory pouchitis

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Background: Many ulcerative colitis (UC) patients develop pouchitis after proctocolectomy with ileal pouch-anal anastomosis (IPAA). Antibiotics have been the treatment of choice for pouchitis, but up to 15% of patients develop refractory disease. Ustekinumab (UST) is effective for the treatment of moderate-to-severe Crohn's disease and has recently been shown to be effective in UC. The aim of this study was to investigate the effectiveness of UST in the treatment of chronic antibiotic-refractory pouchitis.

Methods: This is a retrospective tertiary centre study of patients evaluated between 2016–2018. Included were UC patients who had a total proctocoletomy with IPAA and who subsequently developed chronic antibiotic-refractory pouchitis and were treated with UST with standard Crohn's disease dosing. Patient demographic, clinical and endoscopic data were collected. All pouchoscopies were reviewed based on the endoscopy report and the images obtained. Outcomes of interest included change in the endoscopic subscore of the endoscopic Pouchitis Disease Activity Index (PDAI), change in the ulcerated surface area, clinical response, and number of bowel movements (BM).

Results: We identified 24 UC patients with antibiotic-refractory pouchitis and who received UST. Median time from the start of UST treatment to pouchoscopy was 7.4 months IQR (4.6–10.6). Median follow-up time was 12.9 months IQR (7.9–16). Thirteen patients had pouchoscopies available post-UST treatment. The mean endoscopic subscore of the PDAI decreased from 4.8 to 3.3 (p = 0.0076) post treatment (Figure 1). Before the start of UST therapy, 26.6% of patients had an ulcerated surface area >30%, this decreased to 8.3% after treatment with UST (Figure 2). Twelve patients (50%) achieved a clinical response and a reduction in mean bowel movements within 24 h from 8.4 to 6.5 (p = 0.006) (Figure 3).

Conclusions: In the largest single-centre study of UST treatment for patients with chronic antibiotic-refractory pouchitis, we found that UST therapy led to improvement in clinical and endoscopic endpoints. A prospective study is warranted.

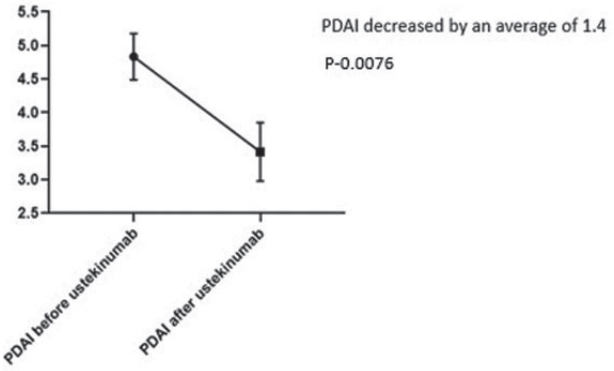

Figure 1. PDAI prior and post ustekinumab treatment of pouchitis (mean+SEM). n = 13.

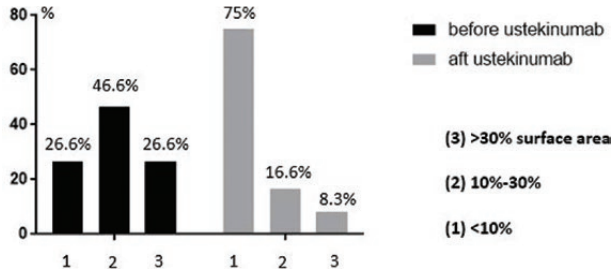

Figure 2. Ulcerated surface area (%) prior and post ustekinumab treatment of pouchitis. n = 13.

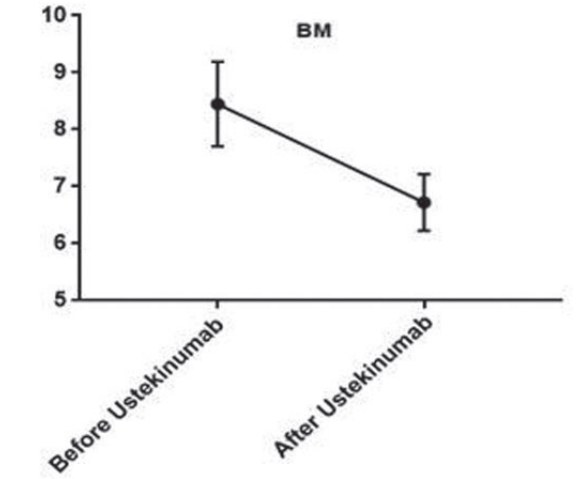

Figure 3. Change in bowel movements in 24 h (mean + SEM). n = 24.

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Budesonide MMX in paediatric ulcerative colitis

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Background: Budesonide is a second generation steroid (CS) with high affinity for the glucocorticoid receptor, over 8.5 times greater than dexamethasone. Due to its low bioavailability, budesonide

exhibits fewer side effects (AEs) than conventional CSs. Currently, available data on budesonide MMX concern the use of the preparation in adults with ulcerative colitis (UC). Data on the use of this preparation in children are single.

Methods: In total, 31 children with UC (K 18, M 13) and a median age of 13.2 years in whom budesonide MMX was used in 2014–2017 were enrolled in the retrospective study. Data from the results of laboratory tests: haematocrit (HT), platelets (PLT), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and severity of clinical disease in the PUCAI score before and after finished therapy were analysed. In 15/31 patients, endoscopic examinations before and after the treatment were also performed, the Mayo score was assessed. Data regarding to the duration of therapy and possible AEs were also collected. As a clinical response the reduction in the PUCAI score below 19 points was considered and as a clinical remission the PUCAI score below 10 points. The endoscopic response a reduction of the Mayo score was considered, while the endoscopic remission was Mayo = 0. The Wilcoxon test was used to assess statistical significance.

Results: There were none statistically significant improvement in analysed laboratory results found, compared with the condition before treatment. From among the study group, 55% of patients managed to achieve both a clinical response and a clinical remission (17/31) with p = 0.007. The endoscopic improvement was obtained by 73% (11/15) of the examined patients, and endoscopic remission by 40% (6/15). The median duration of therapy was 2 months, but 3 patients were treated with budesonide MMX for more than 10 months, of which one over 2 years. The percentage of AEs in the whole study group was 19% (6/31). All patients treated for over 10 months experienced AEs. In the remaining patients treated for a maximum of 3 months, the AEs percentage was 10% (3/31). The main AE observed in patients was the accumulation of adipose tissue on the face (cushingoidal face) and weight gain.

Conclusions: Budesonide MMX is an effective for the induction of remission in children with UC. In 55% of patients cause clinical remission, which is followed by a 40% endoscopic remission. Used in short-term therapy, it rarely causes AEs. Used in long-term treatment, like conventional CS, it causes AEs in children.

P360

Inflammatory microheterogeneity in ulcerative colitis: implications for microscopic assessment of disease activity

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Background: UC is classically a continuous inflammatory disorder. Biopsies to assess disease activity, whether for clinical purposes or to monitor therapeutic responses in drug trials, are typically sampled 1 or 2 per colonic segment on the assumption of homogeneous inflammation throughout targeted regions. Nonetheless, data are lacking to validate this assumption.

Methods: We retrospectively evaluated inflammation in histological sections of ascending (AC) and rectosigmoid (RS) colon from colectomy specimens of 18 random adults with UC. A series of consecutive 2 mm diameter (100×) microscopic mucosal fields was scored by 2 pathologists using the Nancy Histological Index (NHI) to generate a score of 0–4 per field. The Robarts modification of the Geboes Index was used to score 4 individual histological parameters: chronic inflammation, lamina propria neutrophils, intraepithelial neutrophils, erosions. Median NHI scores and proportions of discrepant fields, that is, those with higher or lower scores, were determined for each series. Demographic data, disease durations, indications for surgery, and current drug therapies were obtained from electronic records.

Results: The patients spanned a broad spectrum of clinical characteristics (Table 1). Mean 100× fields assessed per segment were 70.4 ± 24.1. Table 2 shows the breakdown of NHI scores from the AC and RS. Median AC scores exceeded median RS scores in 3/18 series (17%) series and the reverse occurred in 7/18 series (39%). The proportions of discrepant fields were similar in the AC and RS, 31.7 vs. 33.4%, respectively, and their distributions are shown (Figure 1). The range of NHI scores in the AC and RS was ≥3 in 11/18 (61%) and 12/18 (67%) series, respectively. Microheterogeneity was observed in all 4 histological parameters.

Table 1. Characteristics of UC patients.

Patient characteristics (N=18)	
Mean age (y)	43 (range, 18-71)
Sex (M:F)	8:10
Median disease duration (y)	6.0 (range, 0-40.6)
Recent topical therapy	0
Recent systemic medications	
Steroids	12 (67%)
Mesalamine	5 (28%)
Biologics	9 (50%)
Antimetabolites	4 (22%)
Indication for surgery	
Refractory to medical therapy	13 (72%)
Dysplasia	4 (28%)
Extent of colitis	
Pancolitis	16 (89%)
Extensive colitis	2 (11%)

Table 2. Results of scoring of consecutive 100× fields expressed as percentage of discrepant fields.

	Nancy score	0	1	2	3	4	Overall
Ascending colon	Series (N)	2	3	7	5	1	18
	Discrepant fields (%)	0	51.6	26.5	41.4	23.8	31.7 ± 22.6
Rectosigmoid colon	Series (N)	3	1	6	6	2	18
	Discrepant fields (%)	22.9	88.9	24.9	39.7	28.4	33.4 ± 20.2

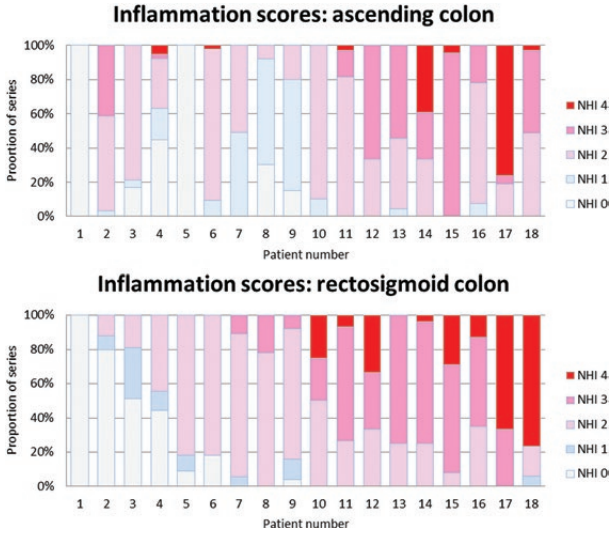

Figure 1. Nancy Histological Index scores of individual 100× fields from the ascending and rectosigmoid colon.

Conclusions: Inflammation in the colectomies of patients with active UC requiring colectomy exhibits both microheterogeneity and AC-RS discordance. The design of biopsy protocols for clinical studies and therapeutic drug trials must take these preanalytical factors into account. Optimum biopsy densities should be determined by means of prospective studies of endoscopic biopsies.

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Laboratory criteria of infliximab therapy inefficiency in children with IBD

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Background: Our aim was to identify the value of the laboratory criteria such as residual level of infliximab (IFX) in blood, antibodies to IFX and circulating cytokine levels in the prognosis of the effectiveness of the therapy in children with IBD.
Methods: Were included in the study 75 children with IBD (31 patients with UC and 44 patients with CD) aged 4–18 years who were treated with IFX. Clinical response was evaluated according PUCAI (UC) and PCDIA (CD) scores. Blood samples were taken 8 weeks after the last infusion of IFX. Residual levels of IFX (Q-IFX) in serum and IFX antibodies (ATI) were assessed by enzyme immunoassay using Shikari Q-INFLIXI, Q-ATI (Turkey) kits. The cytokine levels were measured by multiplex analysis using HumanThl7 MagneticBead Panel (MilliplexMapKit, Germany). Evaluation of the statistical significance was performed using nonparametric Mann–Whitney test and ROC-analysis.
Results: There were observed increase in the inflammatory activity according to PUCAI and PCDIA scores (p = 0.000) in children with the loss of response to IFX. In patients with the loss of the effect to IFX (Group 1) there was a significant decrease Q-IFX compared with a group of children with persistent positive effect (Group 2) in both diseases CD (p = 0.002) and UC (p = 0.019). ROC analysis showed that the cut-off level for patients with UC is 2.55 μg/ml (AUC = 0.813; sensitivity (Se) 64%, specificity (Sp) 92%), and for children with CD 2.21 μg/ml (AUC=0.813; Se 79%, Sp 78%). In the examined patients, IFX antibodies were detected in 17% cases, and the fast formation of IFX antibodies were associated to the younger age of children (R = 0.58). In one patient with a persistent positive effect for 5 years of therapy, the values of Q-IFX were in the range from 4.9 to 9.4 μg/ml in the absence of IFX antibodies. Cytokine analysis revealed significant differences between examined groups in the level of proinflammatory cytokines: IL-23, IL-27, IL-22, INF-γ, TNFα. ROC analysis revealed good quality TNFα as the separation model, the cut-off level was 13.4 pg/ml (AUC = 0.843; Se = 77%, Sp = 79%).
Conclusions: The reduction of the Q-IFX in children with UC below 2.55 μg/ml and in children with CD below 2.21 μg/ml, leads to the decrease of the therapy effect and can adduct to the exacerbation of the disease. These findings correlate with the results obtained in adults (>2 μg/ml, C. Moore *et al.*, 2016). TNFα level (>13.4 pg/ml) can serve as the laboratory criterion of loss of effect from IFX. Elevated levels of proinflammatory cytokines correlates with the lower Q-IFX and loss of the therapy effect.

P362

Faecal calprotectin is an early predictor of endoscopic response and histological remission after the start of vedolizumab

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Background: Early prediction of the effect of vedolizumab (VDZ) In IBD patients is of paramount importance to guide clinical decisions. We aimed to assess the potential of serial faecal calprotectin (FC) levels after start the of VDZ to predict endoscopic response and histological remission.
Methods: Patients who started VDZ with endoscopic inflammation and FC > 100 μg/g were included. FC was tested at Week 2, 4, 8, and 16. Endoscopy was scheduled at Week 16. Endoscopic response was defined as an SES-CD reduction ≥50%, Rutgeerts score reduction or Mayo score reduction of ≥1. At Week 16 endoscopy, ileum and segmental colon biopsies were collected. Histological severity was scored accordingly on a 4-point scale. Median FC levels at the FU time points and the relative change in FC between baseline and Week 16 were assessed with the Wilcoxon rank-sum test. ROC statistics were used to determine an FC cut-off point with the best discriminatory performance and to assess the predictive value of FC levels at the FU time points.
Results: A total of 40 patients (24 CD, 14 UC and 2 IBD-U) (42% males, median age 40 (28–51) years (IQR)) were included. 33/40 patients (83%) were anti-TNF exposed, of whom 28/33 (85%) were refractory. In 26/40 patients (65%) VDZ was combined with steroid

induction therapy and completely tapered at Week 16 in 18/26 (69%) patients. Week 16 endoscopic response rates were 11/16 (69%) in UC and 12/24 (50%) in CD ($p = 0.33$). Median FC levels (µg/g) are depicted in Figure 1, and were significantly lower when compared with FC in patients without endoscopic response. Patients with endoscopic response had a significant decrease in FC level at Week 2 when compared with patients without endoscopic response ($p = 0.015$). FC < 250 µg/g at Week 2 predicted endoscopic response (AUC = 0.77) with a sensitivity of 70%, specificity 93%, PPV 94%, and NPV 67%. At Week 8 (AUC = 0.84) this was a sensitivity of 62%, specificity 100%, PPV 100%, and NPV 55%. FC predicted histological remission at Week 8 (AUC = 0.88): sensitivity 89%, specificity 89%, PPV 80%, and NPV 94%.

Conclusions: Although delayed clinical effectiveness of VDZ has been reported previously, VDZ induces as early as Week 2 a significant decrease of FC levels in IBD patients with an endoscopic response at Week 16. At 8 weeks after the initiation of VDZ, FC <250 µg/g accurately predicts endoscopic response and histological remission in this cohort.

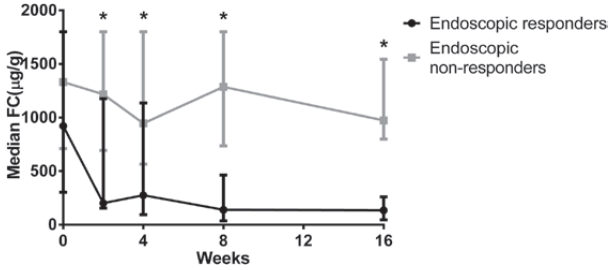

Figure 1. Serial FC measurements in IBD patients after the start of vedolizumab.

Median faecal calprotectin levels (µg/g) in endoscopic responders: 921 at baseline, 201 at Week 2, 276 at Week 4, 139 at Week 8 and 134 at Week 16. In endoscopic non-responders: 1332, 1218 ($p = 0.003$), 946 ($p = 0.005$), 1286 ($p < 0.001$) and 974 ($p < 0.001$).

P363

The minimal invasive surgery in combination with negative pressure wound therapy for perianal fistulas in Crohn's colitis lead to the fast introduction of the biological treatment and improve the results

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Background: Perianal fistula in Crohn's colitis (CC) seems be common complication. The aim of the study was determine the effectiveness of the minimal invasive surgical treatment with vacuum technique and subsequent biological therapy in CC patients with perianal fistulas.

Methods: In total, 59 CC patients were admitted due to perianal fistula (symptomatic or asymptomatic with abscess) to surgical Department. In 24 patients (Group I), minimal invasive surgical treatment was performed (excision of external opening and fistula tract, application of vacuum therapy), than after 2–4 weeks biological therapy was introduced. In 14 patients (Group II), standard surgical procedures were performed (excision with flap, seton drainage). The biological therapy was introduced depend on the wound healing after 6–16 weeks; in 21 patients only surgical procedure (excision with flap, seton drainage) was performed. Follow-up for every patient was minimum 12 months.

Results: Fistula recurrences were observed in 12% in Group I; in 35% in Group II and in 45% in Group III. Faecal incontinence was reported in 0% (Group I), 21% (Group II) and 20% (Group III) .

Conclusions: Use of the vacuum technique ('superficial' or 'endosponge') in the surgical treatment in CC patients with perianal fistulas is effective, safe, and well accepted.

P364

The value of faecal calprotectin for assessing endoscopic activity and predicting future clinical course in patients with active ulcerative colitis treated with granulomonocytapheresis: a prospective study

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Background: Previous studies have reported that Granulomonocytapheresis (GMA) was effective in patients with mild-to-moderately active ulcerative colitis (UC) and had a favourable safety profile. Currently, GMA is widely used in Japan and is available in the European Union countries. Calprotectin is a calcium-binding protein, which can be measured in faecal samples. The faecal level of calprotectin increases during disease activity in ulcerative colitis (UC). Nonetheless, the relevance of faecal calprotectin (FC) measurement during granulomonocytapheresis (GMA) for UC has not yet been fully evaluated. This prospective study was to investigate the value of FC for assessing disease activity and predicting clinical course in UC patients undergoing GMA therapy.

Methods: One hundred and eighty-four patients with moderately active UC with endoscopic activity (Mayo endoscopic subscore [MES]=2 or 3) were investigated. Each patient received a total of 10 GMA sessions with the Adacolumn (JIMRO, Takasaki, Japan) over 5 consecutive weeks. One GMA session was about 90 min at 30 ml/min. Patients who achieved clinical remission during GMA were subsequently given maintenance medications for 12 months. Relapse was defined as worsening of the clinical symptom score with the MES of 2 or 3. FC levels were measured at entry and after treatment.

Results: After GMA, 80 of the 184 patients (43%) achieved clinical remission, and 51 (28%) achieved mucosal healing (MH; MES=0 or 1). The median FC level significantly decreased in patients who achieved MH ($p = 0.02$), but not in those without MH. Thirty-four patients (43%) relapsed during the 12-month follow-up. The median (IQR) FC level at the end of GMA therapy was significantly higher in patients with relapse than in those without relapse, 149.5 (96–211) µg/g vs. 45.5 (23–99) µg/g ($p < 0.001$). A cut-off value of 114 µg/g FC had a sensitivity of 76% (95% confidence interval [CI]: 62–91%), a specificity of 85% (95% CI: 74–95%), a positive predict value (PPV) of 79% (95% CI: 65–93%), and a negative predictive value (NPV)

of 83% (95% CI: 72–94%) to predict future relapse. Relapse was observed in 26 of 33 patients (79%) with elevated FC (≥114 µg/g), but in 8 (17%) of 47 patients with low FC (<114 µg/g) ($p < 0.001$). Similarly, the cumulative relapse rate was significantly higher in patients with elevated FC (≥114 µg/g) compared with those with low FC (<114 µg/g).

Conclusions: FC could become a validated biomarker for the assessment of endoscopic disease activity in UC patients undergoing GMA therapy. Furthermore, FC at the end of GMA treatment course appeared to be a relevant biomarker for the prediction of clinical course in patients who had achieved remission.

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Autologous haematopoietic stem cell transplantation in refractory Crohn's disease: experience of a Brazilian tertiary centre

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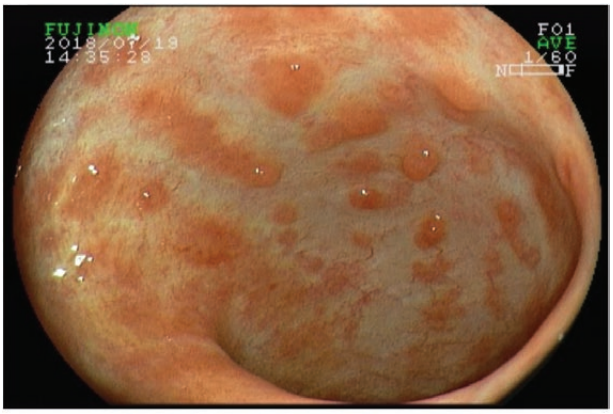
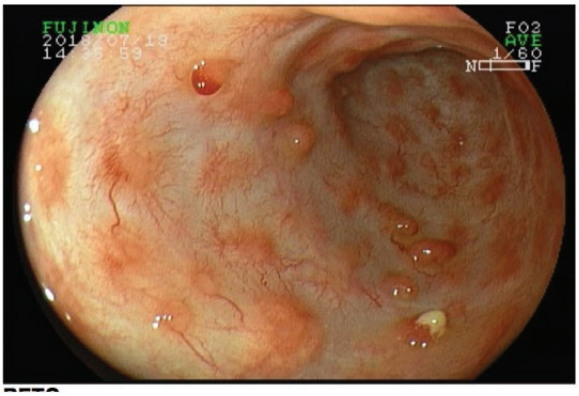
Background: A significant percentage of Crohn's disease (CD) patients suffer an aggressive disease course, refractory to available approved medical therapies. Increasing evidence supports Autologous Haematopoietic Stem Cell Transplantation (AHSCT) could be a therapeutic option.[1]

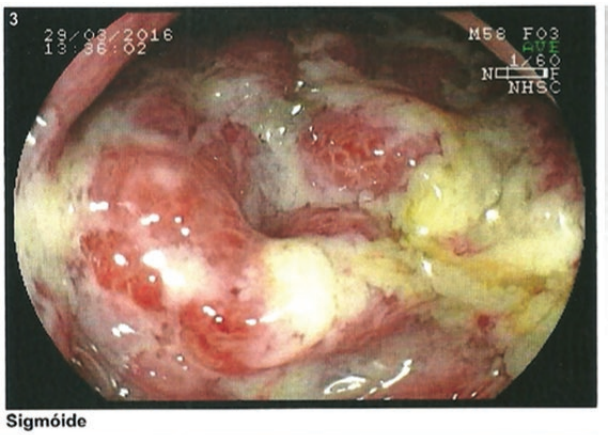
Methods: Six patients between 19 years and 43 years, with refractory CD were submitted to AHSCT. Median course of illness was 14 years (5–23 years) and all were negative for X-linked inhibitor apoptosis protein (XIAP). Four patients had penetrating disease and two had non-stricturing, non-penetrating phenotype. All patients failed to a median of 6 lines mono or combined therapies. Five patients had 2 to 3 previous intestinal surgeries and four had ileostomy and extraintestinal manifestations. Two patients had tuberculosis previously. All patients completed the mobilisation, apheresis, conditioning and transplantation phases, during a time of hospitalisation of 35 days (21–58 days). We postulate the use of CD34(+) selection with Miltenyi Biotec system to improve the results based on the memory cells decrease.[2] Stem cells were mobilised from the peripheral blood using cyclophosphamide (2 g/m^2) and G-CSF (10 µg/kg/day), enriched *ex vivo* by CD34(+) selection, and reinfused after immune suppressive conditioning with cyclophosphamide (200 mg/kg) and (rabbit antithymocyte globulin [ATG] (5 mg/kg))

Results: During mobilisation and after transplantation all six patients had life-threatening complications and severe infectious as KPC and Staphylococcus aureus blood infection, reactivation of cytomegalovirus disease and septic shock by *E. coli*. All had febrile neutropenia, mucositis, anaemia. We did not have any deaths. After 1y follow-up all six patients achieved the primary and secondary outcomes: clinical and endoscopic remission (images 1 and 2)





Sigmoid colon CD patient 1 year 4 months post-AHSCT.



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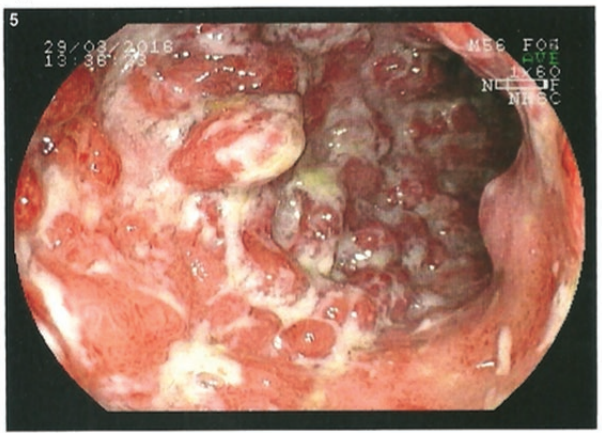

Pre-AHSCT.
and steroid and immunosuppressive free remission (CDAI <150). Currently, all six patients are alive without any malignancy complications and the longest period is 3 years 3 months. All patients relate viral and bacterial infections. Only one patient restarted adalimumab, 1 years 11 months post-AHSCT

Conclusions: We consider AHSCT may be a promising therapeutic option for treatment refractory CD patients. The high complexity, toxicity, risk of death and infections, more accurate protocols need to be discussed between GI and onco-haematology professionals and centre around the world.

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P366

A service evaluation of pre-operative nutritional optimisation in patients with Crohn's disease using exclusive enteral nutrition with or without supplementary parenteral nutrition

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Background: Malnutrition is a significant problem in patients with Crohn's disease (CD) who need surgery and leads to poor post-operative outcomes. The ideal method of pre-operative nutritional optimisation in CD is not known. Limited evidence suggests that exclusive enteral nutrition (EEN) improves nutritional and surgical outcomes. Some patients require supplementary parenteral nutrition (PN) to meet their nutrition requirements due to increased disease severity and/or phenotype. This service evaluation assessed nutritional and surgical outcomes in patients with CD who received pre-operative nutritional optimisation with EEN or supplementary PN.

Methods: Patients with stricturing and/or penetrating CD, who underwent surgery from January 2016 to December 2017 were offered exclusive enteral nutrition (EEN) for at least 6 weeks pre-operatively. Patients who could not meet nutrition requirements from EEN were offered supplementary PN. Comparisons were made between EEN and supplementary PN groups for baseline and pre-operative body mass index (BMI) and weight loss, length of stay (LOS), stoma formation and post-operative complications. Analysis used chi-squared for categorical data and t-test for continuous data. Statistical significance was set at $p < 0.05$.

Results: Forty-seven CD patients (29 males) with mean ± SD age (39.3 ± 14.9 years) received pre-operative nutritional optimisation. The EEN group ($n = 36$) had higher baseline BMI (kg/m^2) (EEN: 23.6 ± 5.1 vs. PN: 18.0 ± 2.8, $p < 0.001$) and less unintentional weight loss at baseline (EEN: 4% ± 7 vs. PN: 14% ± 8, $p < 0.001$) compared with the supplementary PN group ($n = 11$). There was no change between baseline and pre-operative BMI in the EEN group (baseline: 23.6 ± 5.1 vs. pre-operative: 23.9 ± 4.7, $p = 0.151$) but BMI increased in the PN group (baseline: 18 ± 2.8 vs. pre-operative: 19.8 ± 2.7, $p = 0.038$). Patients on EEN had shorter LOS (days) (EEN: 9 ± 8 vs. PN: 26 ± 19, $p = 0.002$) and a lower stoma formation rate (EEN: 22% vs. PN: 64%, $p = 0.01$) compared with patients on supplementary PN. Fewer patients had a high output stoma (>1 l/day) in the EEN group compared with the supplementary PN group (EEN 38% vs. PN: 63%, $p = 0.004$). There were no significant differences between groups for other post-operative complications (ileus, wound breakdown, infection, reoperation and readmission).

Conclusions: This service evaluation highlights the importance of pre-operative nutritional optimisation in CD patients. It shows that patients who can meet their nutritional requirements from EEN have better nutritional and surgical outcomes compared with patients who need supplementary PN.

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Nutrition advice for IBD patients as a useful complementary strategy: a single-centre cohort intervention

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Background: Diet plays an important role in patients with inflammatory bowel disease (IBD) since it may influence intestinal inflammation, through an alteration of gut microbiome, and affecting gastrointestinal permeability. Nutrition problems may have a strong effect on patient health, nutritional status and quality of life. However, scientific studies lack solid evidence to support specific dietary recommendations and this is reflected in conflicting dietary beliefs in clinical practice. In our Multispecialistic Centre for Recto-Intestinal Diseases (IBD Unit) at Negrar Hospital, we give a nutrition consultation to provide tailored dietary advice to all IBD patients. The aim of this investigation was to assess the efficacy of our nutritional intervention on disease symptoms and patients quality of life (QoL).

Methods: From October 2017 to April 2018, we evaluated patients with ulcerative colitis (UC) in clinical remission (according to Partial Mayo Score (PMS) for UC: remission score (rs) < 2) and gave them dietary suggestions, including antioxidant, vitamin, probiotic supplementation and nutritional deficiency screening. Dietary counselling was based on: elimination of dairy products if lactose intolerance was detected, intake limitation of refined sugars, alcohol, gluten-based grains, meat and saturated fats, intake promotion of high-fibre (legumes, vegetable, whole grains), fermented, n-3 rich foods (fish, dried fruit), aliments with antioxidant activity (olive oil, green tea, turmeric, red fruit), and vitamin D supplementation. After dietary advice these patients were reassessed after 1 month, 3 months and 6 months. We also recruited a control group of UC patients, homogeneous in disease activity, current therapy (tp), age, sex and disease extent.

Results: We enrolled 32 UC patients in clinical remission, whom underwent nutritional evaluation, 17 had PMS: 0, 15 PMS: 1 [21 female, mean age 38 years old, 16 left-sided colitis, 9 proctitis, 7 pancolitis, 21 patients treated with mesalazine, 7 azathioprine, 4 biologic tp (3 adalimumab, 1 Infliximab)]. After 6 months, all patients receiving nutrition advice, considered diet to be a very important

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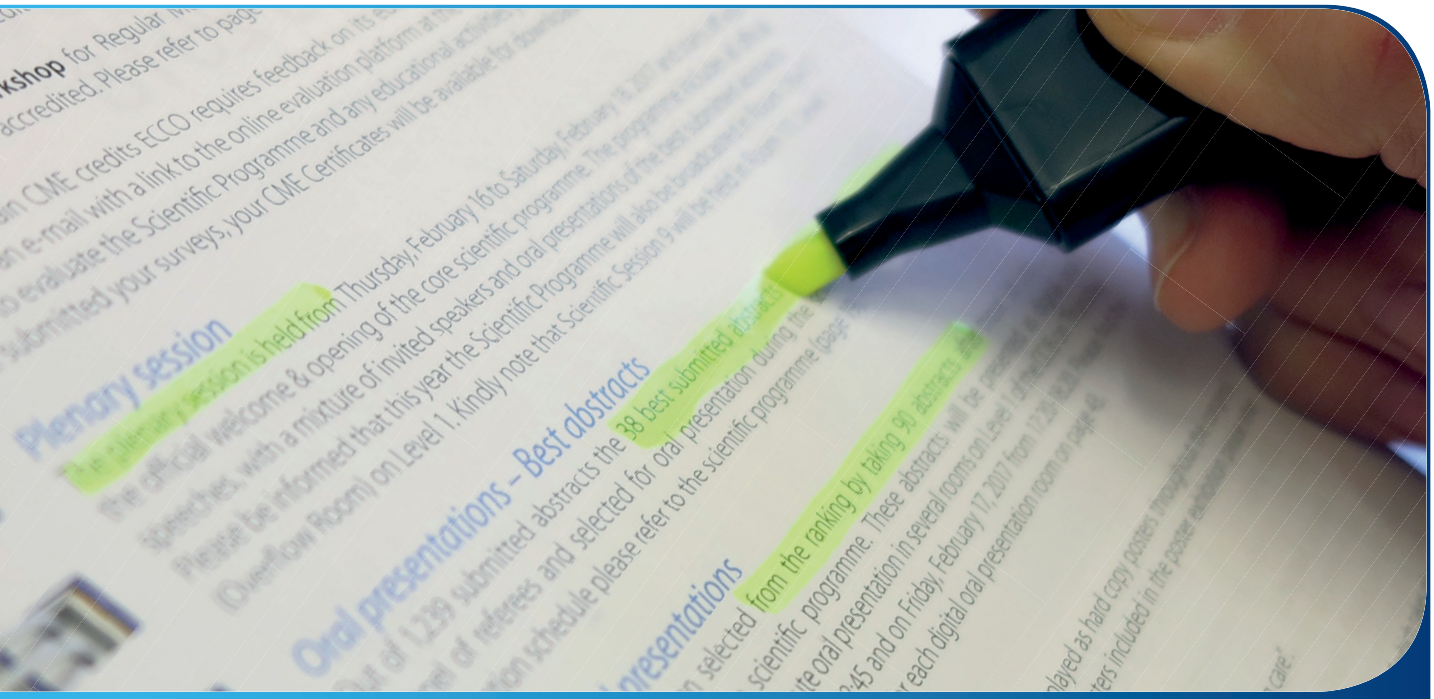

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tool to relieve disease symptoms. Self-reported QoL was improved than control group. PMS was stable or reduced to 0, in comparison to control group, where we could observe mild flares in 9 patients. No nutrition treatment-related adverse events nor vitamin and trace elements deficiency were observed.

Conclusions: Our investigation on nutritional support in IBD shows that diet is important and effective as a complementary tp, in UC patients in remission. High-quality dietary intervention studies are needed to have a better understanding of dietary practices in improving symptoms and to create strong evidence-based dietary guidelines for IBD patients.

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Vedolizumab in inflammatory bowel disease: a retrospective single-centre study

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Background: Vedolizumab is an integrin receptor antagonist used when anti-TNF treatment has failed or is contraindicated in moderate to severe Crohn's disease (CD) and ulcerative colitis (UC). The aim of this study was to evaluate efficacy and side effects of vedolizumab in daily clinical practice.

Methods: A review of medical records for the time period 2014–2018 at Østfold Hospital Trust was performed. Symptoms (based on the Mayo score and the Harvey–Bradshaw Index) and the use of concomitant medications were recorded at 4–6 months, 12 months, >12 months and if applicable, after discontinuation of the treatment. Measurements of faecal calprotectin and vedolizumab drug levels were obtained. The disease activity was classified as complete remission (CR), partial response (PR) or non-response (NR) based on calprotectin levels, symptoms and endoscopy/radiology findings. Calprotectin < 100 mg/kg was used as a marker for CR, 100–300 mg/kg for PR and >300 mg/kg for NR.

Results: A total number of 77 patients (53% with UC) received vedolizumab during the defined period, of which 4/77 were biological-naïve. In 52/77, one biological drug had been used prior to vedolizumab treatment, while 21/77 had used ≥2. Before starting vedolizumab, 65% of CD patients had undergone IBD-related surgery. CR was achieved in 13/77 (17%) and PR in 28/77 (36%). A total number of 36/77 was defined as NR at the most recent follow-up. The mean time of observation was 15 months (median 13, range 2–49 months). Time until achieved CR was 4–6 months (n = 1), 12 months (n = 7) and >12 months (n = 5). Discontinuation of treatment occurred in 28 patients (36%) (therapeutic failure = 16/28, therapeutic failure + side effects = 4/28, side effects only = 4/28, and other causes =4/28). In CD, 14% had undergone surgical intervention during treatment and 6% following discontinuation of vedolizumab. In UC, 32% underwent colectomy shortly after termination (mean/median time between discontinuation and colectomy: 3.4/2 months).

	CR	PR
Calprotectin (mean/median) mg/kg	60.9/23.0	369.0/186.0
Vedolizumab (mean/median) mg/l	22.7/20.4	24.6/22.9

F-calprotectin and p-vedolizumab in CR and PR.

Conclusions: Half of the patients who received vedolizumab responded to treatment, of which 2/3 had PR and 1/3 had CR. The effect tends to be better in UC compared with CD. One in five patients had CR and this effect was noted mainly from 12 months and/or more of active treatment. It is of utmost importance to carry out an objective assessment of therapeutical response before 12 months to evaluate if there is indication for continuation or cessation of treatment.

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The comparative frequency of clostridial infection in patients with ulcerative colitis receiving mesenchymal stromal cells and anti-cytokine therapy

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Background: Patients with inflammatory bowel disease (IBD) experienced more frequent development of Clostridial infection and much higher rates of morbidity and mortality compared with patients without IBD. Risk factors are immunosuppressive therapy.

The aim is to compare the frequency of Clostridial infection (CI) in patients with ulcerative colitis (UC) receiving bone marrow mesenchymal stromal cells (MSC) and biological therapy.

Methods: The patients were divided into three groups: the first group (n = 23) received the MSCs culture according to the scheme (0–1–2 weeks, then every 26 weeks); the second group of patients with UC (n = 21) received infliximab (IFX) in combination with azathioprine (AZA) according to the recommended scheme, the third group received only IFX according to the scheme. The toxins A and B of Clostridium difficile were determined by the enzyme immunoassay in the stool. The comparative analysis was carried out using the method of four-field tables using nonparametric statistical criteria.

Results: In patients of the 1-st group, toxin A was detected in 1/23 patients (4.3%), in the 2-nd group - in 2/21 (9.5%) (RR - 0.45, 95% CI 0.04-4.6, χ^2 - 0.46, $p > 0.05$), in the third - in 2/18 (11.1%) (RR - 0.4, 95% CI 0.04 - 3.98, χ^2 - 0.7, $p > 0.05$). In patients of the 1-st group, toxin B was detected in 2/23 patients (8.6%), in the second group in 3/21 (14.3%) patients (RR - 0.6, 95% CI 0, 1 - 3.3, χ^2 - 0.3, $p > 0.05$), in the third - in 2/18 (11.1%) (RR-0.8, 95% CI 0.12 - 5, 03; χ^2 - 0.07; $p > 0.05$). In patients of the 1-st group toxins A and B were not detected - 0/23 (0,0%), in the 2-nd group toxins A and B were detected in 7/21 (33.3%) patients (χ^2 - 9.5, $p < 0.05$), in the third - in 5/18 (27.8%) (χ^2 - 7.3, $p < 0.05$). Totally in patients of the 1-st group, Clostridium difficile toxin A and B was detected in 3/23 patients (13.1%), in the second group - in 12/21 (57.1%) patients with UC (RR - 0.23, 95 % CI 0.075 - 0.7, χ^2 - 9.5, $p < 0.05$), in the third - in 9/18 (50.0%) (RR - 0.26, 95% CI 0.08 - 0.82, χ^2 - 6.6, $p < 0.05$).

Conclusions: The frequency of Clostridial infection in patients with ulcerative colitis receiving mesenchymal stromal cells is significantly lower than in patients with ulcerative colitis receiving biological immunosuppressive preparations.

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Quality of life of patients with inflammatory bowel diseases in remission on different forms of treatment

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Background: Inflammatory bowel diseases (IBD), Crohn's disease and ulcerate colitis, are mostly common in young people, therefore the practical importance of researching on the quality of life of young people with chronic and lifelong illnesses is extremely high. It is indisputable that the application of biological therapy is a trend of treatment for these patients, but patients can also achieve satisfactory clinical and endoscopic remission with other therapeutic modalities. The goal of this paper was to evaluate and compare socio-demographic characteristics and quality of life of IBD patients on biological and immunomodulatory (IMD) therapy.
Methods: The cross-sectional study was conducted in period February–August 2018, at the Clinical Department of gastroenterology of Clinical Hospital Center Zvezdara, Belgrade, on 80 patients with UC and CD in remission (30 treated with biological therapy and 50 on IMD therapy). For the survey of socio-demographic characteristics and quality of life, Treatment Satisfaction Questionnaire for Medication-TSQM (Version 1.4) and Short Inflammatory Bowel Disease Questionnaire (SIBDQ) were used. Statistical analysis was performed using SPSS-17.0 and included methods of descriptive and analytical statistics (Student's *t*-test, χ^2 test, Fisher's exact test), with statistical significance set at $p < 0.05$, and confidence interval at 95% for all analysis.
Results: The average age of patients on biological therapy was 33.7 years (± 6.5), while average age of patients on other therapy modalities was 38.1 (± 12.7) years, which is a statistically significant difference ($p = 0.045$, $t = -2.039$). Although in patients on biological therapy, comparing the patients on IMD, proportion of males was larger, there was no statistically significant difference in gender representation among the groups ($p = 0.203$, $\chi^2 = 1.617$). Both groups reported small number of therapy negative effects, with no statistically significant difference ($p = 0.10$, $\chi^2 = 3.768$), but the patient overall satisfaction was statistically significantly higher in those on biological therapy ($p < 0.001$, $\chi^2 = 18.613$). The average value of the estimated quality of life of patients on biological therapy was 54.99 out of the maximum 70 points, while in patients on other forms of treatment it was 32.2 (22.79 points less) (95% CI: 19.541–25.793), which is highly statistically significant ($p < 0.01$, $t = 14.436$).
Conclusions: The results of our survey indicate that patients with inflammatory bowel diseases on biological therapy express greater satisfaction and have a significantly higher quality of life in comparison to patients on IMD therapy.

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Outcome of immediate infliximab optimisation based on rapid assessment of serum drug and faecal calprotectin concentrations in Crohn's disease

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Background: Dose intensification strategy based on the parallel assessment of clinical symptoms, serum and faecal biomarkers and serum infliximab (IFX) concentration may increase therapeutic response in inflammatory bowel diseases. The aim of this study was to evaluate the outcome of IFX optimisation based on proactive drug monitoring in combination with the assessment of clinical activity and biomarkers using rapid assays.
Methods: This is a prospective study of Crohn's disease (CD) patients on IFX maintenance therapy, started in May 2018. Blood and faecal samples were obtained at the day when subsequent IFX infusion was scheduled. C-reactive protein (CRP) and haematocrit levels were measured immediately. Serum IFX and faecal calprotectin (FC) concentrations were benchmarked with rapid, lateral flow-based assays (RIDA®QUICK, Quantum Blue®). Clinical activity indices (CDAI) were calculated at the same visit. On the basis of all data, patients were assigned to 4 groups: no intervention (NI) if CRP < 10 mg/l AND FC < 300 µg/g, AND CDAI < 200, AND IFX level was 3–10 µg/ml. Dose increase (DI) if either CRP, FC or the activity indices were elevated, OR IFX level was lower than 3 µg/ml. Stopping IFX (ST) if all the activity markers were in normal range but IFX were undetectable or is in very low concentration. Switch if any of the activity markers were abnormal AND serum IFX were in sub or supra therapeutic level. After optimisation, patients are followed for 6 months with determining all the above-mentioned parameters retrospectively at every 2 month.
Results: Data of 26 CD patients were available to be analysed with a 4 months follow-up. On the basis of the rapid tests, DI was performed in 14 patients, NI in 8 patients, and ST in 4 patients. In DI group, serum level of IFX increased, CDAI decreased significantly at month 2 and 4 compared with the baseline. Level of CRP and FC did not change significantly at month 2, but CRP decreased significantly at month 4. After the dose increase, 2 patients had subtherapeutic drug level with antibody positivity at every examined time point. One patient had to be hospitalised because of a relapse and was switched to ustekinumab. All patients in NI group remained in remission at month 2 and 4. None of the examined parameters, except for serum IFX level at month 4 changed significantly at month 2 and 4. One patient in the ST group required reintroduction of therapy with adalimumab at month 2; the other 3 patients were still in remission at month 2 and 4.
Conclusions: Change in therapy was performed in 18 cases on the bases of benchmarked concentrations of serum IFX and FC levels. Our results suggest benefit of using rapid tests in daily practice. The study is ongoing to evaluate medium- and long-term benefits.

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Neurological symptoms and imaging abnormalities in brain MRI in patients with Crohn's disease receiving anti-TNFa therapy

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Background: Anti-TNFa treatment has been related to CNS demyelination, while history of demyelinating disease is considered as contraindication to anti-TNFa use. The aim of this study was to describe 3 patients with Crohn's disease (CD), who presented with neurological symptoms and had demyelinating lesions of white matter in brain MRI, while receiving treatment with anti-TNF agents.

Methods: We reviewed past medical history, clinical presentation, hospitalisation history, type and duration of anti-TNFa treatment and brain MRI results of the 3 patients.

Results: Patient A (CD diagnosis 6 years ago) presented with right lower limb numbness 2 years after commencing adalimumab therapy. Brain MRI showed few, non-significant white matter lesions. Infliximab was started 3 years later, after R colectomy-syringectomy-anastomosis, with relapse of the neurological symptoms.. Patient B (CD diagnosis 3 years ago) developed right side (face and upper-lower limb) 2 years after adalimumab therapy. Patient C (CD diagnosis a year ago) reported right eye pain occasionally for 4 years with negative ophthalmologic evaluation. A year after commencing therapy with Infliximab-bio and azathioprine, relapse of eye pain and new-onset limb numbness were reported. Brain MRI in all patients demonstrated white matter lesions. The radiological differential diagnosis included microangiopathic or demyelinating lesions. Anti-TNFa therapy was discontinued in all 3 patients with subsequent remission of the symptoms but without full disappearance.

Conclusions: Numbness is reported relatively frequently in CD patients receiving anti-TNFa treatment. The current series demonstrate the difficulty of establishing a firm causal association with the use of anti-TNF treatment due to the absence of earlier imaging. Therefore, we propose that brain-MRI may be considered in IBD patients before starting biological therapy.

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Effect of risankizumab on improved and sustained quality of life in patients with moderate to severe Crohn's disease: Phase 2 trial results

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Background: Risankizumab (RZB), an anti-interleukin 23 antibody, is being investigated as a treatment for Crohn's disease (CD). The impact of RZB on health-related quality of life, measured by Inflammatory Bowel Disease Questionnaire (IBDQ), was assessed in the Phase 2 trial of RZB in CD (NCT02031276).

Methods: Adults (18–75 years) with moderate to severe CD (CDAI 220–450 with mucosal ulcers and CDEIS ≥7 [or ≥4 in patients with isolated ileitis on ileocolonoscopy]) were enrolled. In the double-blind phase (weeks [weeks] 0–12, period 1), patients received RZB (200 mg or 600 mg) or placebo (PBO) IV Q4W for 12 weeks as induction therapy. In the extended induction/washout phase (Weeks 14–26, period 2), those not in deep remission at Week 12 received open-label RZB 600 mg IV Q4W for 12 weeks and those in deep remission at Week 12 entered a washout phase until Week 26. Pts in clinical remission at Week 26 entered the maintenance phase and received open-label RZB 180 mg SQ Q8W for 26 weeks (Weeks 26–52, period 3); those not in clinical remission discontinued. In period 2 and 3, only patients who received open-label RZB treatment were analysed. Percentages of patients with IBDQ response (increase in IBDQ total score ≥16); IBDQ remission (IBDQ total score ≥170); and mean change from baseline (BL) in IBDQ total, domain, and selected individual item scores were calculated at Weeks 12, 26, and 52.

Results: Data from 121 patients were analysed in period 1. At Week 12, the percentage of patients with IBDQ response was significantly greater ($p < 0.05$) in both RZB groups vs. PBO (Table 1). A potential dose–response was observed at Week 12 with greater improvements seen in RZB 600 mg and 200 mg vs. PBO in IBDQ total score, domain scores (Table 2), and item scores from BL including bowel movement frequency, abdominal pain, rectal bleeding, stomach sick, and fatigue (all $p < 0.05$). During period 2, patients receiving extended induction therapy gained additional improvement in IBDQ outcomes at Week 26 vs. Week 12, especially those receiving PBO in period 1. These improvements in IBDQ outcomes were maintained at Week 52 of RZB treatment.

Table 1. Patients with IBDQ response and remission at Weeks 12, 26, and 52 (NRI).

	Placebo	200 mg IV RZB	600 mg IV RZB	Total
Week 12 (period 1 – end of induction; double blinded)				
Number of patients	39	41	41	—
IBDQ response	12 (30.8%)	25 (61.0%)*	29 (70.7%)*	—
IBDQ remission	6 (15.4%)	5 (12.2%)	14 (34.1%)	—
Patients without deep remission[a] at week 12 received 600 mg IV RZB (open label)				
Week 26 (period 2 – end of extended induction; open label)[b]				
Number of patients	33	34	34	101
IBDQ response	17 (51.5%)	26 (76.5%)	26 (76.5%)	69 (68.3%)
IBDQ remission	16 (48.5%)	13 (38.2%)	18 (52.9%)	47 (46.5%)
Patients with clinical remission at week 26 received 180 mg SC RZB (open label)				
Week 52 (period 3 – end of maintenance; open label)				
Number of patients	19	22	21	62
IBDQ response	15 (78.9%)	18 (81.8%)	20 (95.2%)	53 (85.5%)
IBDQ remission	14 (73.7%)	11 (50.0%)	14 (66.7%)	39 (62.9%)

*p<.05 for RZB vs PBO using Cochran-Mantel-Haenszel risk difference stratified by anti-tumour necrosis factor exposure.
Missing data were reported with non-responder imputation (NRI).
[a]Deep remission is defined as clinical remission (CDAI <150) and endoscopic remission (CDEIS ≤4 or ≤2 for patients with baseline-isolated ileitis).
[b]Among 101 patients who received reinduction of RZB.

Table 2. Mean change from baseline in IBDQ total and domain scores (LOCF).

	Placebo		200 mg IV RZB		600 mg IV RZB		Total	
	BL	Change	BL	Change	BL	Change	BL	Change
Week 12 (period 1 – end of induction; double blinded)								
Number of patients	39		41		41		—	
IBDQ total score[a]	123.4	7.4	110.9	22.6	113.2	33.9*	—	—
Bowel symptom	38.6	2.6	36.9	9.1*	36.4	11.0*	—	—
Systemic symptom	15.7	1.7	14.2	3.6	14.9	5.9*	—	—
Emotional function	48.3	2.0	41.9	6.8*	43.6	11.5*	—	—
Social function	20.2	0.9	17.9	2.8	18.2	5.6*	—	—
Patients without deep remission[b] at week 12 received 600 mg IV RZB (open label)								
Week 26 (period 2 – end of extended induction; open label)[c]								
Number of patients	33		34		34		101	
IBDQ total score	131.3	25.3	108.8	44.0	110.6	53.1	116.1	41.6
Bowel symptom	41.4	9.9	36.0	14.0	35.5	16.3	37.5	13.6
Systemic symptom	17.8	3.8	14.1	6.6	14.3	9.6	15.3	6.7
Emotional function	51.1	6.8	41.1	15.4	42.1	19.6	44.5	14.2
Social function	21.4	4.5	17.4	8.0	17.9	8.9	18.8	7.2
Patients with clinical remission at week 26 received 180 mg SC RZB (open label)								
Week 52 (period 3 – end of maintenance; open label)								
Number of patients	19		22		21		62	
IBDQ total score	134.7	47.5	107.8	55.1	116.1	69.3	118.8	57.6
Bowel symptom	42.2	16.2	37.0	17.0	37.4	22.0	38.7	18.5
Systemic symptom	17.2	8.1	14.1	7.9	15.1	12.1	15.4	9.4
Emotional function	50.4	16.1	39.2	19.1	45.1	23.3	44.5	19.6
Social function	20.8	9.3	17.3	11.3	18.5	11.9	18.8	10.9

*p<.05 for RZB vs PBO using Wilcoxon rank sum test.
Missing data were imputed with last observation carried forward (LOCF).
[a]IBDQ total score at week 12 has been reported in Feagan BG, et al. *Lancet* 2017;389:1699–709.
[b]Deep remission is defined as clinical remission (CDAI <150) and endoscopic remission (CDEIS ≤4 or ≤2 for patients with baseline-isolated ileitis).
[c]Among 101 patients who received reinduction of RZB.

Conclusions: In patients with CD, induction treatment with RZB 200 mg or 600 mg IV Q4W led to significant and dose–response improvements in IBDQ outcomes at Week 12. Additional improvement in IBDQ outcomes was observed with extended induction therapy. The treatment benefit of RZB in IBDQ was maintained by Week 52.

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Effects of subcutaneous vedolizumab on health-related quality of life and work productivity in patients with ulcerative colitis: results from the Phase 3 VISIBLE 1 trial

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Background: Patients with ulcerative colitis (UC) experience substantial impairment in quality of life (QOL), and QOL endpoints are therefore considered important measures of treatment outcome. We evaluated the effects of an investigational vedolizumab (VDZ) subcutaneous (SC) formulation on QOL and work productivity in VISIBLE 1 (NCT02611830; EudraCT 2015-000480-14), a Phase 3, placebo-controlled trial that demonstrated the efficacy and safety of VDZ SC in moderately to severely active UC.

Methods: Following an open-label induction phase (VDZ intravenous [IV] 300 mg at Weeks 0 and 2), patients who achieved clinical response at Week 6 were randomised to maintenance phase treatment with: VDZ SC 108 mg every 2 weeks, VDZ IV 300 mg every 8 weeks, or the matching placebo (SC and IV). QOL was assessed using the Inflammatory Bowel Disease Questionnaire (IBDQ) and Euro Quality of Life-5D visual analogue scale (EQ-5D VAS), and work productivity using Work Productivity and Activity Impairment (WPAI-UC). Changes in QOL and work productivity from baseline (Week 0) to Week 52 and from Week 6 to Week 52 in the maintenance phase were compared between the three treatment groups using an analysis of covariance model (covariate: baseline score).

Results: There were 216 patients randomised at Week 6. Mean total IBDQ scores at Week 52 were: placebo, 135.2; VDZ SC, 180.7; VDZ IV, 170.7. Scores were significantly improved from baseline with both VDZ SC (+65.3) and VDZ IV (+58.6) compared with placebo ($p < 0.001$ for both) (Figure 1A). Mean EQ-5D VAS scores at Week 52 were: placebo, 58.1; VDZ SC, 76.1; VDZ IV, 71.4; change from baseline was significantly greater for VDZ SC (+27.1) and VDZ IV (+22.6) compared with placebo ($p \leq 0.001$ for both) (Figure 1B). Similarly, improvements in mean WPAI-UC subscores were consistently greater with both VDZ SC and VDZ IV vs. placebo (Figure 1C). Improvements in IBDQ, EQ-5D VAS, and WPAI-UC scores observed at Week 6 were sustained through Week 52 with VDZ both VDZ SC and VDZ IV (Figure). Across all QOL and work productivity measures, patients who received maintenance placebo had substantial worsening in scores from Week 6 to Week 52 (Figure 1A–C).

Conclusions: VDZ SC treatment was associated with overall significantly meaningful clinical improvements in IBDQ and EQ-5D VAS QOL instruments. Similarly, significant improvements in work productivity measures were observed among patients treated with VDZ SC. Further investigation of the effects of VDZ SC on QOL is needed to validate these findings.

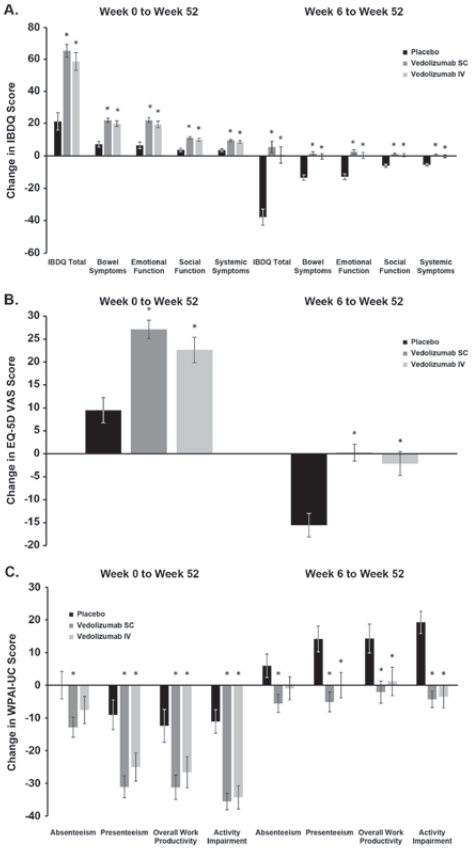

Figure 1. Changes in (A) IBDQ, (B) EQ-5D VAS, and (C) WPAI-UC scores from Week 0 to Week 52 and Week 6 to Week 52 in the three maintenance treatment groups.

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Inflammatory cutaneous lesions in inflammatory bowel disease treated with vedolizumab or ustekinumab: an ECCO CONFER multi-centre case series

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Background: Inflammatory cutaneous lesions are a common extraintestinal manifestation of inflammatory bowel disease (IBD). However, it is unknown whether such lesions, which may be refractory to standard medical therapy including anti-TNFs, would respond to the newer biologic agents ustekinumab (UST) or vedolizumab (VDZ).
Methods: This was a European Crohn's and Colitis Organisation (ECCO) retrospective multi-centre case series, performed as part of the CONFER project. A call to all ECCO members was made to report on cutaneous lesions in IBD treated by UST or VDZ, excluding psoriasiform lesions. Clinical data were recorded in a standardised data collection form.
Results: This report includes 28 patients with cutaneous lesions form 14 centres; 23 had Crohn's disease and 5 had ulcerative colitis whilst 19 were treated with UST and 11 with VDZ (2 patients were treated with both). All had failed immunomodulators and anti-TNF therapy. Metastatic Crohn's disease (MCD) was diagnosed in 10 patients (9 confirmed by histology) and UST therapy led to remission in 5 cases and partial response in 4 cases, with a single report of VDZ inducing remission. All cases of MCD that were treated with UST responded after the first or second dose, whilst for the 5 cases that attained remission, the median time for this was 5 months. Pyoderma gangrenosum (PG) was diagnosed in 4 cases; 3 of these attained remission with UST (median time to remission 4 months) whilst one case did not respond to VDZ. There were 7 cases of erythema nodosum (EN); UST led to remission in 4 cases and partial response in 1 case whilst VDZ had partial response in 2 cases and non-response in 2 cases. There were 7 single cases of other inflammatory lesions, which included: a case of leukoclastic vasculitis that attained remission with VDZ, a case of hidradenitis suppurotiva (HS) with partial response to UST, a case of dissecting cellulitis of the scalp that did not respond to UST; 2 unspecified cases with partial response to VDZ and another two unspecified cases with no response to VDZ.
Conclusions: This is the first case series to describe the efficacy of UST and VDZ in the treatment of cutaneous lesions related to IBD. UST led to a remission or a partial response in all cases of MCD, PG, HS and EN. VDZ caused a partial response or non-response in EN and other inflammatory lesions, as well as a single case of remission in MCD.

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Effects of IV vedolizumab on health-related quality of life and work productivity in patients with Crohn's disease: results from the Phase 3b VERSIFY trial

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Background: The open-label, Phase 3b, single-arm VERSIFY trial demonstrated that intravenous (IV) vedolizumab (VDZ) induced endoscopic healing in patients with moderately to severely active Crohn's disease (CD). We evaluated the effects of IV VDZ on quality of life (QOL) and work productivity over a 52-week study period.
Methods: The VERSIFY trial enrolled 56 patients into an IV vedolizumab 52-week substudy. QOL was assessed using Inflammatory Bowel Disease Questionnaire (IBDQ) and Euro Quality of Life-5D (EQ-5D) utility index and visual analogue scale (VAS), and work productivity using Work Productivity and Activity Impairment (WPAI-CD). For the 52-week substudy population (n = 56), changes over 52 weeks were evaluated. IBDQ remission was considered as a total IBDQ score of ≥170 points, with an improvement of ≥16 points considered clinically meaningful. Outcomes were examined by endoscopic remission status and by prior anti-tumour necrosis factor-α (anti-TNFα) use.
Results: Mean pt age was 39.6 years, 54% were male, 43% had prior anti-TNFα treatment and 29% achieved endoscopic remission at any ileocolonoscopy visit up to Week 52. Improvements in IBDQ total score were observed as early as Week 14 in all subgroups and were sustained up to Week 52; improvements were greater in patients with endoscopic remission (183 vs. 164; Table 1) and in patients with no prior anti-TNFα use (178 vs. 157; Table 2). Similar trends of greater improvements in EQ-5D utility index (0.91 vs. 0.83) and VAS (79 vs. 68) were observed in patients with endoscopic remission. At Week 52, EQ-5D utility scores improved equally regardless of prior anti-TNFα use, whereas EQ-5D VAS scores were slightly higher in patients naïve to anti-TNFα vs. those who had previously failed anti-TNFα treatment (Table 2). Improvements in WPAI-CD subscores were consistently higher in patients with endoscopic remission; overall work impairment and daily activities impairment were substantially improved in patients naïve to anti-TNFα.
Conclusions: Overall, IV VDZ treatment was associated with substantial improvements in both QOL instruments and work productivity measures. The improvements in QOL and work productivity

were greater among patients who achieved endoscopic remission and patients who had no prior anti-TNFα treatment.

Table 1. Changes in QOL and work productivity by endoscopic remission status over 52 weeks.

Instrument	Baseline (Week 0)	Week 14	Week 26	Week 52
IBDQ Total, mean (SD) [N]				
Overall	127.2 (34.1) [55]	167.5 (29.8) [54]	170.1 (30.7) [56]	169.2 (35.3) [56]
Endoscopic remission-Yes	120.1 (35.2) [16]	165.7 (39.4) [15]	171.0 (30.2) [16]	182.8 (29.1) [16]
Endoscopic remission-No	130.1 (33.7) [39]	168.2 (25.7) [39]	169.7 (31.2) [40]	163.7 (36.5) [40]
EQ-5D utility index, mean (SD) [N]				
Overall	0.76 (0.14) [56]	0.84 (0.13) [54]	0.83 (0.15) [56]	0.85 (0.15) [56]
Endoscopic remission-Yes	0.77 (0.14) [16]	0.82 (0.20) [15]	0.84 (0.11) [16]	0.91 (0.13) [16]
Endoscopic remission-No	0.75 (0.14) [40]	0.84 (0.09) [39]	0.83 (0.17) [40]	0.83 (0.15) [40]
EQ-5D VAS, mean (SD) [N]				
Overall	51.7 (20.1) [55]	70.6 (15.8) [54]	71.5 (17.6) [56]	71.0 (21.1) [56]
Endoscopic remission-Yes	56.7 (15.9) [15]	74.1 (23.0) [15]	77.4 (13.3) [16]	79.3 (14.2) [16]
Endoscopic remission-No	49.9 (21.4) [40]	69.3 (12.1) [39]	69.1 (18.6) [40]	67.8 (22.5) [40]
WPAI-CD, mean (SD) [N]				
Absenteeism				
Overall	22.8 (37.2) [23]	7.0 (20.8) [28]	8.6 (20.0) [33]	6.7 (13.0) [35]
Endoscopic remission-Yes	17.2 (32.9) [9]	10.0 (31.6) [10]	4.5 (10.8) [10]	2.0 (4.5) [11]
Endoscopic remission-No	26.5 (40.4) [14]	5.3 (12.3) [18]	10.3 (22.9) [23]	8.8 (15.0) [24]
Presenteeism				
Overall	38.3 (29.2) [23]	23.8 (23.5) [29]	15.8 (19.5) [33]	19.7 (25.1) [36]
Endoscopic remission-Yes	30.0 (23.5) [9]	26.0 (25.0) [10]	17.0 (20.6) [10]	12.5 (28.6) [12]
Endoscopic remission-No	43.6 (32.0) [14]	22.6 (23.3) [19]	15.2 (19.5) [23]	23.3 (23.0) [24]
Overall work impairment				
Overall	47.7 (31.2) [22]	28.0 (26.2) [28]	20.8 (21.3) [32]	21.5 (24.6) [35]
Endoscopic remission-Yes	45.0 (30.0) [9]	28.0 (30.1) [10]	19.5 (23.1) [10]	6.4 (10.0) [11]
Endoscopic remission-No	49.6 (33.1) [13]	27.9 (24.8) [18]	21.4 (20.9) [22]	28.5 (26.3) [24]
Daily activities impairment				
Overall	51.1 (27.8) [53]	33.5 (23.6) [51]	30.5 (27.5) [56]	28.4 (27.2) [56]
Endoscopic remission-Yes	50.6 (27.2) [16]	35.0 (27.4) [14]	24.4 (24.8) [16]	13.8 (20.3) [16]
Endoscopic remission-No	51.4 (28.4) [37]	33.0 (22.3) [37]	33.0 (28.4) [40]	34.3 (27.6) [40]

EQ-5D, Euro Quality of Life-5 Dimensions; EQ-5D VAS, Euro Quality-5D visual analogue scale; IBDQ, Inflammatory Bowel Disease Questionnaire; QOL, quality of life; SD, standard deviation; WPAI-CD, Work Productivity and Activity Impairment-Crohn's disease.
IBDQ: Total score ranges from 32 to 224 points, with lower scores reflecting worse QOL.
EQ-5D utility index: Scores < 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1 are assigned to the health states "dead" and "perfect health," respectively.
EQ-5D visual analogue scale: scale ranges from 0-100, with 100 representing the best possible health state and 0 representing the worst possible health state.
WPAI-CD: Scores are presented as percentages and range from 0% to 100%, with higher percentages indicating greater impairment and less productivity. A negative change over time indicates an improvement in productivity.
Missing data were imputed using the last observation carried forward approach.
Baseline is defined as the last observation before the first dose of the study drug.
Endoscopic remission status defined as a simple endoscopic score for Crohn's disease of ≤4 at any ileocolonoscopy visit.

Table 2. Changes in QOL and work productivity scores by prior anti-TNFα use over 52 weeks

Instrument	Baseline (Week 0)	Week 14	Week 26	Week 52
IBDQ Total, mean (SD) [N]				
Overall	127.2 (34.1) [55]	167.5 (29.8) [54]	170.1 (30.7) [56]	169.2 (35.3) [56]
Prior anti-TNFα use-Yes	128.9 (35.5) [24]	166.5 (27.3) [24]	162.4 (33.6) [24]	157.1 (39.1) [24]
Prior anti-TNFα use-No	125.8 (33.6) [31]	168.2 (32.1) [30]	175.8 (27.4) [32]	178.3 (29.7) [32]
EQ-5D Total, mean (SD) [N]				
Overall	0.76 (0.14) [56]	0.84 (0.13) [54]	0.83 (0.15) [56]	0.85 (0.15) [56]
Prior anti-TNFα use-Yes	0.74 (0.14) [24]	0.84 (0.08) [24]	0.83 (0.15) [24]	0.84 (0.14) [24]
Prior anti-TNFα use-No	0.77 (0.14) [32]	0.84 (0.15) [30]	0.84 (0.15) [32]	0.86 (0.16) [32]
EQ-5D VAS, mean (SD) [N]				
Overall	51.7 (20.1) [55]	70.6 (15.8) [54]	71.5 (17.6) [56]	71.0 (21.1) [56]
Prior anti-TNFα use-Yes	51.6 (16.9) [24]	70.2 (13.6) [24]	69.4 (15.0) [24]	69.3 (16.0) [24]
Prior anti-TNFα use-No	51.8 (22.5) [31]	71.0 (17.6) [30]	73.0 (19.4) [32]	72.4 (24.3) [32]
WPAI-CD, mean % (SD) [N]				
Absenteeism				
Overall	22.8 (37.2) [23]	7.0 (20.8) [28]	8.6 (20.0) [33]	6.7 (13.0) [35]
Prior anti-TNFα use-Yes	20.2 (36.8) [7]	7.8 (14.5) [8]	3.5 (8.4) [12]	1.3 (4.6) [13]
Prior anti-TNFα use-No	24.0 (38.5) [16]	6.7 (23.2) [20]	11.4 (24.0) [21]	9.8 (15.3) [22]
Presenteeism				
Overall	38.3 (29.2) [23]	23.8 (23.5) [29]	15.8 (19.5) [33]	19.7 (25.1) [36]
Prior anti-TNFα use-Yes	40.0 (21.0) [6]	27.5 (24.3) [8]	19.2 (18.8) [12]	21.5 (19.9) [13]
Prior anti-TNFα use-No	37.7 (32.1) [17]	22.4 (23.6) [21]	13.8 (20.1) [21]	18.7 (28.0) [23]
Overall work impairment				
Overall	47.7 (31.2) [22]	28.0 (26.2) [28]	20.8 (21.3) [32]	21.5 (24.6) [35]
Prior anti-TNFα use-Yes	42.5 (24.1) [6]	32.8 (26.8) [8]	22.3 (18.7) [12]	22.4 (20.6) [13]
Prior anti-TNFα use-No	49.7 (34.0) [16]	26.0 (26.4) [20]	19.9 (23.1) [20]	21.0 (27.1) [22]
Daily activities impairment				
Overall	51.1 (27.8) [53]	33.5 (23.6) [51]	30.5 (27.5) [56]	28.4 (27.2) [56]
Prior anti-TNFα use-Yes	51.8 (25.9) [22]	36.7 (23.9) [21]	37.9 (29.5) [24]	36.7 (26.3) [24]
Prior anti-TNFα use-No	50.7 (29.4) [31]	31.3 (23.5) [30]	25.0 (24.9) [32]	22.2 (26.6) [32]

EQ-5D, Euro Quality of Life-5 Dimensions; EQ-5D VAS, Euro Quality-5D visual analogue scale; IBDQ, Inflammatory Bowel Disease Questionnaire; QOL, quality of life; SD, standard deviation; anti-TNFα, anti-tumour necrosis factor-alpha; WPAI-CD, Work Productivity and Activity Impairment-Crohn's disease.
IBDQ: Total score ranges from 32 to 224 points with lower scores reflecting worse QOL.
EQ-5D utility index: Scores < 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1 are assigned to the health states "dead" and "perfect health," respectively.
EQ-5D visual analogue scale: scale ranges from 0-100, with 100 representing the best possible health state and 0 representing the worst possible health state.
WPAI-CD: Scores are presented as percentages and range from 0% to 100% with higher percentages indicating greater impairment and less productivity. A negative change over time indicates an improvement in productivity.
Missing data were imputed using the last observation carried forward approach.
Baseline is defined as the last observation before the first dose of the study drug.
Endoscopic remission status defined as a simple endoscopic score for Crohn's disease of ≤4 at any ileocolonoscopy visit.

P377

Clinical strategies based on patient-reported outcomes and physicians' preferences to monitor biological therapy in inflammatory bowel disease

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Background: There is a growing interest in clinical strategies to monitor and optimise biological treatment in patients with inflammatory bowel diseases (IBD), as this may lead to improved clinical outcomes. Such strategies rely on systematic recording of relevant symptoms, that is, patient-reported outcomes (PROs), combined with objective evaluation using, for example, biomarkers and endoscopy. However, the optimal combination of PROs and objective monitoring tools which is relevant for both patients and physicians is not well defined. The aim of the study was (1) to determine which PROs and examinations were rated most important and acceptable by patients, (2) to investigate which tools physicians consider 'gold standard' to monitor treatment with biologicals, and (3) to which extent healthcare professionals' adhere to a clinical monitoring strategy with scheduled evaluations of patients with IBD on biologicals.
Methods: The study consisted of two parts: (1) questionnaire survey of (a) patients with IBD receiving biologicals and (b) Danish gastroenterologists routinely treating IBD patients with biologicals and (2) a retrospective study of adherence to the systematized clinical strategy.
Results: Part 1 comprised 164 patients. Patients rated fatigue (57%) and stool frequency (46%) as most important PROs. On a scale from 0 to 100 patients found blood samples, faecal calprotectin (FC), endoscopies, magnetic resonance enterography (MRE), and ultrasound examination (US) to be relevant monitoring tools (median (IQR): 97 (80–100), 92 (74–100), 97 (83–100), 86 (71–99), and 83 (53–99)). FC and endoscopies were reported to be highly stressful (median (IQR): 50 (11–77), 83 (61–98)), unlike blood samples, MRE, and US (median (IQR): 13 (12–2), 27 (5–51) and 11 (0–45)). Physicians (n = 87) considered blood samples (99%) and FC (82%) at both fixed time points and in case of flares as gold standard; endoscopy (74%) and MRE (70%) only in case of flares. Therapeutic drug monitoring and US were not considered as gold standard (20% and 23%). Part 2 comprised 139 patients included in the clinical strategy. Blood samples and FC were performed in 93% and 38% of the scheduled cases. Endoscopies scheduled for once a year, were only performed in 32% of cases. Clinical actions were taken in 44%, 55%, and 82% of cases of abnormal blood samples, FC and endoscopies, respectively.
Conclusions: This study shows that patients consider fatigue to be the most important PRO. Physicians and patients found standard monitoring tools relevant indicating that a systematized clinical strategy is feasible in everyday clinical work. The high rate of stress may explain low adherence to scheduled FC and endoscopies even though these examinations more often led to clinically relevant actions.

P378

Changes in Simplified Endoscopic Score for Crohn's disease (SES-CD) during a 16-week induction treatment with upadacitinib: analysis of the randomised controlled CELEST study

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Background: The SES-CD is a validated and widely used outcome measure in clinical trials. We assessed the efficacy of upadacitinib (UPA), an oral selective JAK1 inhibitor, on mucosal inflammation in different disease phenotypes using SES-CD segmental scores.

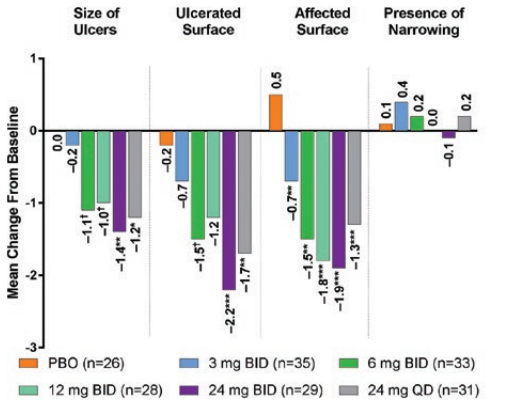
Methods: CELEST (NCT02365649) was a placebo (PBO)-controlled Phase 2 study in adults with moderate to severe CD refractory or intolerant to immunosuppressants and/or biologics. Patients were randomised to PBO or UPA 3 mg, 6 mg, 12 mg, or 24 mg twice daily (BID) or 24 mg once daily (QD) for 16 weeks. Ileocolonoscopy was done at baseline and either Week 12 or 16. This analysis evaluated changes from baseline to Week 12/16 in total SES-CD and its components (size of ulcers, ulcerated surface, affected surface, presence of narrowing) in the overall population and by disease location (ileal, colonic, ileocolonic [based on centrally-read endoscopic scores at baseline]). Statistical difference was analysed via ANCOVA at $p = 0.1$ level.

Results: Of 220 randomised patients, most were female (57%) with disease duration >3 years (88%) and mean age 40.7 years. Most patients ($n = 114$) had ileocolonic disease at baseline (table). In the overall population, mean (SD) change from baseline to Week 12/16 in total SES-CD was significantly greater with UPA 6 mg (–3.9 [6.3]; $p = 0.006$; $n = 33$), 12 mg (–3.9 [9.8]; $p = 0.005$; $n = 27$), 24 mg BID (–5.7 [6.0]; $p < 0.001$; $n = 29$), and 24 mg QD (–3.9 [7.2]; $p = 0.003$; $n = 31$) vs. PBO (0.4 [7.3]; $n = 26$). SES-CD subscores were generally significantly improved with UPA vs. PBO except for presence of narrowing (Figure). When assessed by disease location, mean (SD) changes from baseline to Week 12/16 in total SES-CD were significantly greater with UPA 12 mg (–7.5 [9.4]; $p = 0.099$; $n = 8$) and 24 mg BID (–7.9 [7.2]; $p = 0.025$; $n = 11$) vs. PBO (4.3 [9.3]; $n = 3$) in patients with colonic disease and with 6 mg (–5.5 [6.5]; $p = 0.023$; $n = 17$), 12 mg (–3.1 [10.7]; $p = 0.079$; $n = 17$), and 24 mg BID (–5.1 [5.0]; $p = 0.018$; $n = 14$) and 24 mg QD (–6.8 [5.4]; $p = 0.005$; $n = 14$) vs. PBO (–0.3 [8.0]; $n = 18$) in patients with ileocolonic disease. No significant differences were observed for UPA ($n = 3$–9) vs. PBO ($n = 5$) in patients with ileal disease.

Table. Crohn's disease location and total SES-CD at baseline.

	PBO n=37	UPA 3 mg BID n=39	UPA 6 mg BID n=37	UPA 12 mg BID n=36	UPA 24 mg BID n=36	UPA 24 mg QD n=35
Disease location,* n (%)						
Ileal (n=46)	9 (24)	10 (26)	6 (16)	5 (14)	6 (17)	10 (29)
Colonic (n=60)	6 (16)	9 (23)	13 (35)	11 (31)	11 (31)	10 (29)
Ileocolonic (n=114)	22 (59)	20 (51)	18 (49)	20 (56)	19 (53)	15 (43)
Total SES-CD, mean (SD)						
Overall (n=220)	15.8 (8.6)	14.7 (8.8)	16.3 (8.9)	15.6 (9.4)	14.3 (7.3)	13.4 (7.4)
Ileal disease (n=46)	7.9 (2.9)	6.8 (2.5)	7.2 (2.1)	7.0 (2.7)	7.3 (2.7)	6.2 (2.3)
Colonic disease (n=60)	15.3 (7.4)	18.0 (8.3)	16.8 (7.9)	18.5 (9.3)	14.1 (7.9)	14.4 (5.9)
Ileocolonic disease (n=114)	19.1 (8.4)	17.2 (8.9)	18.9 (9.1)	16.2 (9.5)	16.7 (6.8)	17.5 (7.2)

BID, twice daily; PBO, placebo; QD, once daily; SES-CD, Simplified Endoscopic Score for Crohn's disease; UPA, upadacitinib.



BID, twice daily; BL, baseline; PBO, placebo; QD, once daily; SES-CD, Simplified Endoscopic Score for Crohn's disease; UPA, upadacitinib.
Week 12/16: patients were equally randomized for ileocolonoscopy at either weeks 12 or 16 to evaluate optimal timing for assessment.
Observed data (modified intent-to-treat population); the missing SES-CD individual variable had the following imputation rules applied if the same individual variable is: missing at both BL and Week 12/16, the missing value was imputed as zero at both time points and no change was assumed; present at Week 12/16 but missing at BL, the missing BL value was imputed based on the value given at Week 12/16 and no change was assumed; present at BL but missing at Week 12/16, the missing Week 12/16 value was imputed based on the value given it at BL and no change was assumed.
Statistical comparison between each UPA dose group and PBO using analysis of covariance with treatment, baseline disease severity (SES-CD <15 and ≥15), and baseline value as covariate; †$P<0.1$, *$P<0.05$, **$P<0.01$, ***$P<0.001$ vs PBO

Figure. Change from baseline to Week 12/16 in SES-CD subscores in the overall population.

Conclusions: UPA induction treatment at doses ≥6 mg BID significantly improved total SES-CD vs. PBO, with improvements in all subscores except for presence of narrowing.

P379

Comparison of real-world treatment outcomes with infliximab vs. vedolizumab in biologic-naïve patients with inflammatory bowel disease

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Background: Inflammatory bowel disease (IBD), including ulcerative colitis [UC] and Crohn's disease [CD], is a chronic condition characterised by recurrent episodes of active disease resulting in considerable morbidity. There is a lack of long-term, real-world comparative effectiveness data on biologic-naïve patients with IBD using infliximab (IFX) vs. vedolizumab (VDZ).

Methods: A retrospective study on adult patients with IBD who received IFX or VDZ as first biologic (index biologic) between May 2014 (when both biologics were available for moderately/severely active UC/CD treatment [TX]) and September 2018 from the US Explorys Universe database was conducted. Biologic-naïve patients with maintenance TX initiation (≥4 consecutive infusions of the index biologic) were included. Entropy balancing (EB) was used to address potential unbalanced confounding factors. TX persistence, increased dosing frequency, and healthcare resource utilisation (HRU) composite endpoint including IBD-related hospitalisation/surgery or IV corticosteroids (proxy for flares) were compared between IFX and VDZ patients using weighted Kaplan Meier (WKM) analyses.

Results: 776 biologic-naïve IBD patients received IFX and 292 VDZ. After EB, mean age was 51 years, 51% were female, 48% were diagnosed with UC, 54% used non-biologic therapies in the 90 days before index biologic initiation, and median time from first IBD diagnosis to index biologic initiation was 3.9 years in both cohorts; 41% IFX and 30% VDZ patients were observed ≥24 mos following TX initiation. Overall, for IFX vs. VDZ, respectively, TX persistence was lower for IFX (WKM rates: 12 months, 78% vs. 87%; 24 months, 62% vs. 80%; all $p < 0.05$), rates of increased dosing frequency were higher (WKM rates: 12 months, 14% vs. 8%; 24 months, 21% vs. 16%; all $p \leq 0.05$), and rates of HRU composite endpoint were higher (WKM rates: 12 months, 48% vs. 41%; 24 months, 59% vs. 54%; all $p < 0.05$) (Table 1). For UC, IFX patients had significantly higher rates of increased dosing frequency, numerically lower TX persistence and higher rates of HRU composite endpoint vs. VDZ patients. For CD, IFX patients had significantly lower TX persistence and higher rates of HRU composite endpoint, and numerically higher rates of increased dosing frequency vs. VDZ patients.

Conclusions: Biologic-naïve IBD patients initiated on VDZ had significantly higher TX persistence, lower rates of increased dosing frequency, and lower rates of HRU composite endpoint, particularly at long-term time points (24 months), compared with those initiated on IFX in a real-world setting.

P380

A prospective multi-centre observational cohort study assessing the effectiveness of Budesonide MMX® for mild-to-moderate ulcerative colitis

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Background: Budesonide MMX® is currently approved for the treatment of mild-to-moderate active ulcerative colitis (UC), where 5-ASA is not sufficient. Data on its effectiveness and safety in a real-life setting are lacking.

Methods: This was a multi-centre prospective observational cohort study. Effectiveness (clinical benefit, full symptom resolution, time to symptom resolution, change in quality of life, change in health economic parameters, treatment satisfaction, biomarker normalisation, endoscopic healing and endoscopic remission), safety, and tolerability of Budesonide MMX® in a real-life setting of patients treated for mild-to-moderate UC was investigated. Patients were prescribed Budesonide MMX® in accordance with the terms of the SmPC, within a 5 days' time window before the enrolment. The primary endpoint was the clinical benefit of Budesonide MMX® in routine practice, defined as the percentage of patients achieving ≥3-point decrease in the UCDAI score at the end of induction treatment).

Results: Real-world data from 349 patients with mild-to-moderate UC were analysed. Baseline characteristics are summarised in Table 1. Clinical improvement at the end of treatment induction was achieved in 196/326 patients (60.1%), with a median reduction of 3.0 UCDAI point (<0.0001). Symptom resolution (rectal bleeding of 0 and stool frequency of 1) at the end of the Budesonide MMX® treatment was achieved in 63.2% of patients. The median time to symptom resolution was 30 days (range 29.0–36.0 days). The overall median increase in the SIBD-Q was 10.0 points ($p <$ 0.001) compared with baseline assessment. Treatment satisfaction was high (VAS scale from 7 to 10) in 61.3% of patients. Endoscopic improvement (Mayo endoscopic subscore ≤ 1) was achieved in

Abstract P379 – Table 1. Weighted Kaplan–Meier rates for treatment persistence, increased dosing frequency, and HRU composite endpoint in biologic-naive IBD patients using IFX vs. VDZ.

Cohorts	Real-world outcomes	Weighted Kaplan Meier rates (%)								
		3 Months			12 Months			24 Months		
		IFX	VDZ	Log-rank tests	IFX	VDZ	Log-rank tests	IFX	VDZ	Log-rank tests
IBD (IFX, N=776; VDZ, N=292)	TX persistence[a]	93.3	97.1	0.0543	77.7	86.8	**0.0099***	62.4	79.6	**0.0006***
	Increased dosing frequency[b]	6.0	1.8	0.0634	14.4	8.4	0.0529	20.8	15.5	**0.0470***
	HRU composite endpoint[c]	31.4	20.9	**0.0026***	47.6	41.2	**0.0371***	58.9	54.0	**0.0457***
UC (IFX, N=296; VDZ, N=124)	TX persistence[a]	93.1	98.2	0.2179	79.5	86.9	0.3483	65.4	81.5	0.1354
	Increased dosing frequency[b]	10.8	0.0	**0.0209***	21.1	5.4	**0.0143***	24.1	10.9	**0.0267***
	HRU composite endpoint[c]	27.3	17.8	0.2075	42.3	38.2	0.3466	57.4	53.5	0.3158
CD (IFX, N=480; VDZ, N=168)	TX persistence[a]	92.9	96.3	0.1591	79.3	86.5	0.0704	66.0	78.1	**0.0437***
	Increased dosing frequency[b]	4.9	3.0	0.5268	11.8	10.2	0.6884	17.9	18.5	0.7187
	HRU composite endpoint[c]	32.3	23.2	**0.0418***	50.4	43.1	0.0723	62.1	54.5	0.0720

IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; IFX, infliximab; VDZ, vedolizumab; N, number; %, proportion; pts, patients; WKM, weighted Kaplan Meier; HRU, healthcare resource utilization; TX, treatment; IV, intravenous

*** Statistically significant at the 5% level**

[a] WKM rates following maintenance TX initiation

[b] Dosage strength was not readily available in data for IFX. WKM rates following maintenance TX initiation

[c] HRU composite endpoint including IBD-related hospitalization/surgery, and IV corticosteroids (proxy for flares); WKM rates following index biologic initiation

16/32 patients (50.0%). 24.1% (n = 84) of patients reported at least one adverse event. Fifty patients (14.3%) discontinued Budesonide MMX® for adverse events; 17.5% of patients (n = 61) reported at least one adverse event related to the study drug. Nine patients had worsening of the underlying colitis (3%). All the other adverse events were reported in <1% of patients.

Table 1. Baseline characteristics of the study population.

CHARACTERISTICS	TOTAL (N=349)
GENDER	
MALES	183 (52.4%)
FEMALES	166 (47.6%)
AGE (YEARS, MEDIAN)	40.0
SMOKING STATUS	
CURRENT SMOKER	14 (4.0%)
FORMER SMOKER	65 (18.6%)
NON-SMOKER	270 (77.4%)
MAXIMAL EXTENSION OF UC IN THE PAST	
PROCTITIS	31 (8.9%)
PROCTOSIGMOIDITIS	47 (13.5%)
LEFT-SIDED COLITIS	142 (40.7%)
PANCOLITIS	112 (32.1%)
UNKNOWN	17 (4.9%)
PREVIOUS ORAL STEROIDS	
NONE	224 (64.2%)
PREDNISONE OR PREDNISOLONE	101 (28.9%)
BECLOMETHASONE	6 (1.7%)
BETAMETHASONE	0 (0%)
BUDESONIDE	2 (0.6%)
BUDESONIDE MMX®	8 (2.3%)
OTHER	8 (2.3%)
HISTORY OF IMMUNOSUPPRESSANTS	
YES	98 (28.1%)
NO	242 (69.3%)
UNKNOWN	9 (2.6%)
HISTORY OF BIOLOGICS	
YES	36 (10.3%)
NO	304 (87.1%)
UNKNOWN	9 (2.6%)

Conclusions: This large real-life cohort study demonstrates for the first time that Budesonide MMX® is effective in about two-thirds of UC patients, and that Budesonide MMX® was safe and well tolerated.

P381

Infliximab induction regimes in steroid refractory acute severe colitis: a multi-centre retrospective cohort study with propensity score analysis

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Background: While infliximab is used as rescue therapy for steroid refractory acute severe colitis (ASUC), between 30 and 40% of patients do not respond and undergo colectomy. Accelerated induction regimes of infliximab have been proposed to improve response rates. We aimed to evaluate colectomy rates in steroid refractory ASUC patients receiving standard induction (SI) vs. accelerated induction (AI) of infliximab.

Methods: Data collected on hospitalised patients receiving rescue therapy for steroid refractory ASUC. The choice of rescue therapy was at the discretion of the treating clinician. Accelerated induction (AI) was defined as receiving second dose of infliximab within 8 days of first rescue therapy or receiving front loading dose of 10 mg/kg. Our primary outcome was the short-term (in-patient, 30 days and 90 days) colectomy rate. Secondary outcomes were 12-month colectomy rates, length of hospital stay (LOS), and complication rates. We used a propensity score analysis with optimal calliper matching using *a priori* defined high-risk covariates at the start of rescue therapy (albumin, CRP, CRP–albumin ratio, haemoglobin nadir and pancolitis) to reduce potential provider selection bias.

Results: A total of 131 patients receiving infliximab rescue therapy were included, of whom 102 patients received SI and 29 received AI. There was no difference in age, duration of diagnosis, age at rescue therapy, Montreal class or use of steroids, 5ASAs or thiopurines prior to index admission. In the unmatched overall cohort, there was no difference in colectomy during index admission (13% vs. 20%, p = 0.26), 30-day colectomy (18% vs. 20%, p = 0.45), 90-day colectomy (20% vs. 24%, p = 0.38) or 6 month colectomy (25% vs. 27%, p = 0.49). The LOS was shorter in the SI group (14.87 ± 8.1 days vs. 19.31 ± 5.8 days, p = 0.007). In patients who underwent colectomy, there were no differences in complications or serious infection rates. In the propensity score-matched cohort of 52 patients, there was no difference in overall colectomy rates between SI and AI groups (57% vs. 31%, p = 0.09), but the index admission colectomy (53% vs. 23%, p = 0.045) and 30-day colectomy (57% vs. 27%, p = 0.048) rates were higher in those receiving SI. There was no significant difference in LOS between SI and AI groups (23.6 ± 4.3 vs. 18.2 ± 7.1 days, p = 0.09) or in overall complication and infection rates but there was a mortality in AI group.

Conclusions: In this retrospective cohort study, there was no difference in overall colectomy rates in ASUC patients receiving different induction dosing regimens of infliximab. However, using propensity score matching, the short-term colectomy rates appear to be better in those receiving accelerated induction regime. A prospective study to confirm findings is planned.

P382

Combination therapy with TNF-inhibitors and immunomodulators are associated with shorter duration to first serious infection: the DEVELOP experience

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Background: DEVELOP is a multi-centre, international, prospective, observational registry of the long-term safety and clinical status of 6070 paediatric patients with inflammatory bowel disease (IBD) diagnosed prior to 18 years of age who were treated with anti-tumour necrosis factor biologics (aTNF) and/or other medical therapies for IBD. Our aim was to assess the risk factors that lead to first serious infection (SI): an infection requiring hospitalisation and/or IV therapy.

Methods: Physicians participating in the registry prescribe IBD treatments based on their usual clinical practice and standards of care. Patients are categorised into cohorts according to their IBD medication exposure representing prevalent or incident exposure. The registry started enrolment in 2007 and completed enrolment in 2017. After the initial enrolment visit, data are obtained by the registry physician or designee every 6 months. SI data includes infections that occurred within 91 days of exposure to aTNF relative to non-biologics. The most recent available data cut (30 June 2018) includes 33 586 patient-years (PY) of follow-up in the registry.

Results: The analysis of the stepwise Cox regression model for time to first SI among aTNF only patients relative to the non-biologics cohort included 3,566 Crohn's disease (CD) patients and 1063 ulcerative colitis (UC) patients who had at least 1 post-baseline follow-up visit, complete baseline covariate data, and complete disease severity data at event. Results of this analysis are seen in Table 1. In CD patients, combination therapy with aTNF/IMM, monotherapy with aTNF or CS, disease severity (hazard ratio [HR] 3.193), recent hospitalisation, gender, length of diagnosis and geographic region were all significantly associated with shorter duration of time to first SI. In UC patients, monotherapy with aTNF or CS (HR 3.913), combination therapy with aTNF and IMM, disease severity and recent hospitalisation were significantly associated with shorter duration of time to first SI.

Conclusions: In both CD and UC patients, combination therapy with aTNF and IMM was significantly associated with shorter time to first SI, as was monotherapy with CS or aTNF, disease severity and recent hospitalisation. Monotherapy with IMM was not associated with shorter duration in either disease state. Disease severity was the strongest predictor by hazard ratio in the CD cohort while CS use was the strongest predictor in the UC cohort.

P383

One-year experience with ustekinumab in therapy-refractory or -intolerant patients with ulcerative colitis

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Background: We had lately shown that the IL12/23 antibody ustekinumab can be used as rescue therapy in ulcerative colitis (UC) and most recently first results of the Phase 3 approval trial UNIFI were released, showing a sound effect of ustekinumab in refractory UC after 8 weeks. Our aim was to report the clinical and endoscopical 1-year outcomes achieved with ustekinumab treatment in our patients.

Methods: In total, 19 patients who had received ustekinumab between 2016 and 2017 as rescue off-label therapy in our IBD centre were followed-up to 1 year. All patients received ustekinumab as approved for Crohn's disease. The primary outcome was achievement of clinical remission and mucosal healing at 1 year. Data of the last endoscopy before study start were used as a comparator. Clinical remission was defined as score of ≤5 points in the modified Truelove and Witts colitis activity index (CAI), mucosal healing defined as Mayo endoscopy subscore of 0 or 1.

Results: All 19 UC patients who were treated with ustekinumab, had previously been steroid refractory or dependant and had recently failed all of the following drugs: purine-analogues, anti-TNF and anti-integrin antibodies. Of those, 42% (8/19) had

Abstract P382 – Table 1. Cox proportional hazards model analysis to evaluate risk factors (including Anti-TNF Biologics, using exposure within 91 days) associated with time to first serious infection

CROHN'S DISEASE PATIENTS	Adjusted Hazard Ratio	95% Confidence Interval	p-value
Anti-TNF Biologics and Immunomodulator (Yes vs. No A/I)	2.061	1.422-2.986	0.0001
Immunomodulator Only (Yes vs. No A/I)	1.014	0.681-1.508	0.9469
Anti-TNF Biologics Only (Yes vs. No A/I)	1.603	1.113-2.307	0.0111
Corticosteroids (Yes vs. No)	2.122	1.685-2.672	<.0001
PCDAI Score (Mild vs. Inactive)	1.55	1.244-1.931	<.0001
PCDAI Score (Moderate to Severe vs. Inactive)	3.193	2.430-4.196	<.0001
Gender (Female vs. Male)	1.302	1.071-1.582	0.0080
Time Since IBD was Diagnosed	1.083	1.037-1.131	0.0003
Hospitalization in the Year Prior to Enrollment (Yes vs. No)	1.761	1.434-2.163	<.0001
Country (EU vs. US)	1.432	1.140-1.799	0.0020
ULCERATIVE COLITIS PATIENTS			
	Adjusted Hazard Ratio	95% Confidence Interval	p-value
Anti-TNF Biologics and Immunomodulator (Yes vs. No A/I)	1.898	1.027-3.511	0.0410
Immunomodulator Only (Yes vs. No A/I)	1.22	0.667-2.232	0.5180
Anti-TNF Biologics Only (Yes vs. No A/I)	2.288	1.321-3.961	0.0031
Corticosteroids (Yes vs. No)	3.913	2.537-6.033	<.0001
Partial Mayo Score (Mild vs. Inactive)	1.905	1.127-3.220	0.0161
Partial Mayo Score (Moderate to Severe vs. Inactive)	1.216	0.546-2.708	0.6318
Hospitalization in the Year Prior to Enrollment (Yes vs. No)	1.805	1.181-2.759	0.0064

Analysis performed using a stepwise selection procedure.
Time dependent: Variable status using exposure within 91 days for Anti-TNF Biologics, Immunomodulator and Corticosteroids.
Data from patients who were only exposed to anti-TNF biologics or who had not been exposed to any biologics were included in the analysis.
For Crohn's patients: Modified PCDAI: 0-8 inactive disease, 9-24 mild disease, >24 moderate to severe disease.
For Ulcerative Colitis Patients: Partial Mayo: 0-2 inactive disease, 3-4 mild disease, >=5 moderate to severe disease.
Key: A=Anti-TNF; I=Immunomodulators

failed infliximab plus either golimumab or adalimumab, and 26% (5/19) had also failed i.v. ciclosporine. At the start of ustekinumab, 12 of 19 patients (63.2%) had moderately or severely active disease and, in contrary, 36.8% (7/19) were in remission, but had intolerable side effects under TNF- or integrin-blocking treatment, which had to be stopped. In 4 patients ustekinumab was stopped due to refractory disease, in one at 3 months, in one at 6 months, and in two at 9 months. In another patient, therapy was stopped due to drowsiness at Week 4. Three patients underwent colectomy, 2 were received other studies medications. Including these 5 patients who dropped out, clinical remission was achieved in 68.4% (13/19) of patients at 12 months, whereas only 36.8% (7/19) of patients were in remission at the start of the study. The CAI at the start of the therapy in 19 patients ranged between 1 and 12, with a median of 7.5 points. In 14 patients who continued ustekinumab throughout 1 year, the median CAI at 12 months fell to 2 points (range 0–5.5). In 14 patients, we were able to perform colonoscopy at 1 year: MAYO endoscopy scores fell from a median of 2 points (range 1–3) and a mean of 2.3 points at start of the observation to a median of 1 point (range 0–3) and a mean of 1.3.

Conclusions: Ustekinumab is an effective short- and long-term medication in therapy-refractory or -intolerant ulcerative colitis. It is therefore likely, which large ongoing long-term trials will confirm our findings and ustekinumab will become a new therapeutic option for refractory UC.

P384

High incidence of hyperglycaemia in steroid treated hospitalised inflammatory bowel disease (IBD) patients and its risk factors identified by machine learning methods

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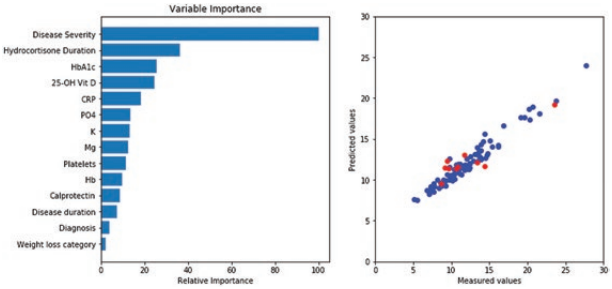
Background: Glucocorticoids (GC) have been first-line treatment for hospitalised IBD patients for over 60 years, despite the introduction of biologic therapy. IBD patients often have systemic inflammation complicated by malnutrition leading to metabolic stress. The frequency of and specific risk factors for hyperglycaemia in hospitalised IBD patients receiving GC are unknown.

Methods: In total, 93 consecutive IBD inpatients receiving intravenous hydrocortisone (IVH) for an acute flare had capillary blood glucose (CBG) monitoring automatically triggered by the electronic prescription. CBG, biomarkers, IBD severity scores (Harvey–Bradshaw, partial Mayo) and weight loss were prospectively recorded. Undiagnosed Diabetes Mellitus (DM) was defined as HbA1c >48 mmol/mol. Machine-learning (random forest regressor, RFR) was applied to the data to evaluate risk factors of hyperglycaemia.

Characteristic	Crohn's disease	Ulcerative colitis	IBDU	Combined
Total	54	32	7	93
Female	27 (50%)	18 (56%)	4 (57%)	49 (52%)
Age	41 (18–80)	46 (19–80)	51 (25–75)	44 (18–80)
Disease duration	8 (0–52)	5 (0–18)	1 (0–1)	6 (0–52)
HBI /partial Mayo	15 (6–31)	7 (3–9)	7 (3–9)	n/a
Admisison CRP	65 (<1–303)	86 (<1–440)	179 (114–300)	81 (<1–440)
Calprotectin	2652 (7–7049)	3266 (628–7091)	3692 (218–6000)	2915 (7–7091)
Pre-existing DM	6	1	1	8
Max CBG >11.0	27 (50%)	19 (59%)	5 (71%)	51 (55%)

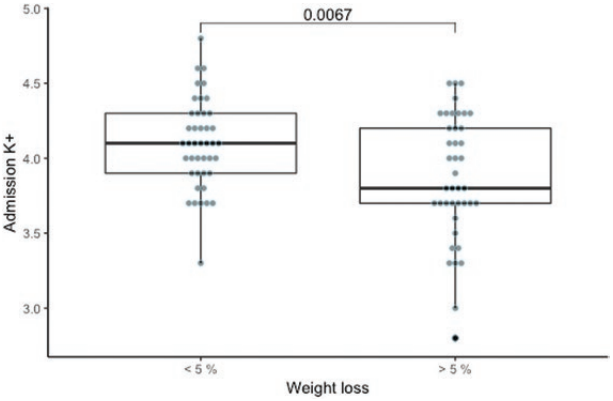
Characteristics of cohort and frequency of hyperglycaemia.

Results: Fifty-five per cent of hospitalised IVH-treated IBD patients met the WHO criteria of DM (CBG >11 mmol/l), while 22% and 8% had a CBG >14 mmol/l and >20 mmol/l, respectively. Only 8 patients had pre-existing DM, which was confirmed by admission HbA1c. RFR indicated disease severity score, duration of IVH, HbA1c and electrolyte imbalances (which affected 64%) were best predictors of hyperglycaemia.



Relative importance of input features of RFR model for prediction of CBG_max (left). Predictive value from RFR model vs. true value for training data set (blue) and test data set (red) (right).

Sixty-four per cent reported previous weight loss, which did not predict hyperglycaemia, although those with >5% weight loss had significantly lower admission serum potassium ($p = 0.0067$).



Admission serum potassium and preceding weight loss.

Conclusions: Our data demonstrate that hyperglycaemia is common in IVH-treated inpatients, therefore CBG monitoring should be routine practice. Predictive modelling (RFR) identifies more

severe disease activity, duration of IVH treatment and HbA1c as risk factors for hyperglycaemia. Preceding weight loss and electrolyte imbalance in the cohort demonstrate a tendency towards malnutrition-associated metabolic instability. The importance of IVH duration suggests hyperglycaemia risk may be physician modifiable. Alternative treatment strategies such as earlier introduction of biologics, rapid steroid taper and nutritional support could be used to minimise medication-associated metabolic instability in high-risk patients.

P385

TREM1, the first anti-TNF specific biomarker guiding therapeutic decision

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Background: With the expanding therapeutic armamentarium for inflammatory bowel diseases (IBD), biomarkers predicting efficacy are urgently needed. To predict outcome to anti-TNF therapy, we studied whole blood and mucosal expression of genes previously reported to predict outcome to anti-TNF therapy, and investigated whether the signature was specific for these agents.
Methods: We prospectively included 35 (discovery) and 19 (validation) consecutive IBD patients with active disease (both Crohn's disease and ulcerative colitis) initiating anti-TNF therapy, as well as 22 patients initiating ustekinumab and 51 patients initiating vedolizumab. Whole blood expression levels of OSM, TNF, TNFR2 and TREM1 (total and all individual transcripts separately) were measured prior to start of therapy using qPCR, and mucosal gene expression in inflamed biopsies using RNA-sequencing. Endoscopic remission was defined as an SES-CD ≤2 at Week 24 for Crohn's disease and a Mayo endoscopic sub-score ≤1 at Week 8–14 for ulcerative colitis.
Results: Baseline whole blood TREM1 expression was significantly down-regulated in future anti-TNF healers ($p < 0.001$, both discovery and validation cohort) (Figure).
Conclusions: We identified and validated low TREM-1 as a specific biomarker for anti-TNF-induced endoscopic remission. These results can aid in the selection of therapy in biological-naïve patients, but should be confirmed in a randomised trial prior to translation into daily clinical practice.

P386

Association of Infliximab trough levels and perianal disease activity in Crohn's disease

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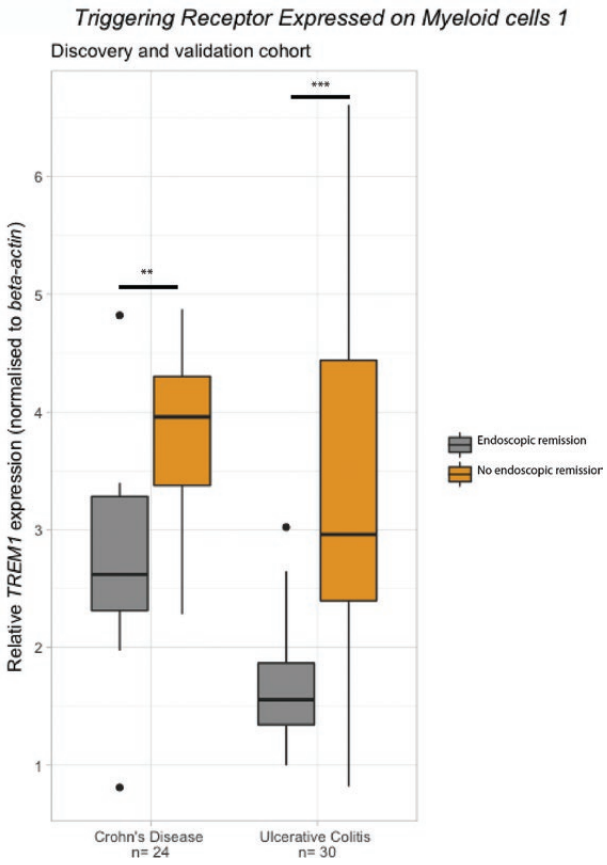
Abstract P385



Baseline whole blood TREM1 expression in relation to endoscopic remission later on in both the discovery and validation cohort, visualised by diagnosis. ** $p < 0.005$, *** $p < 0.001$.

Receiver operator characteristic statistics showed an area under the curve (AUC) of 0.78 ($p = 0.001$), resulting in post-test probabilities of 77.1% and 90.0% for endoscopic remission and non-remission, respectively. A similar accuracy could be observed in mucosal TREM1 expression (AUC 0.77, $p = 0.003$), which outperformed the accuracy of serum TREM1 at the protein level (AUC 0.58, $p = 0.31$). Whole blood TREM1 expression did not significantly correlate with CRP (Spearman = –0.08, $p = 0.38$), faecal calprotectin (Spearman = –0.06, $p = 0.64$) or serum TNF (Sspearman = –0.15, $p = 0.63$). OSM, TNF, and TNFR2 were not differentially expressed in whole blood ($p = 0.09$, $p = 0.13$, $p = 0.24$, respectively), whereas they were at the mucosal level ($p = 0.007$, $p = 0.02$, $p = 0.008$, respectively). The whole blood TREM1 predictive signal was anti-TNF specific, as no changes in expression were seen in ustekinumab and vedolizumab treated patients, neither in whole blood ($p = 0.82$, $p = 0.53$, respectively), nor in tissue ($p = 0.24$, $p = 0.10$, respectively).

Background: Infliximab (IFX) has been proven to be efficacious in the treatment of perianal disease in patients with Crohn's disease (CD). Previous studies have shown a correlation between higher IFX trough levels and perianal fistula healing. We aimed to replicate these findings using a larger cohort of patients with Crohn's disease.
Methods: Retrospective cohort study including consecutive patients with Crohn's disease and perianal disease receiving treatment with infliximab between January 2016 and October 2018. Drug levels were compared between patients with active and inactive perianal disease. Active perianal disease was defined as an active draining fistula at physical examination and/or magnetic resonance imaging.

Patients with unavailable IFX trough levels and/or without clinical information were excluded.

Results: A total of 252 measurements from 48 patients were available. Median age was 39 (22–80) and 26 (54.2%) were male. Forty-two (87.5%) patients were under concomitant immunomodulators. The majority (n = 40) of patients had ileo-colonic disease (L1: 62.5%, L2: 18.8% , L3: 18.8%). Median IFX trough levels were significantly higher in patients with inactive perianal disease (n = 230) compared with patients with active disease (n = 22): [median 5.89 - 16.38 vs. 3.98 –9.28, p = 0.014]. Using the median off all IFX trough levels for each patient, the AUROC for perianal remission was 0.818 (95% CI: 0.649–0.987). An IFX >5.55 µg/ml presented high positive predictive value 97.0% (95% CI: 83.3–99.5), high specificity 88.89% (95% CI: 51.9–99.7) albeit with low sensitivity 68.09% (95% CI: 52.9–80.9) for perianal disease remission.

Conclusions: There is a significant association between IFX trough levels and fistula healing in Crohn's disease. Therapeutic drug monitoring aiming at higher IFX trough levels may be beneficial in this hard to treat population.

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Efficacy of combination therapy of fresh faecal microbiota transplantation and triple-antibiotic therapy for ulcerative colitis

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Background: We previously demonstrated that fresh faecal-microbiota transplantation (FMT) following triple-antibiotic therapy [amoxicillin, fosfomycin, and metronidazole (AFM); A-FMT] induced dramatic changes in the phylum Bacteroidetes, which constitutes a critical factor correlated with clinical responses.[1] Furthermore, we also reported that A-FMT combination therapy contributed to the microbiological improvement of intestinal dysbiosis in UC patients via successful transplantation of live Bacteroidetes cells from donors.[2] Eradication of dysbiotic indigenous Bacteroidetes species by AFM pre-treatment may promote the entry of living Bacteroidetes cells, thereby improving the dysbiosis of intestinal microbiota induced by UC. Here, we evaluated the efficacy of A-FMT compared with AFM monotherapy and examined factors correlated with clinical response.

Methods: This was an open-label, non-randomised, prospective control study. These patients were diagnosed with active UC, with a Lichtiger's Clinical Activity Index (CAI) of 5 or more, or with an endoscopic Mayo clinic score of 1 or more, between July 2014 and March 2017. Patients' spouses or relatives were selected as donor candidates. AFM was administered to patients with UC for 2 weeks, and up to 2 days before fresh FMT. Donor faecal samples were collected on the day of administration and transferred into the patient's colon via colonoscopy within 6 h. The clinical features of UC were judged using CAI before treatment and 4 weeks after treatment. Clinical responses were defined as a CAI of less than 10 points and a decrease of 3 or more points, and clinical remission was defined as a CAI of 3 points or less.

Results: Patients with mild-to-severe active UC (n = 55 A-FMT; n = 37 AFM) were included in this assessment. Seventy-nine patients completed this assessment (n = 46 A-FMT; n = 32 AFM). At 4 weeks after treatment, clinical responses and were observed in 31 patients {Per Protocol Set (PPS): 67.3%) in A-FMT, which higher than in AFM (PPS:56.2%)}. In A-FMT, the clinical remission was observed to be higher than AFM (A-FMT41.3%, AFM18.7%; p = 0.06). In A-FMT, endoscopic sum score was associated with clinical responses (responders 7.5 ± 3.2, non-responders 5.1 ± 3.6; p = 0.03), and clinical responses and remission were significantly higher in proctitis than other type of colitis (n = 38, 8; p = 0.03, p = 0.005). In addition, decrease of CAI was significantly higher in users of anti-TNFα and PSL than in non-users (p = 0.01, p = 0.01). These factors correlated with clinical responses were not observed in AFM monotherapy.

Conclusions: Further follow-up studies are required to evaluate the long-term efficacy of this FMT protocol, and it is possible that this protocol may become a useful strategy for the management of patients with UC.

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P388

Analysis of the impact of body mass index on efficacy and safety in the tofacitinib OCTAVE ulcerative colitis programme

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Background: High body mass index (BMI) can be associated with increased risk of treatment failure in biologic-treated patients with ulcerative colitis (UC).[1] Tofacitinib is an oral, small-molecule JAK inhibitor approved in several countries for the treatment of UC. We present analysis of BMI effect on tofacitinib efficacy and safety in the tofacitinib UC clinical programme.

Methods: Data from two identical, 8-week (week) induction studies (OCTAVE Induction 1 and 2, NCT01465763 and NCT01458951)[2] and a 52-week maintenance study (OCTAVE Sustain, NCT01458574)[2] were analysed. Patients received placebo, tofacitinib 5 or 10 mg twice daily (BID). Patients were stratified by BMI <25, 25–<30 or ≥30 for analysis at Week 8 (Induction 1 and 2) and Week 52 (Sustain) for efficacy endpoints remission, clinical response and mucosal healing (MH), and for safety outcomes including infections.

Results: Patient demographics and baseline characteristics were similar for placebo and tofacitinib groups. The majority of patients in each group had BMI <25 (table). In Induction 1 and 2 and Sustain, tofacitinib-treated patients had a gradual increase in body weight

Abstract P388 – Table. Summary of safety sad efficacy outcomes for patients in the Phase 3 OCTAVE Induction 1 and 2 and OCTAVE Sastain studies, stratified by BMI (FAS, NRI).

	OCTAVE Induction 1 & 2						OCTAVE Sustain								
	Placebo (N=234)			Tofacitinib 10 mg BID (N=905)			Placebo (N=198)			Tofacitinib 5 mg BID (N=198)			Tofacitinib 10 mg BID (N=197)		
Demographic and baseline characteristics															
Female, n (%)	102 (43.6)			369 (40.8)			82 (41.4)			95 (48.0)			87 (44.2)		
Race, n (%)															
White	186 (79.5)			726 (80.2)			155 (78.3)			164 (82.8)			153 (77.7)		
Asian	28 (12.0)			114 (12.6)			26 (13.1)			23 (11.6)			25 (12.7)		
Age (years), mean (SD)	41.1 (14.4)			41.2 (13.8)			43.4 (14.0)			41.9 (13.7)			42.9 (14.4)		
Total Mayo score, mean (SD)	9.0 (1.5)			9.0 (1.4)			3.3 (1.8)[a]			3.3 (1.8)[a]			3.4 (1.8)[a]		
Height (cm), mean (SD)	171.8 (10.1)			171.7 (9.6)			171.5 (10.0)			170.7 (9.5)			171.0 (9.5)		
Weight (kg), mean (SD)	73.0 (16.5)			73.6 (16.8)			76.2 (16.7)			73.4 (17.8)			74.6 (15.1)		
BMI, mean (SD)	24.6 (4.7)			24.9 (5.0)			25.8 (4.9)			25.1 (5.1)			25.5 (4.8)		
Subgroups by BMI, kg/m²	**<25**	**25–<30**	**≥30**	**<25**	**25–<30**	**≥30**	**<25**	**25–<30**	**≥30**	**<25**	**25–<30**	**≥30**	**<25**	**25–<30**	**≥30**
n (%)[b]	132 (56.7)[c]	68 (29.2)[c]	33 (14.2)[c]	533 (58.9)	247 (27.3)	125 (13.8)	107 (54.0)	60 (30.3)	31 (15.7)	119 (60.1)	56 (28.3)	23 (11.6)	113 (57.4)	55 (27.9)	29 (14.7)
Efficacy outcomes															
Remission, n (%)	6 (4.5)	5 (7.4)	3 (9.1)	105 (19.7)	36 (14.6)	18 (14.4)	14 (13.1)	7 (11.7)	1 (3.2)	36* (30.3)	25*** (44.6)	7* (30.4)	49*** (43.4)	15* (27.3)	16*** (55.2)
Mucosal healing, n (%)	17 (12.9)	11 (16.2)	4 (12.1)	165 (31.0)	73 (29.6)	33 (26.4)	15 (14.0)	9 (15.0)	2 (6.5)	42** (35.3)	25** (44.6)	7* (30.4)	54*** (47.8)	19* (34.5)	17*** (58.6)
Sustained steroid-free remission, n/N (%)	N/A	N/A	N/A	N/A	N/A	N/A	2/35 (5.7)	0/18 (0.0)	1/6 (16.7)	12/38* (31.6)	7/18* (38.9)	4/9 (44.4)	17/39** (43.6)	4/8* (50.0)	5/8 (62.5)
Clinical response, n (%)	36 (27.3)	26 (38.2)	10 (30.3)	307 (57.6)	143 (57.9)	71 (56.8)	24 (22.4)	13 (21.7)	3 (9.7)	62*** (52.1)	29** (51.8)	11* (47.8)	70*** (61.9)	30** (54.5)	22*** (75.9)
Safety outcomes of special interest															
n (%)	132 (56.7)	68 (29.2)	33 (14.2)	533 (58.9)	247 (27.3)	125 (13.8)	100 (50.5)	65 (32.8)	33 (16.7)	111 (56.1)	61 (30.8)	26 (13.1)	103 (52.3)	61 (31.0)	32 (16.2)
Infections (all), n (%)	N/A	N/A	N/A	N/A	N/A	N/A	24 (24.0)	16 (24.6)	8 (24.2)	41 (36.9)	24 (39.3)	6 (23.1)	35 (34.0)	30 (49.2)	13 (40.6)
Serious infections, n (%)	N/A	N/A	N/A	N/A	N/A	N/A	2 (2.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.1)
Opportunistic infections, n (%)[d]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.8)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)	1 (1.0)	2 (3.3)	1 (3.1)

*p<0.05; **p<0.001; ***p≤0.0001; all comparisons are vs placebo, chi-squared test
[a]Baseline of OCTAVE Sustain
[b]Pt subgroups at baseline of Induction 1 & 2
[c]Placebo N=233 for proportion calculations
[d]Adjudicated events, excludes tuberculosis and herpes zoster with two adjacent dermatomes
Efficacy outcomes are shown at Wk 8 for OCTAVE Induction 1 & 2 and at Wk 52 for OCTAVE Sustain. Remission was defined as a total Mayo score of ≤2 with no individual subscore >1, and a rectal bleeding subscore of 0. Mucosal healing was defined as a Mayo endoscopic subscore of 0 or 1. Clinical response was defined as a decrease from induction study baseline total Mayo score of ≥3 points and ≥30 %, plus a decrease in rectal bleeding subscore of ≥1 point or an absolute rectal bleeding subscore of 0 or 1. Sustained steroid-free remission was defined as being in remission and steroid-free at both Wk 24 and Wk 52; both the N and n numbers for pts achieving this are shown. Stratified data by BMI for infection and serious infection events are not available for OCTAVE Induction 1 & 2
BID, twice daily; BMI, body mass index; FAS, full analysis set; N, total number of patients; N/A, not available; n, number of patients with characteristic/event; NRI, non-responder imputation; pts, patients; SD, standard deviation; Wk, Week

and BMI over time vs. placebo. In Induction 1 and 2, for tofacitinib 10 mg BID at Week 8, patients with BMI <25 had numerically higher proportions of remission vs. other BMI groups. Proportion of patients with MH was lower in BMI ≥30. Clinical response was similar in all BMI groups. At Sustain Week 52, for tofacitinib 5 mg BID, BMI 25–<30 had highest proportions of remission and MH; BMI ≥30 had highest proportion of sustained steroid-free remission and lowest proportion for MH and clinical response vs. other BMI groups. Clinical response was similar for all BMI groups. In Sustain, for tofacitinib 10 mg BID, BMI ≥30 had highest proportions of remission, sustained steroid-free remission, MH, and clinical response. For tofacitinib patients in Induction 1 and 2, opportunistic infections (OI) were rare; proportions were similar across BMI groups. BMI stratification for infections and serious infections (SI) was not available. In Sustain, for tofacitinib 5 and 10 mg BID, infections were numerically higher for BMI 25–<30 vs. others. There were few OI or SI, and proportions were similar among subgroups.

Conclusions: The majority of patients with UC in the OCTAVE programme had BMI <25. In subgroup analyses by BMI, patients with high BMI receiving tofacitinib did not demonstrate lower efficacy endpoints or greater infection rates. However, limitations include low patient numbers in the BMI ≥30 group and rare OI/SI events.

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Systematic review and meta-analysis of risk factors for recurrent primary sclerosing cholangitis

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Background: Primary sclerosing cholangitis (PSC) is a chronic inflammation of the bile ducts leading to fibrosis and eventually cirrhosis. Aetiology of PSC remains unknown and no specific treatment can delay or arrest the progressive course of the disease with orthotopic liver transplantation (OLT) remaining the only curative option.

Nonetheless, recurrent primary sclerosing cholangitis (rPSC) can occur after liver transplantation (rPSC) with considerable morbidity often leading to retransplantation. In the past decade large cohorts of patients with PSC undergoing OLT were analysed to identify risk factors for rPSC. The current systematic review and meta-analysis was conducted to summarise all available data to define risk factors for rPSC.

Methods: The search of the following databases was performed: PubMed, Embase, Web of Science, Cochrane library for articles published until March 2018 using the medical subject headings sclerosing cholangitis, recurrence, liver transplantation, risk and risk factors. Studies addressing risk factors for developing rPSC after liver transplantation were eligible for inclusion in the review. Studies able to provide data to calculate hazard ratios (HR) and 95% confidence intervals (95% CI) were included in the meta-analysis. Quality of included studies was independently evaluated by two authors with the Newcastle Ottawa Scale (NOS) for cohort studies. Statistical analysis was performed using Cochrane Review Manager.

Results: The electronic database search yielded 449 results. Sixteen retrospective cohort studies met the inclusion criteria for the review. Twelve studies were included for meta-analysis. Studies scored a median of 8 points (6–9) on the NOS. After excluding possibly overlapping cohorts we analysed recurrence a total cohort of 1899 patients, with median age ranging from 31 to 49 years, 1330 were male (70.0%) and 321 developed rPSC (16.9%). We found that colectomy before OLT, HR 0.63 (95% CI: 0.41–0.99), presence of cholangiocarcinoma (CCA) before OLT, HR 2.81 (95% CI: 1.34–5.87), presence of inflammatory bowel disease (IBD), HR 1.76 (95% CI: 1.19–2.61), donor age, HR 1.02 (95% CI 1.01–1.04), MELD score per point, HR 1.05 (95% CI: 1.02–1.08) and development of acute cellular rejection (ACR), HR 2.37 (95% CI: 1.30 – 4.32) were associated with the risk of rPSC.

Conclusions: IBD presence, CCA before transplantation, donor age, MELD score and development of ACR were risk factors for recPSC. Performing a colectomy before liver transplantation was protective for rPSC.

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The impact of anti-TNF therapy in adjuvant setting on postoperative recurrence patterns over decades in complicated Crohn's disease

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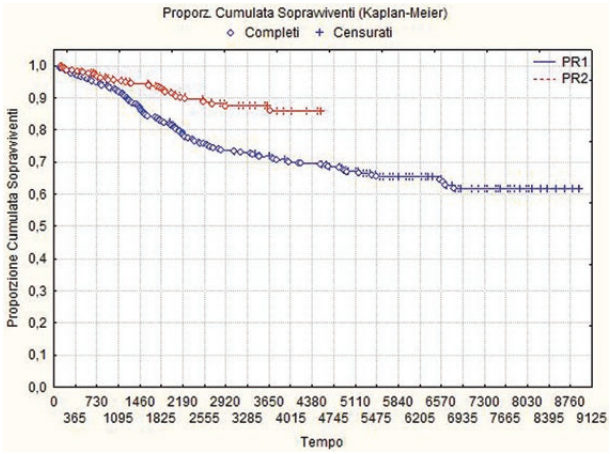
Background: Surgical resection of diseased bowel in complicated Crohn's disease (CD) is frequently not curative and post-operative recurrence remains a significant problem in a large amount of patients. The aim of the study was to evaluate the impact of anti-TNF therapy in the prevention of CD patients' surgical recurrence in a Tertiary Italian IBD Center over decades.

Methods: The Prospective Sacco Database for Surgery of CD (ProSaDS-CD) was retrospectively reviewed to analyse primary (Pr) and re-operative (Re) characteristics of patients operated on in the two decades 1994–2004 (Pr1–Re1) and 2005–2015 (Pr2–Re2). Gender, age, location, behaviour, smoking habit, perianal disease (PCD), time to surgery, indication for surgery, number and length of intestinal locations, number of resection and strictureplasty (SP), postoperative adjuvant therapy, and 25 years surgical recurrence were analysed using the chi-square test, Fisher exact test, Student's *t*-test, Kaplan–Meier time-to-event estimates, and log-rank test where appropriate.

Results: From the ProSaDS-CD, 807 primary and 154 recurrent patients were divided in Group-Pr1 (n = 337), Group-Pr2 (n = 470), Group-Re1 (111), and Group-Re2 (43). Group-Pr2 patients have more frequent diagnosis at A1 and A3 ages (p = 001), same Location (p = 0.5) and Behaviour (p = 0.74), longer disease duration (p = 0.001), less smoking habit (p = 0.0007), more intestinal locations (p = 0.0001) and extension (p = 0.0001), more anti-TNF-α adjuvant therapy (p < 0.0001), and lower long-term surgical recurrence (p = 0.0001). Overall surgical recurrence at 10 and 20 years was 20% and 32%. At 10 years, Group-Re1 and Group-Re2 have 30% and 12% recurrence, respectively (p = 0.0001). At time of recurrence, Group-Re2 patients have more penetrating indication to surgery (p = 0.05), more SP procedures (p = 0.002), more small bowel locations (p = 0.007) and extension (p = 0.02), and less smoking habit (p = 0.04).



Period 1 (Pr1) vs. period 2 (Pr2) postop 25 years recurrence.

Conclusions: In the last decade, surgery for CD has increased in paediatric patients and in the elderly, with a more aggressive pattern in terms of number and extension of locations, and penetrating complications. Strictureplasties in recurrent patients may reduce further intestinal damage. Anti-TNF-α adjuvant treatment and stop smoking seems to significantly change the course of recurrent disease.

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Are cut-off ranges of Infliximab serum levels in Crohn's disease always the same in clinical practice?

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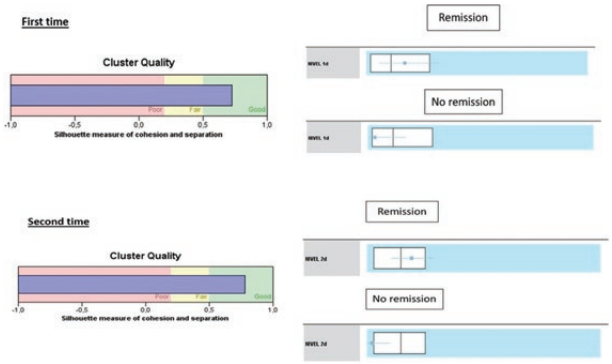
Background: It has been seen that 30–40% of patients treated with Infliximab (IFX) who achieve an initial response to induction therapy lose this response over time with maintenance treatment. Therapeutic drug monitoring (TDM) could be used to optimise management in such situations. However, IFX serum levels are not well defined. The aim of the study was to find our cut-off range of Infliximab serum levels in Crohn's disease (CD) patients in remission in clinical practice.

Methods: An observational retrospective study was developed from 1 February 2016, to 30 November 2017, in our hospital. Patients with established CD who had been on maintenance dosing schedule of IFX were included. IFX and antibody to IFX levels were measured before each infusion at least twice and after 6 months of treatment in all patients. All the tests were performed using enzyme linked immunosorbent assay (ELISA) with Progenika kits (PROMONITOR®). Clinical remission was defined using Harvey–Bradshaw Index (HBI ≤ 4). The interpretation of data was by cluster analysis (Silhouette measure of cohesion and separation: cluster quality >0.5[1]).

Results: 105 CD patients were included in the study, 57.1% men, with a mean age of 39 (DE ± 12.9). The median (range) time of the disease was 11 years (7–15). The median (range) time of follow-up was 32 months (22–38). Montreal phenotypes were: 76% A2, 35.2% L2 and 53.3% B1. Perianal disease was present in 51.4%. 265 IFX levels were measured during the follow-up.

Patients who achieved remission had IFX serum levels between 4.26 and 8.26 µg/ml vs. 0.06 and 1.43 µg/ml in patients who did not achieve remission (silhouette 0.72) the first time; and 2.84–7.75 µg/ml vs. 0.05–2.69 µg/ml in patients who achieved remission vs. those who did not achieve remission, respectively the second time (silhouette 0.78) (Figure 1).



Cluster IFX-levels both times.

4.26–7.75 µg/ml were the best cut-off range for remission (Table 1).

Crohn´s disease			
Time 1	*Time 2*	*Most restrictive interval*	
0.06-1.43	0.05-2.69	0.06-1.43	No remission
1.43-4.26	2.69-2.84	1.43-4.26	Uncertainly zone
4.26-8.26	2.84-7.75	4.26-7.75	Remission

IFX-levels range in both times.

We found that perianal disease does not have any influence on IFX serum levels for achieved remission.

Conclusions: In our practice, the best value to predict remission status in patients undergoing IFX TDM was found to be 4–8 µg/ml, which was higher than in other studies.

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P392

Body mass index has no effect on treatment response in Crohn's disease patients with moderate disease activity who receive adalimumab

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Background: There is ample evidence that obesity negatively affects treatment response to biologics in patients with autoimmune diseases. Data regarding the impact of obesity on treatment success of non-weight-based biologic therapies like adalimumab in patients with inflammatory bowel disease (IBD) are conflicting.

Methods: Ambulatory patients with Crohn's disease of at least moderate severity (Harvey–Bradshaw Index-HBI > 7) and active endoscopic disease at baseline were eligible for inclusion to the study. We only included patients with minimal systemic toxicity and normal serum albumin levels. The primary outcome of the study was clinical, biological, and endoscopic remission 24 weeks post treatment initiation. All patients received induction with adalimumab 160/80 mg at Weeks 0/2 followed by adalimumab 40 mg every 2 weeks. C-reactive protein (C-RP) and faecal calprotectin were measured (BÜHLMANN IBDoc® home based test) in all patients at baseline and 3 and 6 months later. All patients were evaluated by endoscopy 6 months after treatment was started. Clinical remission was defined as HBI <5, biological remission as faecal calprotectin < 250 µg/g and C-RP normalisation, and endoscopic remission as absence of ulcers. Patients with a body mass index (BMI) >30 were characterised as obese.

Results: We included 49 patients over a period of 2 years: 18 males, mean age 41.3 years, mean BMI 27.13 (range 19–41), 33 bio-naive, 44 on monotherapy. Clinical and biological remission was achieved by 33 patients (67.3%) and mucosal healing by 29 patients (59.1%). Obese patients had similar remission rates with non-obese patients. We did not observe any correlation of any BMI cut-off value with clinical, biological, and endoscopic remission. Post hoc analysis revealed that only elevated baseline calprotectin (p = 0.047) and disease duration longer than 2 years (p = 0.042) were predictive of treatment failure.

Conclusions: Treatment success of adalimumab was not affected by BMI in this single-centre real life study of patients with Crohn's disease of strictly moderate disease activity. Lower inflammatory burden (as indicated by calprotectin levels) and short disease duration were associated with higher remission rates. The role of obesity in response to current fixed-dose biologic dosing regimens in IBD merits further investigation.

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P-ECCO Mission

- Improve knowledge and care of paediatric-specific IBD issues
- Support and facilitate research into paediatric IBD
- Interact with the Porto IBD WG of ESPGHAN

P-ECCO Activities

- Paediatric-specific IBD guidelines
- Education on diagnostic and therapeutic issues in paediatric IBD and on adolescent-specific aspects
- Supporting research in Paediatric IBD and contributing to publications on transitional and combined aspects of paediatric/adult IBD
- Creation of P-ECCO Network
- P-ECCO Educational Course

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Outcome of treat to target strategy in paediatric patients with Crohn's disease and ulcerative colitis on infliximab

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Background: Treat to target strategy has been proposed in adult IBD to improve Quality of Life, symptoms and to treat inflammation. There are little data in the paediatric population for this approach. The aim of this study was to look if set goals (reduced PCDAI/PUCAI and Mayo/SES-CD) were achieved.
Methods: We conducted a retrospective analysis of children with IBD who received Infliximab (IFX) in our institution. Data were collected to evaluate mucosal healing for UC from colonoscopy results, using Mayo Scoring and for CD using SES-CD. We also compared These data with activity scores (PUCAI and PCDAI), CRP and Faecal Calprotectin, (FC).
Results: A total of 61 patients were identified, 46 (Group 1) with Crohn's disease (CD), 15 (Group 2) with ulcerative colitis (UC); Male *n* = 38, age range 3–15 years, median 10 years. Group 1: there were 46 patients, male *n* = 26, age range 0–15 years, median 9 years. SES-CD was assessed in all patients pre-treatment with IFX, median score was 3 with a range from 0 to 8; In 36 patients, 1 year after treatment SES-CD score dropped to a median of 1 with a range between 0 and 7. Pre-treatment median FC (*n* = 37) was 2282 mg/kg with a range of 133–6000 mg/kg and post-treatment FC was (*n* = 39) 105 mg/kg with a range of 15–6000 mg/kg. Median CRP pre-commencing (*n* = 42) was 12 mg/l with a range of 5–167 mg/l. Post-treatment (*n* = 42) the median was 5 mg/l with a range of 0.6–67 mg/l. The 1-year follow-up PCDAI was 78% (PCDAI <10). Group 2, 15 children were identified, male *n* = 13, age range 4–13 years, median 10 years. Mayo pre-commencing (*n* = 15) median was 2, range 1–3, post (*n* = 10) was median of 1 with range of 0–3. FC pre-commencing (*n* = 13) median was 1032 mg/kg with a range of 23–3000 mg/kg and was decreased to 69 mg/kg with a range of 15–1852 mg/kg (*n* = 14).
CRP pre-commencing median (*n* = 15) was 6 mg/l with a range of 5–19 mg/l and after (*n* = 15) it was 5 mg/l with a range of 5–8 mg/l. PUCAI was found to be <10 after 1 year of follow-up in 60% of the children with UC.
Conclusions: Our data suggest that set goals were achieved in CD with a decrease of SES-CD and in UC a decrease of the Mayo scoring with an improvement of PCDAI and PUCAI. We suggest that Paediatric patients get targets set at the beginning of their treatment and assess outcomes at set times.

P394

Contribution of the CDEIS in the new therapeutic approach of Crohn's disease

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Background: Deep remission, currently considered the major goal in Crohn's disease (CD), as well as the emergence of the concept of treating beyond symptoms, leads that colonoscopy has become the cornerstone in assessing the severity of lesions to guide the therapeutic decision. As a result, the Crohn's disease endoscopic index score (CDEIS) makes possible the use of a common language to standardise the reports and therefore to comply with a codified treatment. The purpose of our work is to evaluate the contribution of the CDEIS in the CD by studying the attitudes adopted by clinicians and comparing them to those that would have been appropriate by referring to the CDEIS after treatment.
Methods: A retrospective study spread over 5 years, collecting patients diagnosed with a CD at the gastroenterology department of Sousse. The first relapse has been studied. CDEIS after treatment was calculated. The endoscopic response was defined by a reduction of the CDEIS of more than 50% while the endoscopic remission by a score <3. The criteria of non-inclusion were the complications which necessitated an emergency surgical treatment without endoscopy. Three groups were individualised: Group 1: CDEIS < 3 (*n* = 9); Group 2: decrease of the CDEIS > 50% (*n* = 72); Group 3: decrease of the CDEIS <50% (*n* = 28).
Results: We collected 135 patients of mean age 38.6 years and sex ratio of 0.43. Induction of remission was based on intravenous corticosteroids in 22.9% and oral in 66.6% while TNF-α antagonists was used in 10.3% of cases. The clinical remission was obtained in 80.7% and in this case, the maintenance of remission was based on azathioprine in 74.3%, combotherapy (TNFα antagonists + azathioprine) in 16.5% and an TNF-α antagonist alone in 9.1% of cases. Colonoscopy after treatment was performed in a mean time of 14.7 months. Endoscopic remission was obtained in 11% and a response in 66% of cases. In the first group, no therapeutic modification was performed while the clinician opted for a therapeutic escalation in the second group in 11.1%. For the third group, a more aggressive therapeutic attitude was achieved in 32.1%. In univariate analysis, the specific complications of the disease (intraabdominal abscess, bowel obstruction, perforation) were significantly more frequent in the third group compared with the second for an average duration of follow-up of 2.4 years (25% vs. 16.6%, $p = 0.03$).
Conclusions: In our study, our therapeutic attitude was more conservative than the appreciation of the CDEIS in 17.4% of cases. Certainly, the intuition of the clinician is very important but the CDEIS, allows a more objective assessment of endoscopic lesions and therefore a better management aimed at modifying the natural history of the disease.

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Postoperative immunosuppressive therapies decrease the risk of second intestinal surgery in patients with Crohn's disease: a retrospective cohort study

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Background: In patients with Crohn's disease (CD), postoperative recurrence frequently occurs and a certain proportion of patients

require second intestinal surgery during the clinical course. Immunomodulators (IM) and anti-tumour necrosis factor-alpha (anti-TNF) agents can be prophylactic against postoperative recurrence, however, it remains unclear whether such medications can decrease second intestinal surgery in CD. The present study aimed to investigate the preventive effect of postoperative medications on the second intestinal surgery in postoperative CD.

Methods: This is a retrospective cohort study. 112 CD patients who had undergone initial intestinal surgery during 2002 and 2017 in our institutions were enrolled. Postoperative clinical course of the patients was carefully reviewed, and possible factors associated with second intestinal surgery were investigated. Medications initiated within a year after surgery was defined as the postoperative therapies. Intestinal resection due to complication of CD or strictureplasty was defined as intestinal surgery. Cumulative probabilities of second intestinal surgery were estimated using Kaplan–Meier method, and compared by the log-rank test. Cox proportional hazard model was used to analyse factors associated with second intestinal surgery.

Results: Of the 112 patients, IM and anti-TNF agent were applied to 25 (22%) and 58 (52%) patients as the postoperative medications, respectively. Among them, both medications were used in 14 patients (13%). During median follow-up of 60.5 months, 30 patients (27%) required second intestinal surgery. Cumulative probabilities of second intestinal surgery were estimated to be 19.4% at 5 years, and 33.4% at 10 years after surgery, respectively. Under univariate analysis, clinical characteristics including age at diagnosis, smoking status and CD behaviour were not associated with second intestinal surgery. However, postoperative IM and anti-TNF agent were associated with reduced risk of second intestinal surgery (p = 0.014 and 0.047, respectively). The multi-variate analysis by Cox proportional hazard model revealed that postoperative IM [hazard ratio (HR); 0.12, 95% confidence interval (CI); 0.01–0.54] and anti-TNF agent [HR; 0.40, 95% CI; 0.15–0.96] were independent factors associated with the reduced risk of second intestinal surgery.

Conclusions: Both postoperative IM and anti-TNF agent might decrease the risk of second intestinal surgery in patients with CD.

P396

Monitoring adalimumab compliance using smart sharp bin technology

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Background: Adalimumab is a patient-administered subcutaneous anti-TNF agent used in both Crohn's disease and ulcerative colitis. It has previously been shown that there is significant non-compliance with patient-administered subcutaneous therapies. The aim of this study was to evaluate compliance with adalimumab among our patient cohort enrolled in the Health Beacon programme.

Methods: We collated data supplied by Health Beacon on a monthly basis to determine rates of non-compliance with adalimumab therapy including, early, late and missed dosing. A drop is counted as administration of adalimumab and placement of the pre-filled pen or syringe into the smart sharps bin.

Results: A total of 496 drops were counted among 26 patients. Fifteen males and 11 females are currently enrolled in the programme with an average age of 40.6 years. Seventeen patients have a diagnosis of Crohn's disease and 9 with ulcerative colitis. 355 drops were recorded as being on-time, giving an overall compliance rate of 71.5%. Compliance among males is 76.8% and females 63.8%. Compliance is 71.7% and 70.6 in Crohn's disease and ulcerative colitis, respectively. 46.2% of patients have missed at least two doses.

Conclusions: We have shown high rates of non-compliance with adalimumab therapy in patients who have agreed to have their compliance tracked. This may be attributed to the administration of the medication by the patient at home. In this case, infusion therapy may show benefit over subcutaneous therapy. Further correlation with inflammatory markers, endoscopic findings and faecal calprotectin may aid in deescalating therapy in those patients who are non-compliant, yielding significant savings for our department.

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Autologous stem cell transplantation in refractory Crohn's disease: evaluation of a modified mobilisation regimen and analyses of the cost-effectiveness

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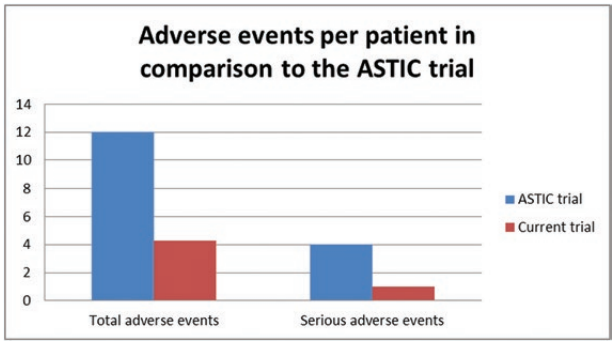
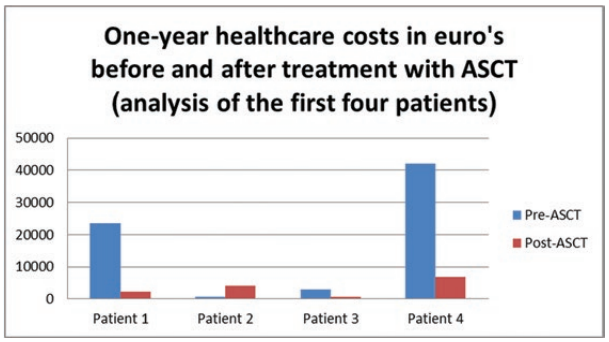
Background: Autologous stem cell transplantation (ASCT) is a last resort treatment in patients with refractory Crohn's disease (CD), but is associated with high costs and considerable toxicity. In this study, we evaluate the impact of a modified mobilisation regimen on toxicity, efficacy and costs.

Methods: In this prospective observational study, adult patients with refractory CD were included between 2014 and 2017 from six University Medical Centres. We eliminated cyclophosphamide from the mobilisation regimen to limit toxicity. The aims of this study were to assess the sustained remission at 1 year (clinical remission (CDAI < 150) AND no use of immunosuppressives or biologicals AND no endoscopic or radiologic evidence of active disease), the clinical benefit (CDAI < 150 or a significant decrease of 100 points), toxicity, cost effectiveness and quality of life (QoL).

Results: Eight patients (5 females, median age 49 years, range 40–67 years) underwent ASCT. Seven patients completed a follow-up of 52 weeks. None of the patients reached the combined primary endpoint at Week 52. However, 3/5 (60%) patients reached clinical remission defined as CDAI < 150, and a fourth had a significant decrease of 100 points in the CDAI (clinical benefit in 4/6 patients). The CDAI was not assessed in two patients, because of the presence of an endostomy. In 2/6 patients no radiologic and in another 2/6 no endoscopic disease activity was observed at Week 52. In 4/7 patients QoL significantly increased (IBDQ increase of >16 points, range 28–49 points). All patients were discharged from the hospital within 4 weeks after ASCT. In total, 35 adverse events were reported of which 8 were considered serious. Analysis of the healthcare costs (1 year before vs. 1 year after ASCT) of the first 4 patients shows a substantial reduction in the costs.



Adverse events per patient



Healthcare costs

Conclusions: Although the combined primary endpoint was not reached, we observed clinical benefit in more than half of the patients with refractory CD treated with ASCT. The use of a less toxic regimen for the mobilisation may lead to a substantial reduction in the incidence of adverse events without impacting efficacy. ASCT may lead to a considerable decrease in the healthcare costs.

P398

Leptin controls immune cell composition and activity in acquired generalised lipodystrophy with combined Crohn's disease

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Background: Leptin, a fat-derived adipokine, has been suggested to modulate intestinal inflammation in mice. However, clinical evidence regarding its immune-stimulatory potential in Crohn's disease remains sparse. We here describe a 21-year-old patient with the solitaire combination of acquired generalised lipodystrophy and combined Crohn's disease (AGLCD) featuring a complete lack of visceral and subcutaneous adipose tissue, absent leptin production and severe intestinal inflammation, who received daily injections with 2.5 mg recombinant *n*-Methionylleptin (rLeptin).

Methods: Using mass and flow cytometry, immunohistochemistry (IHC), ELISA and Seahorse analyses, we characterised the effects of rLeptin substitution on the patient's immune cell composition and function *in vivo* and *in vitro* and compared our results to a cohort of healthy donors and Crohn's disease patients. Furthermore, the immune-stimulatory effects of leptin substitution were assessed in a mouse model of acute DSS colitis.

Results: In the absence of mesenteric fat, we observed a unique immune cell composition in the peripheral blood of the AGLCD patient, characterised by reduced frequencies of NK cells and $CD14^+$ monocytes, an accumulation of lipid droplets in monocytes, NK and $CD8^+$ T cells, decreased expression of CCR7 on T cells and an increased expression of CD38 on T and NK cells compared with healthy donors and Crohn's disease patients. Treatment of the AGLCD patient with rLeptin reduced the lipid droplet contents of immune cells and *in vitro* application of leptin decreased fatty acid oxidation in macrophages. Furthermore, rLeptin treatment led to increased expression of pro-inflammatory markers in monocytic cells as well as increased TNFα production in monocytes and T cells, ultimately resulting in a high inflammatory disease activity and subsequently ileocolic resection. Accordingly, IHC of the resected specimen of the AGLCD patient showed a higher infiltration of TNFα-producing cells and reduced numbers of $CD206^+$ anti-inflammatory cells compared with CD patients. Likewise, injection of leptin aggravated intestinal inflammation in colitic mice by inducing TNFα-producing $CD4^+$ T cells. Importantly, these pro-inflammatory effects of rLeptin in the AGLCD patient could be overcome by treatment with the TNF-blocking antibody adalimumab, which resulted in complete clinical and endoscopic remission 6 month after initiation of therapy despite ongoing rLeptin treatment.

Conclusions: Our results suggest that leptin might play a crucial role in human immune cell homeostasis and that in the setting of a pre-existing inflammatory condition leptin therapy might fuel inflammation and increase disease activity via the induction of TNFα-producing cells, which can be reversed by TNFα-blockade.

P399

Cost-effectiveness of utilising proactive Infliximab therapeutic drug monitoring for inflammatory bowel disease in routine clinical practice

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Background: Therapeutic drug monitoring(TDM) is increasingly utilised in IBD practice to guide dosing of anti-TNFs. Proactive TDM assessment has not, however, been clearly shown to improve clinical outcomes compared with empiric dose optimisation. The aim of our study was to assess whether a proactive-TDM strategy, with the aim of dosing patients to an IFX-level in the therapeutic range, is a cost-effective strategy in routine practice.

Methods: IFX TDM has been available at SJH for a 1-year period. On a pilot basis, IBD patients receiving IFX had a single trough sample collected. IFX-levels and antibody-to-IFX concentrations (ADA) were determined. IFX levels from 3 to 7 µg/l were considered therapeutic. ADA of 50 AU/ml and above were considered significant . IFX treatment decisions based on TDM were documented. Costs/savings related to TDM use were estimated by documenting alterations to IFX regimens prompted by TDM and extrapolating annualised total dose increases / reductions.

Results: A total of 64 IBD patients were included, 51% male, 63% Crohn's disease. Twenty-seven per cent, 43% and 30% of patients had a therapeutic, subtherapeutic and supratherapeutic IFX-level. *n* = 21 (33%) had significant ADA present. *n* = 35 patients (55%) patients had alterations to IFX dosing based on TDM: 23% had IFX dosing interval increased, 20% had IFX dosing interval decreased and 11% discontinued IFX therapy. The use of proactive-TDM was found to be cost-effective with annual savings of €70,083.34.
Conclusions: While Anti-TNF TDM has certainly been shown to be of value in the setting of loss of response to treatment, it remains unclear whether a proactive-TDM improves clinical outcomes. Our study suggests proactive TDM may at least be a cost-effective strategy.

P400

Discordance in patient and physician perspectives and priorities in communication and management of ulcerative colitis: results of the European ulcerative colitis narrative survey

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Background: The ulcerative colitis (UC) narrative is a global survey of patients and gastroenterology physicians (GIs), aimed at identifying the impact of UC and comparing and contrasting perceptions of UC burden and management approaches. Here, we present data from a European survey of patients and GIs.
Methods: Surveys were conducted online and by phone by The Harris Poll between August 2017 and February 2018. 1159 patients and 784 GIs in Finland, France, Germany, Italy, Spain and the UK completed the survey. Eligible adult patients with UC were those who had visited a GI in the previous 12 months and had ever received prescription medication for UC. Self-reported medication history was used as a proxy for disease severity, with patients with moderate to severe UC defined as patients who had ever taken immunosuppressants, tumour necrosis factor inhibitors, other biologics, or corticosteroids for >4 of the past 12 months. Patients who had only ever taken 5-aminosalicylates or had a colectomy were excluded. Mean age of patients was 39.9 years, 60% were male, and 84% had moderate-to-severe UC; 67% described their UC as controlled with few to no symptoms. Eligible GIs were those who saw ≥10 UC patients each month (of whom ≥10% were taking a biologic) and did not practise in a long-term care facility or hospice. GIs had been in speciality practice for a mean of 16.1 years and saw a mean of 43.4 patients with UC each month.
Results: 86% of patients were very/somewhat satisfied with their current treatment; however, 74% wished they had more UC medication choices. Sixty-one per cent of patients wished their GI had discussed all available treatment options with them earlier, so they had a better idea of their choices; 74% of GIs wished they had more time for these discussions. The top indicators for considering changing medications were similar for patients and GIs: continued flares (38% of patients; 58% of GIs) and continued symptoms (31% of patients; 54% of GIs). The ability to manage symptoms was a top priority for patients and GIs for discussion at routine appointments; however, cancer risk was a pt priority, but not a GI priority (table). Discussion of treatment side effects at routine appointments was a GI priority (table). Both patients (68%) and GIs (81%) wish they had more time at appointments.
Conclusions: Pts and GIs were in agreement regarding the symptoms leading to the consideration of changes in medication. Symptom control is a high priority for discussion among patients and GIs, but cancer risk was viewed as less of a priority for GIs. Shortage of appointment time was identified as a communication barrier.

Table. The most important topics to prioritise during routine appointments[a]

	Pts, % (overall ranking)	GIs, % (overall ranking)
How to control inflammation	29% (1)	24% (6)
Cancer risk	28% (2)	11% (9)
The ability to manage symptoms	27% (3)	38% (3)
Symptoms experienced since last visit	24% (4)	57% (1)
Side effects of current treatment	22% (5)	47% (2)
New medications that are available for UC	22% (6)	17% (8)
What to expect from UC in the long term	21% (7)	26% (5)
The physical impacts of UC	21% (8)	17% (7)
The ability to manage fatigue	18% (9)	5% (13)
What to expect next from UC treatment (including possible treatment changes)	17% (10)	30% (4)
The emotional impacts of UC	16% (11)	7% (11)
The impacts of UC on sex life and personal relationships	8% (12)	5% (12)
Where to go for additional information and support	7% (13)	8% (10)

[a]Pts and GIs could select up to three topics
GIs, gastroenterology physicians; pts, patients; UC, ulcerative colitis

P401

Association between induction vedolizumab drug levels and therapy outcome in inflammatory bowel disease

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Background: Vedolizumab (VDZ) is a monoclonal antibody which targets α4β7 integrin which has demonstrated efficacy in induction and maintenance of remission in both ulcerative colitis (UC) and Crohn's disease (CD). We aim to determine the association between

induction trough VDZ levels and therapy outcome at Week 14. We also assess the association between baseline patient characteristics and induction trough VDZ levels.

Methods: Patients were recruited prospectively from three Irish Academic Medical Centres. They were included if >18 years old, with an established diagnosis of UC or CD and due to initiate VDZ therapy for standard clinical indications. Partial Mayo score (PMS) and Harvey–Bradshaw index (HBI) were assessed as appropriate a Week 0 and 14. All patients received VDZ as per standard induction and maintenance protocol. Steroid-free clinical remission (CR) at Week 14 was defined as a PMS less than or equal to 1 or a HBI <5 and no requirement for corticosteroids. Serum was collected pre-VDZ infusion at Weeks 2, 6 and 14. VDZ trough levels were determined using IDKmonitor ELISA kit (Immunodianostik). Statistical comparisons were made with p values <0.05 considered significant.

Results: 32 patients were included, n = 24 had available follow-up to Week 14. Fifty-eight per cent had CD, age (median[range]) was 49.2 years (18.2–75.8). Proportion with concomitant immunomodulator, corticosteroid use and prior biologic exposure at VDZ initiation were 17%, 28% and 71%, respectively. At baseline (median[range]) PMS was 4 [2–6], while HBI was 7 [1–17]. Baseline (median[range]) CRP 4.7 mg/l [1–43], albumin 41 g/l [31–52] and faecal calprotectin 872 µg/g [23.7–1250]. Week 2, 6 and 14 trough VDZ levels (median [range]) were 21.9 [5–47] µg/ml, 18.6 µg/ml [2–39.2], 13 µg/ml [2.9–38.8], respectively. Week 14 steroid-free CR was achieved in 45% of patients. There was no association between Week 2 or 6 trough VDZ levels and Week 14 steroid-free CR, p = 0.61 and p = 0.27, respectively. An elevated baseline CRP (>5 mg/l) and reduced albumin (<40 g/l) were significantly associated with a lower Week 6 trough VDZ level, p = 0.02 and p = 0.03, respectively.

Conclusions: VDZ is an effective induction therapy for UC and CD in a cohort with significant prior biologic exposure. Induction VDZ drug levels are not associated with therapy outcome at Week 14. Increased CRP and reduced albumin are associated with lower induction VDZ trough levels suggesting inflammatory burden may affect VDZ induction pharmacokinetics.

P402

Systemic steroids vs. local acting steroids: Relative risk for corticosteroid-related adverse events

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Background: The efficacy of systemic corticosteroid to treat active inflammatory bowel diseases is well known. However, these corticosteroids, due to their systemic availability are associated with potentially serious side effects. Budesonide offers an effective therapy option, being a locally acting steroid. Budesonide has a targeted delivery system for ileum/colon. Absorption is followed by rapid inactivation by the liver resulting in low systemic circulation and activity. The safety profile with respect to steroid-related adverse events favours budesonide (RR=1.64; 95% CI 1.34–2.00) (Table 1).[1]

Methods: In this review, the number of adverse events (AE) reported to the Eudravigilance (covering the EU), FAERS (USA), and Vigibase (covering 110 countries worldwide) stating steroid-related AEs were collected for budesonide and methylprednisolone, prednisolone, prednisone and hydrocortisone. All AEs under the specified clinical concept were selected for the products under review. The data were used to calculate estimated measures of effect as reporting odds ratio (ROR) and 95% CI.

Results: The three databases contained a total of 559 130 reports for all the active ingredients which comprised of 54 988 for budesonide, 108 775 for methylprednisolone, 159 343 for prednisolone, 202 345 for prednisone and 33 679 hydrocortisone. Of these a total of 48 947 concerned corticosteroid AEs associated with the products under consideration.

Table 1. AEs with highest RORs

	Systemic steroids	Systemic steroids	Budesonide	Budesonide
Corticosteroid AEs	*n* of AEs	ROR (95% CI)	*n* of AEs	ROR (95% CI)
Haemat-opoietic cytopenias	13 527	9.33 (9.18–9.49)	162	0.11 (–0.05–0.26)
Osteonecreo-sis	5095	4.48 (4.30–4.66)	125	0.22 (0.05–0.40)
Hyponatrae-mia	1349	2.42 (2.16–2.67)	61	0.41 (0.16–0.67)
Diabetes	9043	2.09 (1.99–2.18)	477	0.48 (0.39–0.57)
Adrenal insuf-ficiency	2438	0.50 (0.41–0.60)	526	1.99 (1.89–2.08)

Table 2. Other AEs

	Systemic steroids	Systemic steroids	Budesonide	Budesonide
Corticosteroid AEs	n of AEs	ROR (95% CI)	n of AEs	ROR (95% CI)
Pancreatitis	2892	1.56 (1.41–1.70)	203	0.64 (0.50–0.78)
Cushingoid	3554	0.69 (0.60–0.78)	561	1.45 (1.36–1.54)
Glaucoma	1464	0.79 (0.65–0.94)	201	1.26 (1.11–1.41)
Cataract	2582	0.62 (0.52–0.72)	451	1.61 (1.51–1.71)
Osteoporosis	3883	1.20 (1.09–1.31)	353	0.83 (0.72–0.94)
All corticosteroid AEs	45 827	1.48 (1.45–1.51)	3120	0.60 (0.56–0.64)

Conclusions: The data confirms the more favourable safety profile of budesonide (the most widely used locally acting steroid) in comparison to systemic steroids. However, for specific events such as cushingoid, cataract and glaucoma the calculated ROR was higher for budesonide with a low absolute number of reports. This is not predicted considering the pharmacology of budesonide. This is likely to be explained by the unexpectedness factor which may have increased the reporting rate. It is possible that reporter were much more likely to report an AE if they thought it was unusual for the product.

References

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P403

Intravenous iron infusion in inflammatory bowel disease: efficacy and ferro-economics

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Background: Iron deficiency anaemia (IDA) is a common association of inflammatory bowel disease (IBD). The mechanism of IDA in IBD is multifactorial and includes blood loss, systemic inflammation causing anaemia of chronic disease as well as malabsorption. Patients with active IBD do not respond to oral iron due to the hepcidin block and need intravenous iron. Inactive IBD patients do not tolerate oral iron and need parenteral iron. The aim was to assess the efficacy and cost of IV iron treatment in IBD patients.
Methods: Retrospective case note and haematology tests review of all patients who received IV Iron as Ferric Carboxymaltose (Ferrinject®) infusion for IDA at Darlington Memorial Hospital between March and August 2017 was done. Data were inputted into an Excel spreadsheet for analysis; patients who received Iron infusion for non-gastrointestinal diseases were excluded from analysis. Patients with IBD were classified into ulcerative colitis (UC), Crohn's disease (CD) and unclassified/indeterminate colitis (IBDU). The reasons for IV iron were classified as intolerance, active disease or no response to oral Iron preparations. Response to iron therapy was determined by target haemoglobin being achieved within 3 months post infusion. Patients who needed more than one infusion of Ferinject were noted. Costs were calculated using national tariff for drug acquisition and day care treatment costs.
Results: Of 78 patients with IDA, 36 had iron infusion for gastrointestinal diseases. Twenty-four of these had IBD (10 UC, 13 CD, and 1 IBDU). Of the IBD patients, 5 had active disease, 13 were intolerant of oral iron, 3 had no response to oral iron, and 3 patients by clinician choice. Mean weight of the patients was 72.69 kg (range 51.6–119.4 kg). Mean haemoglobin (Hb) prior to iron infusion was 102.79 g/l (range 49–142). Nineteen patients (79%) required 2 infusions of Ferrinject based on calculated dose. Mean Ferrinject dose required was 1479 mg (range 1000–2000 mg). Post Ferrinject, 15/24 (62.5%) patients achieved target Hb (>120). Mean Hb level post infusion was 130.4 g/l, range 90–156. None of the patients had any allergic reactions. Cost of treatment ranged from £2000 for the 5 patients who needed a single infusion to £15 200 for the remaining 19 patients, indicating that there is a significant cost for IV iron treatment in IBD using Ferinject.
Conclusions: Intolerance to oral iron is very common in patients with IBD. IV Iron replacement is an effective therapy with good response in patients for whom oral Iron is not appropriate. A significant number of patients require more than one infusion to achieve desired haemoglobin levels requiring increased use of resources such as bed space in day units and treatment costs. Single total dose iron infusions could reduce these costs.

P404

Stopping 5-aminosalicylates in Crohn's disease patients starting biologic therapy does not increase the risk of adverse clinical outcomes: analysis of two nationwide population-based cohorts

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Background: The impact of discontinuing 5-aminosalycilates (5-ASA) in Crohn's disease (CD) patients who initiate anti-tumour necrosis factor α (anti-TNF) biologics is unknown. We aimed to compare clinical outcomes in CD patients already on 5-ASA who started anti-TNF and then either stopped or continued 5-ASA.
Methods: We analysed two national databases: the USA (U.S.) Truven MarketScan health claims database and the Denmark health registers. CD patients who started anti-TNF after having been on oral 5-ASA for at least 90 days were included. Patients were classified as stopping 5-ASA if therapy was discontinued within 90 days of starting anti-TNF. Our primary outcome was any adverse clinical event defined as a composite of new corticosteroid use, CD-related hospitalisation or surgery. We performed Kaplan–Meier analyses and multivariable Cox regression models controlling for age, gender, duration of 5-ASA treatment before anti-TNF initiation, prior CD-related surgery, disease duration (Danish database only) and healthcare utilisation (corticosteroid use, hospitalisations and emergency department visits in year prior to anti-TNF). Adjusted hazard ratios (aHR) with 95% confidence intervals (95% CI) are reported comparing stopping 5-ASA with continuing 5-ASA.
Results: A total of 3,178 CD patients were included (2,960 USA and 218 Denmark). 1,044 patients in the US cohort and 106 patients in the Danish cohort stopped 5-ASA after starting anti-TNF. In both cohorts, cumulative rates of the adverse clinical events composite primary outcome were similar when comparing those who stopped vs. those who continued 5-ASA (Figures 1 and 2). In multivariable analysis, stopping 5-ASA after initiating anti-TNF was not associated with an increased risk of adverse clinical events in the U.S. cohort (aHR 0.89, 95% CI 0.77–1.03, p = 0.13) nor in the Danish cohort (aHR 1.13, 95% CI 0.68–1.87, p = 0.63). Results were similar in sensitivity analyses investigating concomitant immunomodulator use and duration of 5-ASA treatment before initiating anti-TNF.
Conclusions: In two national databases, stopping 5-ASA in CD patients starting anti-TNF therapy did not increase the risk of adverse clinical events. These results should be validated in a prospective clinical trial.

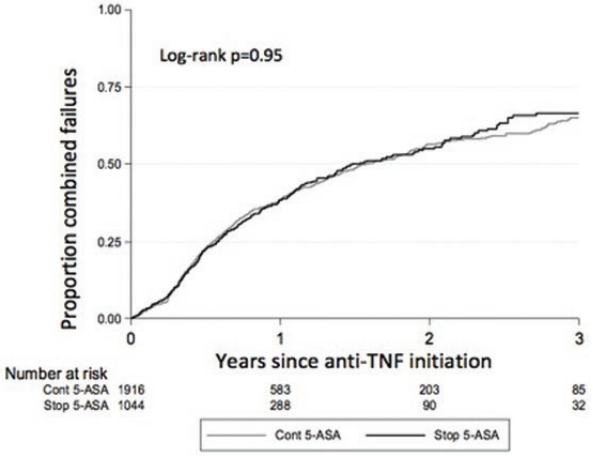

Figure 1. Cumulative rates of CD patients with adverse clinical events (composite of new corticosteroid use, CD-related hospitalisation or surgery) comparing those who continued or stopped 5-ASA in the USA cohort.

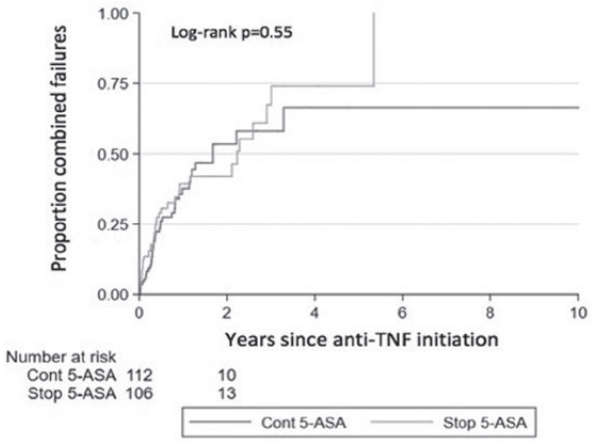

Figure 2. Cumulative rates of CD patients with adverse clinical events (composite of new corticosteroid use, CD-related hospitalisation or surgery) comparing those who continued or stopped 5-ASA in the Danish cohort.

P405

Sustainability of biologic therapies is less in UC than CD patients independent of prior biologic experience

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Background: Treatment of inflammatory bowel disease (IBD) with biologics is usually effective but may be discontinued due to inadequate response or adverse effects. Few studies have examined what determines sustainability of treatment in a real-world setting.
Methods: To determine factors which determine sustainability of biologic therapy we performed a single-centre retrospective study of a prospectively maintained database of 4200 IBD patients. Patients were subdivided on whether they had ulcerative colitis (UC + IBD-U included) or Crohn's disease (CD), whether they were biological-naïve vs. experienced when they received a particular biologic. Our primary endpoint was time to discontinuation of biologic (due to inadequate response or adverse effects) in biologic naïve (Group 1) and biologic experienced patients (Group 2) depending whether they were diagnosed with UC or CD. The impact of immunomodulator co-therapy and other disease characteristics was examined.
Results: A total of 765 patients with complete data were included in our analysis. Group 1: 539 patients were in our biologic naïve group. 117 (21.71%) were treated with Infliximab (IFX). 375(69.57%) with adalimumab (ADA). Fifteen (2.78%) were on Vedolizumab (VD). Thirty-two(5.94%) were on golimumab (GB). 192(35.6%) had UC. 347(64.4%) patients have CD. Median time to discontinuation was 2.84 years in UC which was significantly shorter than in CD patients with median time to discontinuation of 3.59 years (p = 0.000) (Table 1, Graph 2).Group 2: 226 patients were in our biologic experienced group. Seventy-nine(35%) were treated with IFX, 53 (23.45%) with ADA, 28(12.4%) with VD. 28(12.4%) were treated with GB, 38 (16.81%) with Ustekinumab (UST). 74(32.74%) had UC. 149(65.93%) had CD. Median time to discontinuation in UC was 2.58 years compared with 3.83 years in CD (p = 0.010) (Table 1, Graph 1). No significant differences in time to biologic discontinuation were observed between biologic naïve and biologic experienced treatments.

Table 1. Median time to discontinuation.

	UC	Median time to discontinuation	CD	Median time to discontinuation	*p*-value
Total (*n* = 762)	266	2.68	496	3.50	0.000
Biologic naive (*n* = 539)	192	2.84	347	3.59	0.000
Biologic experienced (*n* = 226)	74	2.58	149	3.83	0.010

Conclusions: Our real-world data indicate that the sustainability of biologic treatment is less in UC than in CD patients and is not strongly determined by prior biologic exposure. These findings are important in determining how biologic therapies are employed in both IBD subtypes and suggest the need for new non-biologic/small molecules to demonstrate their relative sustainability as IBD therapies.

P406

General health status in patients with moderate to severe ulcerative colitis receiving ustekinumab: results from the Phase 3 UNIFI induction and maintenance studies

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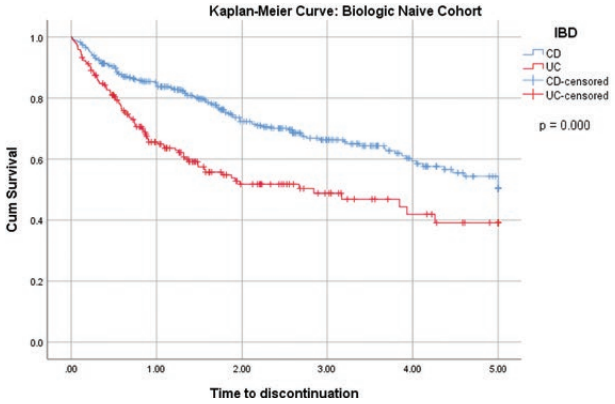
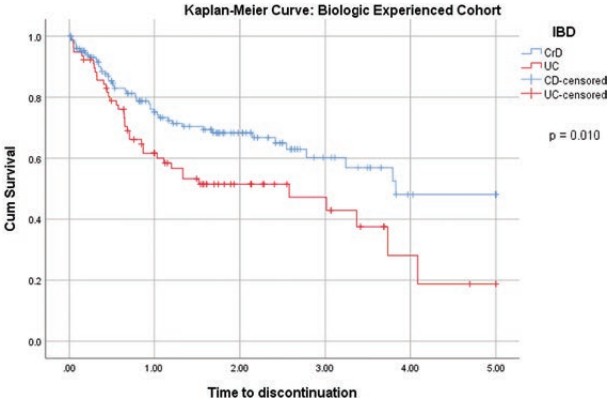
Background: The UNIFI studies evaluated the safety and efficacy of ustekinumab (UST) intravenous (IV) induction and subcutaneous (SC) maintenance in patients with moderately to severely active ulcerative colitis (UC). We evaluated patient-reported outcomes related to general health status in these studies.
Methods: In the induction study, eligible patients were randomised to a single IV dose of placebo (PBO, *n* = 319), UST 130 mg (*n* = 320), or UST ~6 mg/kg (*n* = 322). Patients who were in clinical response 8 weeks after receiving UST induction were eligible for the maintenance study and were randomised to SC PBO (*n* = 175), UST 90 mg q12w (*n* = 172), or UST 90 mg q8w (*n* = 176). General health status was assessed using the 36-item Short Form Health Survey (SF-36) and the visual analogue scale of EuroQoL-5D Health Questionnaire (EQ VAS). SF-36 measured 8 functional areas that were summarised into physical and mental component summary scores (PCS and MCS). EQ VAS ranges from 0 to 100. Higher SF-36 and EQ VAS scores indicate better health status.
Results: At baseline of the induction study, mean SF-36 PCS and MCS scores were below the USA general population norm of 50 and indicative of patients with significantly impaired general health status (Table 1).





Abstract P405 – Graph 1. Biologic naive and experienced Kaplan–Meier curve.

Table 1. Patient-reported outcomes related to general health status at Week 8 in patients who received IV induction treatment with ustekinumab or placebo.

Outcome	Placebo IV	Ustekinumab IV 130 mg	Ustekinumab IV ~6 mg/kg[a]
Primary efficacy analysis set, n	319	320	322
SF-36 physical component score			
Induction baseline	43.6 (7.96)	43.1 (7.85)	43.1 (7.73)
Change from baseline to Week 8	2.1 (6.39)	4.7 (6.49)	5.2 (6.16)
p-value		<0.001	<0.001
Patients with improvement from baseline to Week 8 ≥5 points, n (%)	83 (26.0%)	154 (48.3%)	146 (45.3%)
p-value		<0.001	<0.001
SF-36 mental component score			
Induction baseline	40.5 (11.43)	40.1 (10.85)	40.5 (10.59)
Change from baseline to Week 8	2.2 (10.20)	5.3 (9.63)	5.1 (9.72)
p-value		<0.001	<0.001
Patients with improvement from baseline to Week 8 ≥5 points, n (%)	100 (31.3%)	140 (43.9%)	143 (44.4%)
p-value		0.001	<0.001
EQ VAS			
Induction baseline	55.11 (20.815)	54.14 (20.545)	55.76 (19.333)
Change from baseline to Week 8	5.71 (19.584)	13.64 (20.394)	13.51 (18.447)
p-value		<0.001	<0.001
Patients with improvement from baseline to Week 8 ≥10 points (half the standard deviation of the baseline value), n (%)	97 (30.6 %)	146 (45.8%)	151(46.9%)
p-value		<0.001	<0.001

Values are mean (standard deviation) unless otherwise indicated.
[a]Weight range-based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55 kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight > 85 kg).

Eight weeks after IV induction, patients receiving UST reported significantly greater improvements in mean SF-36 PCS and MCS and EQ VAS scores compared with PBO ($p < 0.001$). Statistically significant differences between UST and PBO were observed for each of the individual subscales of the SF-36 ($p \leq 0.002$). Through Week 44 of the maintenance study, mean SF-36 PCS scores worsened in the PBO group, were maintained in the UST q12w group, and improved in the UST q8w group (Table 2).

Mean SF-36 MCS also worsened in the PBO group and were maintained in the UST q12w and q8w groups ($p \leq 0.009$). The proportions of patients with clinically meaningful improvements in SF-36 PCS and MCS (≥5 points) and EQ VAS (>10 points) from induction baseline to maintenance Week 44 were significantly greater in the UST groups compared with PBO ($p \leq 0.001$).

Conclusions: Patients reported significantly greater improvements in general health status after UST IV induction compared with PBO. In patients who responded to UST IV induction, improvements were sustained or increased with 44 weeks of SC UST maintenance therapy.

Abstract P406 – Table 2. Patient-reported outcomes related to general health status at Week 44 in patients who responded to ustekinumab induction and received SC maintenance treatment with ustekinumab or placebo.

Outcome	Placebo SC[a]	Ustekinumab SC 90 mg q12w	Ustekinumab SC 90 mg q8w
Primary efficacy analysis set, n	175	172	176
SF-36 physical component score			
Maintenance baseline	50.0 (6.65)	50.7 (6.86)	50.0 (6.88)
Change from maintenance baseline to Week 44	-1.7 (6.45)	-0.4 (7.14)	1.3 (5.68)
p-value		0.009	<0.001
Patients with improvement from induction baseline to Week 44 ≥5 points, n (%)	53 (30.3%)	86 (50.0%)	94 (53.4%)
p-value		<0.001	<0.001
SF-36 mental component score			
Maintenance baseline	47.6 (9.41)	47.1 (9.99)	48.1 (8.63)
Change from maintenance baseline to Week 44	-2.4 (9.89)	0.3 (8.41)	0.3 (9.51)
p-value		0.006	0.002
Patients with improvement from induction baseline to Week 44 ≥5 points, n (%)	50 (28.6%)	81 (47.1%)	95 (54.0%)
p-value		<0.001	<0.001
EQ VAS			
Maintenance baseline	75.2 (13.57)	75.7 (16.28)	73.2 (16.24)
Change from maintenance baseline to Week 44	-7.7 (18.75)	-2.2 (19.87)	2.4 (17.28)
p-value		<0.001	<0.001
Patients with improvement from induction baseline to Week 44 >10 points, n (%)	58 (33.1%)	99 (57.9%)	104 (59.1%)
p-value		<0.001	<0.001

Values are mean (standard deviation) unless otherwise indicated.
[a]Patients who responded to ustekinumab IV induction dosing and were randomly assigned to placebo SC upon entry into the maintenance study.

P407

Real-world safety of tofacitinib in inflammatory bowel diseases: a multi-centre study

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Background: Our aim was to examine adverse events (AEs) during real-world usage of tofacitinib in inflammatory bowel diseases (IBD).
Methods: A multi-centre cohort was assembled across six tertiary IBD centres in the US. Data on demographics, IBD-specific variables, concomitant medications and AEs (including herpes zoster [HZ], hyperlipidaemia and leukopoenia) were collected. AEs were defined as serious AE if life-threatening, resulting in a hospitalisation, disability or discontinuation of therapy. Abnormal lipid profile was defined as total cholesterol 200 mg/dl, LDL 130 mg/dl, HDL <40 mg/dl or triglycerides 150 mg/dl.
Results: A total of 140 IBD patients were analysed, 125 with UC, 11 Crohn's disease (CD) and 4 IBD unclassified. Median age of the cohort was 36 years (interquartile range (IQR), 26–46) with a majority of males (77, 55%) and median follow-up 75.5 days (IQR, 49.8–124.5). A majority of patients (133, 95%) were initiated at 10 mg twice a day (bid) dose with 102 (72.9%) continuing therapy to date. Nineteen patients experienced an AE; of which, 8 (42.1%) were serious AE resulting in discontinuation of therapy: 5 with HZ, 2 with leukopoenia, and 1 with increased urinary frequency/incontinence. There were no significant differences in baseline characteristics between those with or without an AE (Table 1). Five patients (3.6%) initiated on 10 bid dose developed HZ at median age 30 years (range 16–47) and median time from initiation of Tofacitinib of 7 weeks (range, 5–24). Three of these patients were female while 2 each were African-American and Hispanic and 1 was Caucasian. Three of the 5 patients were on concomitant steroids and none had received Shingrix vaccine. The HZ was single-dermatome in 4 and multi-dermatome in 1 patient. One hundred and nine patients (77.9%) had baseline lipid levels checked with 73 (52.1%) having it repeated at Week 8. Nine out of 49 patients (18.4%) with previously normal lipids had abnormal lipids at 8 weeks of treatment at 10 mg twice a day (bid), 4 of whom were initiated on a statin. Other AEs reported include rash (1 patient) and joint pain (1 patient). Sixteen patients underwent surgery (4 CD, 12 UC) within 4 weeks of last dose of Tofacitinib. Five patients required readmission within 30 days of surgery (3 UC, 2 CD). Four patients (3 UC, 1 CD) had an infection within 30 days of surgery. No post-operative thrombotic complications or reoperations occurred within 30 days of surgery.
Conclusions: The safety profile of tofacitinib in IBD looks similar in real life to what has been observed in clinical trials. No new safety signal was detected.

Table 1. Comparison of baseline characteristics of patients with adverse events. *Missing data in 3; **missing data in 10; (a) Mann–Whitney test; (b) χ^2 test; (c) Fisher exact test)

Characteristic*	Adverse event, n = 19	No adverse event, n = 121	p-Value
Age at Tofacitinib initiation, mean (SD)*	44.6 (17.7)	36.2 (13.5)	0.075[a]
Male sex, n (%)*	10 (52.6)	66 (55.9)	0.79[b]
Caucasian race, n (%)	9 (47.4)	73 (61.9)	0.23[b]
Body mass index, mean (SD)**	27.7 (4.8)	26.2 (6.1)	0.21[a]
Tofacitinib induction dose at 10 mg bid, n (%)	19 (100)	114 (94.2)	0.59[c]

P408

Switching from infliximab originator to a biosimilar does not affect efficacy, pharmacokinetics and immunogenicity in paediatric patients with inflammatory bowel disease

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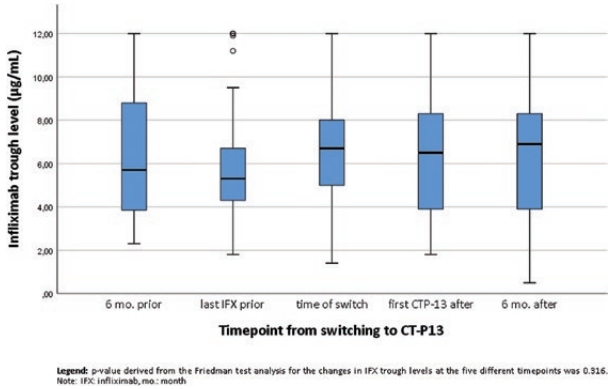
Background: Rising evidence reveals no differences in efficacy and safety between infliximab (IFX) originator and IFX biosimilar CT-P13 in inflammatory bowel diseases (IBD). However, most data are derived from adult patients and data on pharmacokinetics are limited. We evaluated long-term IFX trough levels (TL), immunogenicity and remission rates in children with IBD who switched from IFX originator to biosimilar CT-P13.
Methods: In this single-centre study, all children with Crohn's disease (CD) and ulcerative colitis (UC) receiving maintenance IFX therapy between July 2017 and January 2018 were included. The switch to CT-P13 was imposed by the hospital for all patients regardless of the indication as from January 2018. Demographics, disease activity indices, IFX TL and antibodies to IFX (using Ridascreen IFX Monitoring ELISA) were collected from 6 months before (baseline) till 6 months after switch. Clinical remission was defined as PUCAI/PCDAI <10 and biological remission as CRP ≤5 mg/l and ESR ≤20 mm/h. For paired comparison of data obtained at the different time points, a Wilcoxon signed-rank-sum test and a McNemar test were used for continuous and dichotomous variables, respectively. All data are presented as median [interquartile range]. Alpha was set at 0.05.
Results: A total of 47 children received maintenance therapy with the IFX originator at our centre. Forty-two children (26 CD and 16 UC), were eligible for the study as 3 patients were transferred to the adult department and 2 patients stopped IFX just before the switch (due to loss of response or delayed infusion reaction). Included patients had a median duration on IFX originator of 13.5 [6.8–35.5] months prior to switch. No significant changes in IFX TL occurred after switch (Figure 1). The median baseline IFX TL was 5.7 [3.8–9.3] µg/ml vs. 6.5 [3.9–8.6] µg/ml at month 6 after switch (p = 0.90). The cumulative IFX dose administered over a 6 month period was not significantly different before switch (36.6 [24.0–53.3] mg/kg) compared with after switch (35.8 [26.7–55.6] mg/kg; p = 0.21). Antibodies to IFX appeared in 1 patient after switch. The proportion of patients in clinical and/or biological remission did not significantly change after switch (all $p > 0.05$). No significant changes were observed in CRP, ESR, albumin or weight and BMI (expressed as z-score) after switch. No new safety signals were observed.
Conclusions: Paediatric IBD patients on IFX originator can be successfully switched during maintenance to CT-P13 without affecting efficacy, pharmacokinetics, immunogenicity and safety.



Boxplots showing the distribution of the maintenance IFX trough levels at the different time points before and after switching from the originator to the biosimilar CT-P13.

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Non-medical reverse switch between the originator infliximab and its biosimilar in patients with inflammatory bowel disease: clinical outcomes and therapeutic drug monitoring

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Background: Switching from the originator to a biosimilar infliximab (IFX) in patients with inflammatory bowel disease (IBD) has proven to be successful, although clinical evidence is lacking on reverse and/or multiple switching. The aim of the present study was to evaluate medium-term drug sustainability, safety and immunogenicity profile of reverse switching from a biosimilar to the originator IFX in a consecutive multi-centre real-life cohort.

Methods: We performed a prospective observational study of 174 consecutive patients with IBD (136 with Crohn's disease [CD] and 38 with ulcerative colitis [UC]) who were switched from the biosimilar infliximab CT-P13 to the originator Remicade during maintenance therapy. Previous exposure to the originator was 8% (n = 14). In September 2017, a non-medical reverse switch took place in all Hungarian patients from the biosimilar to the originator infliximab due to change in reimbursement policies. We collected clinical and biochemical information from patients at baseline (time of the switch) and 8, 16 and 24 weeks thereafter. Serum drug trough levels and anti-drug antibodies were measured at baseline and Week 16.

Results: Complicated disease behaviour and perianal manifestation was present in 39.7% and 48.5% of CD patients. 54.1% of UC patients had extensive colitis. Previous exposure to the originator was 8.0% (n = 14). There was no significant difference between the proportion of patients in clinical remission (based on Crohn's disease Activity Index <150 points or no fistula drainage; partial Mayo score <3) at Week 8 before switch, at switch/baseline and at Week 16 and 24 (CD: 82.6/80.6/77.5/76.3%, p = 0.60; UC: 82.9/81.6/83.7/84.8%, p = 0.98). In all IBD patients, mean serum IFX trough levels were 5.33 µg/ml (SD: 4.70) at baseline and 5.69 µg/ml (SD: 4.94) at week 16 (p = 0.71). No significant differences were observed in anti-drug antibody (ADA) formation either (overall ADA positivity: 16.2% vs. 16.9% at baseline/week16; p = 0.87). Four infusion reactions occurred up to Week 24 follow-up. There was no difference in clinical outcomes or TDM between patients with or without previous exposure to the originator.

Conclusions: This is the first real-life cohort on mandatory reversed switch from biosimilar to originator IFX in IBD patients. No significant changes were observed in trough levels or ADA status after the reversed switch in parallel with good medium-term drug sustainability. No new safety signals were detected.

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Extraintestinal manifestations and quality of life in patients with ulcerative colitis: 1-year data from ICONIC

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Background: In addition to their primary disease, ulcerative colitis (UC) patients may concomitantly suffer from extraintestinal manifestations (EIMs), increasing overall disease-related burden. Impact of EIM-augmented burden to patients is poorly understood. ICONIC is the largest ongoing, prospective, multicountry (n = 33) observational study assessing cumulative UC disease burden in patients receiving routine standard of care. Disease severity, activity, and life impact were captured at 6-month intervals through 2 years. This analysis assessed global and regional EIM-associated burden from 1 year of ICONIC.

Methods: Adults with early UC (diagnosed ≤36 months) were enrolled irrespective of disease severity or treatment. EIM presence and impact at baseline and over 1 year were assessed, focussing on health-related quality of life (HRQoL) measures: Short Inflammatory Bowel Disease Questionnaire (SIBDQ) and anxiety/depression (Patient Health Questionnaire-9 [PHQ9]). Patients were stratified by physician-assessed baseline disease severity (severe, moderate, mild, in remission). Regional differences in EIM burden and associated site services supporting EIM management were also evaluated. Observed data using descriptive statistics are presented; statistical comparison was performed using Fischer's exact test.

Results: Of 1794 patients with evaluable 1-year data, 14.1% (n = 253) presented with ≥1 EIM at baseline. At 1 year, 20.1% (n = 361) patients had EIMs, with 3.5% of patients (62/1794) presenting new-onset EIMs at 6 months and 2.6% (46/1794) at 1 year (42.7% increase from baseline to 1 year). Rheumatoid arthritis, ankylosing spondylitis, and erythema nodosum were the most common EIMs. Japan had the lowest overall EIM rate over 1 year (4.3%; 5/117); Western Europe/Canada had a 5.2-fold higher total EIM rate over the same period (22.2%; 184/830). Patients with moderate or severe baseline disease had a significantly higher total EIM rate over 1 year

(24.2% or 28.0%, respectively) vs. those with mild disease (14.8%) or in remission (16.1%) at baseline ($p < 0.0001$). For total study population or when stratified by region, patients with ≥1 EIM had higher PHQ9 and lower SIBDQ mean scores over 1 year vs. patients with no EIMs. Of 231 global sites, 134 (58%) had established multidisciplinary teams (MDTs) and 86 (37.2%) psychologist *in situ*.

Conclusions: New-onset EIMs are common in UC, even after 1 year disease course. EIM presence is associated with poorer HRQoL. Despite regional EIM differences, overall EIM impact on HRQoL was similar across the global study population. EIM-augmented patient burden is a concern in UC, and, with >40% sites lacking MDTs and >60% sites lacking *in situ* psychologists, awareness of EIM impact is essential.

P411

Using wearable devices to assess pain in inflammatory bowel disease

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Background: We previously reported that increased pain is associated with decreased health-related quality of life (HRQoL) in inflammatory bowel disease (IBD) patients (AIBD 2017). However, there have been few studies to predict or to manage pain in IBD patients, and no technologies validated to monitor pain, HRQoL, or disease activity. We combined passive biosensor data with patient-reported outcomes (PROs) in IBD patients to develop a predictive model of pain.

Methods: As part of a year-long prospective study on the use of biosensors in IBD, outpatients and inpatients with IBD were provided a Fitbit (Charge or Alta HR, San Francisco, CA) and a proprietary smartphone app (Litmus Health, Austin, TX) for data collection and completion of PROs. Daily steps, heart rate (HR), and sleep data were collected with the Fitbit device. Patients input daily information using the Wong-Baker (WB) FACES™ Pain Rating Scale, and visual analogue scale questions about their sleep quality and overall well being. Every 2 weeks they complete the previously validated questionnaires, the SIBDQ and the Pittsburgh Sleep Quality Index. WB scores range between 0 (no pain) to 5 (worst pain), with scores >2 categorised as "increased pain". Baseline disease activity status was recorded using the Harvey–Bradshaw Index or the Simple Clinical Colitis Activity Index (this is routinely performed in our clinic template). We performed logistic regression analysis to determine the association between WB score on a given day and the steps, median HR variability, resting HR, or number of night time awakenings that had occurred the prior day. The model was controlled for disease status, age, BMI, sex, days since study enrolment, and the previous days' WB score.

Results: 91 patients were enrolled (66 Crohn's disease, 25 ulcerative colitis). Median age was 39 years (range = 18–74), median length of disease was 12.5 years (range 0.25–37), median BMI was 25.8 (range = 18.0–51.5). Twenty patients had active disease upon enrolment. There was no association between median HR variability, steps, or number of awakenings and WB score the subsequent day (OR 9.7, $p = 0.685$; OR 0.89, $p = 0.51$; OR 1.05, p-value = 0.84 respectively). However, resting HR was significantly associated with reported pain the subsequent day (OR 1.05, $p = <0.001$). Each 1 bpm increase in daily resting HR increased the odds of experiencing pain on the subsequent day by 5%.

Conclusions: We demonstrate the feasibility of combined biosensor and PRO data in IBD patients and have identified a predictive association between increasing resting HR and subsequently reported pain. This is the first study to demonstrate the utility of wearable devices for IBD management and informs our ongoing work in this area.

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Efficacy and safety of additional autologous platelet-rich stroma in transanal mucosal advancement flap repair of complex cryptoglandular anal fistulas

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Background: Treatment of complex cryptoglandular fistulas is challenging and associated with high recurrence rates. Flap repair fails in almost one of every three patients, probably due to chronic inflammation in the remnants of the fistulous tract. Mucosal advancement flap and platelet rich plasma (PRP) combined with progenitor cells from autologous Stromal Vascular Fraction (SVF), obtained from liposuction, could suppress chronic inflammation and therefore improve success rates. We aimed to assess the feasibility, safety and efficacy of additional injection of autologous SVF combined with PRP (Platelet Rich Stroma; PRS) in flap repair of complex cryptoglandular fistulas.

Methods: All patients with complex cryptoglandular fistulas who underwent transanal advancement flap repair between December 2017 and October 2018 were included after informed consent. Inclusion criteria included complex fistulas with only one internal opening (or a second one very close by) and absence of pelvic sepsis. All patients underwent standardised transanal mucosal repair and standardised preparation of autologous PRS. A preoperative MRI and postoperative MRI following the diagnosis of 'clinical healing' (closure of the internal and external openings at physical examination) were performed.

Results: This pilot study includes 22 consecutive patients (12:10 male:female; median age 44.0 (IQR 33.6–55.0). Follow-up data of at least 4 months are available for 18 of these patients to date. All patients had one or more previous operations ranging from curating the fistula tract and leaving a seton in place to previous mucosal advancement (3/18) or ligation of the intersphincteric fistula tract (LIFT; 2/18). Clinical healing was reached in 16 out of 18 (89%) patients after a median postoperative follow-up of 6 months (IQR 5–7). Two of the 18 patients did not show clinical healing at their last consultation at 4 months follow-up. Of the available 14 MRIs to date (4 are pending), 13 showed complete closure of the fistula tract. Some patients experienced transient severe postoperative pain. One patient developed a haematoma due to liposuction. One patient experienced postoperative haemorrhage underneath the mucosal flap.

Conclusions: In 18 patients with cryptoglandular fistula treated with the addition of autologous SVF and PRP during transanal advancement flap repair, 93% (13/14) indeed showed a complete fibrosed fistula tract at MRI. The addition of autologous PRS appears to be feasible, safe, cheap and highly promising. Further research could focus on the effects of PRS on Crohn's fistula.

P413

A simple scoring tool predicts exposure–response relationship, onset of action, response to interval shortening, and surgical risk with vedolizumab therapy for Crohn's disease

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Background: We previously created and validated a clinical decision support tool (CDST) for predicting response to vedolizumab (VDZ) in Crohn's disease (CD). We now aim to further validate this tool in an additional CD cohort and assess its performance for predicting other health outcomes.
Methods: Using GEMINI II data, we explored correlations between VDZ exposure and onset of action across CDST-predicted probability of response groups (low, intermediate, high). The operating properties of the CDST for prediction of clinical remission and onset of action in the GETAID VDZ cohort were evaluated. In the GETAID and VICTORY cohorts, response to dose optimisation was assessed, and in the VICTORY cohort, we assessed the ability of the CDST to predict risk of surgery while on active therapy.
Results: A linear relationship was observed between CDST-predicted probability of response groups, VDZ exposure, onset of action, and efficacy in the GEMINI cohort for Week 2 through Week 52 ($p < 0.001$). In the GETAID cohort, the CDST predicted clinical remission at Week 14 (AUC 0.68), and a significant difference in speed of onset of action was observed between low- and intermediate–high-probability groups ($p = 0.04$). In both the GETAID and VICTORY cohorts, only patients in the low-probability group significantly benefited from shortening of VDZ intervals to Q4 weeks for non-response. In the GETAID cohort, a single infusion at Week 10 for patients in the low-probability group overcame differences in speed of onset of action seen between this group and the intermediate–high-probability group. In the VICTORY cohort, the CDST predicted a 2-fold increase in risk for surgery over 12 months of VDZ therapy among low–intermediate-probability patients compared with high-probability patients (HR 2.06, 95% CI 1.33–3.21).
Conclusions: The CD VDZ CDST demonstrated good performance during external validation in the GETAID cohort. This tool was able to prognosticate VDZ exposure-efficacy relationships and speed of onset of action, identify patients who would most benefit from interval shortening for lack of response, and stratify patients at greatest risk for surgery while on active therapy.

P414

Ustekinumab endoscopic response at Week 16 is associated with early normalisation of faecal calprotectin after induction

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Background: Ustekinumab (UST) induction therapy may result in rapid symptom improvement in Crohn's disease (CD) patients. However, the onset of faecal calprotectin (FC) and endoscopic response during the induction phase is largely unknown. We aimed to assess the onset of effect of UST during the induction phase, based on FC and endoscopy.
Methods: In this single-centre prospective study, patients who were started on UST and had endoscopic inflammation with FC>100 µg/g were included. FC was determined at baseline, Week 2, 4, 8 and 16. Endoscopy was performed at baseline and at Week 16. Endoscopic response was defined as SES-CD reduction ≥50% or Rutgeerts score reduction ≥1. At Week 16 endoscopy, ileum and segmental colon biopsies were collected for histological assessment. Histological severity was scored on a 4-point scale based on pathology reports. Median FC levels at the FU time points and the relative change in FC between baseline and Week 16 were assessed with Wilcoxon Rank-sum test. ROC statistics were used to determine the best FC cut-off and to assess the predictive value.
Results: A total of 38 patients (42% males, median age 39 (28–55) years (IQR)) were included. Thirty-eight/38 patients (100%) received previous anti-TNF therapy, of whom 96% anti-TNF were refractory. In 24/38 patients (63%) UST was combined with corticosteroid induction and completely tapered at Week 16 in 16/24 (67%) patients. Data on histology were available in 23/38 patients. Endoscopic response was observed in 9/38 (24%) and endoscopic remission in 5/38 (13%). Histological remission was observed in 9/23 (39%) patients. Median FC level (µg/g) was 595 at baseline, 488 at Week 2, 447 at Week 4, 401 at Week 8 and 943 at Week 16. Median FC levels at Week 8 ($p = 0.012$) and 16 ($p = 0.020$) were significantly lower in patients with endoscopic response (vs. non-responders), see Figure 1. Although not statistically significant, we observed a steep decrease in FC levels from baseline to Week 2 in patients with endoscopic response. For patients with histological

remission, no statistical difference in FC was observed. A FC cut-off value of 250 µg/g at Week 8 predicted endoscopic response (AUC=0.75) sensitivity 54%, specificity 82%, PPV 64% and NPV 75%. At Week 16 (AUC=0.77) sensitivity 46%, specificity 95%, PPV 86% and NPV 73%.

Conclusions: Ustekinumab induces as early as Week 2 a steep decrease of FC levels in Crohn's disease patients with endoscopic response at Week 16. Reliable prediction of endoscopic response trough early serial FC measurements remains challenging in this cohort.

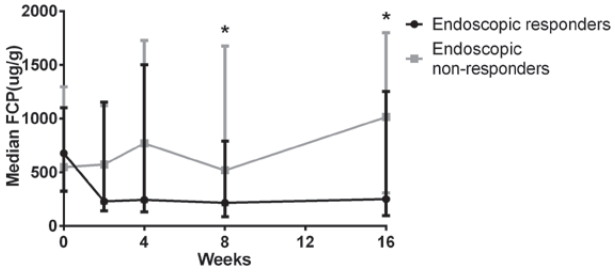

Figure 1. Serial FC measurements in CD patients after the start of ustekinumab.

Median FCP levels (in µg/g) in endoscopic responders: 678 at baseline, 230 at Week 2, 244 at Week 4, 181 at Week 8 and 251 at Week 16. In endoscopic non-responders: 595 (p = 0.69), 643 (p = 0.15), 830 (p = 0.18), 596 (p = 0.012) and 1156 (p = 0.02).

P415

Predictive factors of a subsequent ano-perineal abscess in patients with fistulising ano-perineal Crohn's disease in remission

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Background: Fistulising ano-perineal (FAP) lesions occur in more than 20% of patients with Crohn's disease (CD). Despite advanced surgery techniques and anti-tumour necrosis factor (anti-TNF) agents use, relapse rate of FAP-CD remains 30%. The objective of the present study was to identify predictors of a subsequent ano-perineal abscess in patients with FAP-CD in remission.

Methods: We conducted a retrospective study including all consecutive FAP-CD patients achieving clinical ano-perineal remission between 2007 and 2015 in one referral centre. Remission was defined by the absence of any draining fistula or abscess within 3 months after the last drainage surgery. Patient characteristics were collected at drainage, at 3 months – corresponding to the inclusion date - and during follow-up. Primary outcome was the occurrence of a subsequent ano-perineal abscess related to FAP-CD and confirmed by examination under anaesthesia and/or MRI. Predictive factors of subsequent abscess were determined in anti-TNF naïve and anti-TNF treated populations.

Results: One hundred and thirty-seven patients (57% female, median age 35 years) corresponding to 157 abscesses [120 (76.4%) treated by anti-TNF at inclusion] were included. Patients not treated by anti-TNF at inclusion were significantly older (40 years vs. 34 years, p = 0.005) and had more often simple fistulas [10 (29%) vs. 66 (58%), p = 0.004]. During the follow-up period [median duration of 43 (IQR 26–63) months], 35 (22%) experienced a subsequent abscess, which occurred within a median time of 1.8 years. Survival without abscess was 96.7% at 1 year, 78.4% at 3 years and 74.4% at 5 years. In the subgroup of 120 patients treated with anti-TNF agents (84 infliximab and 36 adalimumab) at inclusion, ileo-colonic (OR 5.19, p = 0.017) location, stricturing phenotype (OR 5.32, p = 0.013) and discontinuation of anti-TNF therapy during the follow-up period (OR 3.37, p = 0.049) were associated with a subsequent abscess in multi-variate analysis. Conversely, discontinuation of immunosuppressive therapy was associated with a reduced risk of a new abscess (OR 0.22, p = 0.29). Neither the type of anti-TNF agent nor combotherapy use were associated to FAP-CD relapse.

Conclusions: In CD patients with fistulising ano-perineal disease achieving remission, survival without subsequent abscess was approximately 75% at 5 years. Colonic disease location, stricturing phenotype and discontinuation of anti-TNF therapy were associated with a higher risk of new abscess.

P416

Faecal calprotectin can predict mucosal healing in patients with inflammatory bowel diseases treated with vedolizumab: a prospective single-centre study

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Background: Vedolizumab (VDZ) is currently a good therapeutic option for ulcerative colitis (UC) and Crohn's disease (CD); nevertheless, according to real-life studies, despite a good effectiveness in terms of clinical response, only 40% of patients achieve Clinical Remission (CR), and even less Mucosal Healing (MH). There is little knowledge about early markers of therapeutic response, especially of MH.

Methods: A prospective observational study was carried out among patients with moderate-to severe UC and CD who started VDZ between June 2016 and June 2017. Primary non responder were excluded. Partial Mayo Score (PMS) for UC and Harvey–Bradshaw Index (HBI) for CD, C-Reactive Protein (CRP) and faecal calprotectin (FC) were assessed before treatment, at Week 6 and every 8 weeks during the follow-up. All the patients underwent colonoscopy at baseline and at Week 54 or in case of discontinuation of therapy due to loss of response (LOR). We defined as MH a Mayo Endoscopic Score ≤ 1 for UC, and the absence of ulcerations for CD. All the colonoscopies were performed by a single blinded operator. Clinical remission (PMS<2 or HBI<5), a normal CRP value (<0.5 mg/dl), and the values of FC were evaluated as potential predictors of MH and CR at Week 54. Statistical analysis was carried out using ROC curves and Fisher's test as appropriate.

Results: We enrolled 45 patients (31 UC and 14 CD). Thirteen (29%) patients (10 UC and 3 CD) experienced LOR. MH was reached in 18 patients (40%)—14 UC and 4 CD—whereas CR in 26 (58%)—17 UC and 9 CD. FC at Week 6 correlated with MH, and ROC curve analysis identified an AUC of 0.822 with a sensitivity of 82% and

a specificity of 83% at the cut-off of 180.5 µg/g ($p < 0.001$). The same results were observed for CR, where ROC curve identified an AUC of 0.739 with a sensitivity of 84% and a specificity of 69% at the cut-off of 195.5 µg/g ($p < 0.01$). CR and CRP values at Week 6 showed no correlation with MH or CR at Week 54.

Conclusions: Our results showed that an early drop of FC levels is a good predictor of MH and CR at 1 year in UC and CD patients treated with VDZ. FC assessment could represent a promising early marker of response to therapy, especially considering the slow onset of action of VDZ.

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10 years of endoscopic therapy of symptomatic Crohn's disease stenoses: a retrospective analysis of long-term results

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Background: Endoscopic dilation of stenoses in patients with Crohn's disease provides a less invasive way to avoid or reduce the number of bowel resections and, thereby, improve the quality of life. To the best our knowledge, only few studies with small patient numbers are available on long-term results.

Methods: Patients with Crohn's Disease above the age of 18, who underwent endoscopic therapy of gastrointestinal symptomatic stenoses in our hospital from January 2008 to May 2018, were enrolled in the study. The therapy was defined as clinically successful if endoscopic re-treatment was not required within 30 days.

Results: We performed 562 endoscopic interventions in 163 patients (n = 82 women/n = 81 men, mean age = 46 years, mean disease duration until first endoscopic therapy = 18 years) with a mean of 3.4 interventions per patient (range 1–76). In 75 patients (46%) only one endoscopic treatment was performed; 88 patients received a total of 399 re-endoscopies (mean 4.5 per patient). Follow-up information was available for 136 of 163 patients (83.4%) with an average period of 36 months (range 2–3567 days). Dilation procedures were performed in the ileocaecal region (230 in 104 patients), in the colon (126 in 36 patients), oesophagus (108 in 2 patients), upper small intestine (83 in 15 patients), lower small intestine (11 in 5 patients) or stomach (4 in 1 patient). We treated 95 patients with anastomotic stenoses (58.3%) and 68 with non-anastomotic stenoses (41.7%). Therapeutic methods included 556 hydrostatic balloon dilations (n = 386 Through-The-Scope balloon dilations (TTS), n = 170 TTS + over-the-wire dilations), five bougienage dilations and in one case the insertion of a covered metal stent. The dilation was performed to an average width of 14.3 mm (range 7 to 20 mm); clinical success was documented in 440/562 procedures (78.3%). We observed complications in 11 cases (1.9% of all endoscopies), resulting in bleeding (n = 6), infection (n = 1) or perforation (n = 4) which lead to an extension of hospital stay (n = 8), antibiotic therapy (n = 1) or surgery (n = 2). Irrespective of complications, 48 out of 163 patients (29.4%) had to undergo surgical resection of the stenosis until the end of the study period.

Conclusions: Endoscopic therapy of symptomatic stenoses in Crohn's Disease is safe and effective, with complications occurring in only 1.9% of all endoscopic procedures. Repeated dilation is effective and only 29.4% of patients had to undergo surgical resection of the stenosis in the further course of disease.

P418

Safety and efficacy of olorinab, a peripherally restricted, highly-selective, cannabinoid receptor 2 agonist in a phase 2A study in chronic abdominal pain associated with Crohn's disease

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Background: Patients with Crohn's disease (CD) often experience abdominal pain despite effective control of inflammation, contributing to opioid and cannabis use. Visceral pain may be modulated by cannabinoid receptors CB1 and CB2, but clinical development of non-selective agonists has been limited by unwanted psychotropic effects from CB1 agonism. Olorinab (APD371) is a peripherally restricted, highly-selective agonist of the CB2 receptor. Olorinab was generally well tolerated without psychotropic effects in healthy volunteers. This study evaluated the effects of olorinab in CD patients with minimal inflammation experiencing abdominal pain.

Methods: This randomised, open-label, parallel group, multi-centre Phase 2a study enrolled subjects aged 18–66 years diagnosed with quiescent CD (simple endoscopic score-CD <10 or faecal calprotectin <500 µg/g) experiencing abdominal pain, defined as weekly average abdominal pain score (AAPS; daily pain scores averaged over 1 week) ≥4 on a scale of 0 (no pain) to 10 (worst possible). Subjects were randomly assigned 1:1 to receive 25 or 100 mg oral olorinab 3 times a day (TID) for up to 8 weeks. The primary objectives were safety and tolerability. Efficacy endpoints included change in AAPS from baseline week (BL) to Weeks 4 and 8, change in AAPS from pre-dose to 1.5 h post-dose, and proportion of subjects who were clinical responders (≥30% reduction in weekly AAPS from BL).

Results: In all, 14 subjects (57% female, 86% white, mean age of 36 years, 12 on active treatment for CD) were randomised with a mean BL AAPS of 5.6. Eleven subjects with mean BL AAPS of 6.0 provided Week 8 AAPS data. Adverse events (AEs) were generally mild-to-moderate and limited in duration and were reported in 67% (4/6) of subjects who received 25 mg TID and in 75% (6/8) of subjects who received 100 mg TID. No subjects discontinued because of AEs. AEs in ≥2 subjects included drug hypersensitivity, pain in extremity, and hypomagnesaemia. The only 2 serious AEs (pneumonia, worsening interstitial pneumonia) occurred in the same subject and were not considered treatment-related. No clinically significant changes in vital signs or clinical safety lab results were observed. The AAPS was significantly improved from BL at Weeks 4 and 8. Change in AAPS from BL to the time of peak concentration (1.5 h post-dose) during Week 8 was –4.6 on an 11 point scale (n = 11; $p < 0.001$). Clinical response in AAPS (≥30% reduction) was seen in 85% (11/13) of subjects with evaluable data at Week 4 and 100% (11/11) at Week 8.

Conclusions: Results from this open-label olorinab study provide evidence for an improvement in AAPS without psychotropic effects in subjects with quiescent CD experiencing abdominal pain.

P419

Outcomes for patients with severe acute ulcerative colitis

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Background: Acute severe ulcerative colitis (ASUC) usually requires hospitalisation, immediate management and is considered a medical emergency. Historically, the management of ASUC has been with intravenous steroids followed by colectomy in unresponsive patients. Management of ASUC has since evolved with the introduction of rescue therapy as second-line treatment such as cyclosporine and infliximab. Surgical therapy is usually considered if there is no response to medical therapy. The aim of this study was to evaluate the impact of second-line medical therapies and assess whether these had improved patient outcomes.
Methods: We assessed patients admitted to a single-centre with acute ulcerative colitis between November 2011 and October 2016. All patients received intravenous steroids as the first-line medical therapy. Patients with previous colectomy or other variants of UC were excluded. Data were collected retrospectively from electronic patient records. Data included demographics, medical and surgical management prior to, during and after admission. Treatment response was defined as discharge from hospital with no further acute medical or surgical treatment. Clinical findings for the first 10 days on admission, such as radiological, haematological and biochemical test results, were collected. Statistical analysis of data included comparisons with χ^2 and Fisher exact test.
Results: In total, 362 patients were analysed, the youngest being 3 years old and the oldest 88. A total of 151 of these patients were newly diagnosed with UC. One patient died during admission before receiving second-line treatment. Over the 5-year period, 106 patients received second-line treatment of which 86 received cyclosporine and 20 received biologics. Amongst this group, 65 responded to treatment. Use of biologics did not change over the 5 years, averaging at 4 patients per year. In the first year, 5.1% of patients required colectomy after second-line treatment. This became 4.1%, 1.2%, 1.5% and 4.9% in subsequent years, observing a trend towards improvement. It was observed that some patients were not suitable for second-line treatment and proceeded directly to surgery (3.0%).
Conclusions: There seems to be a downward trend of colectomy rates in patients who have received second-line treatment. There was no increase in use of biologics but this may be seen in data from more recent years. Further evaluation on a longer time scale and a larger sample size may provide more information on the evolution of management strategies.

P420

Correlation between Infliximab trough levels and endoscopic activity in ulcerative colitis

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Background: Mucosal healing (MH) is currently the main treatment goal in patients with inflammatory bowel disease. Although there is growing evidence supporting the use of therapeutic drug monitoring (TDM) in patients upon loss of response, data correlating TDM and specific treatment target is still lacking. We aimed to assess the correlation between Infliximab (IFX) trough levels and MH in ulcerative colitis (UC).
Methods: Retrospective cohort study including patients with UC under treatment with IFX and at least 1 colonoscopy performed within a 2.6 ± 1.8-month interval of an IFX pharmacokinetic measurement. MH was defined as a Mayo Endoscopic subscore (MES) ≤1. IFX trough levels and antibodies were measured using a drug-sensitive assay (Theradiag®).
Results: Seventy-four pairings of colonoscopy-IFX trough levels were available corresponding to 56 patients (53.6% male with a median age of 36 (range 17–72); 57.1% of the patients were under concomitant immunomodulator therapy. MH was present in 51.4%. Median IFX trough levels were 3.75 (range 0.3–16 µg/ml) and anti-drug antibodies were present in 16.2%. Higher median IFX trough levels were significantly associated with lower endoscopic activity (MES 0–6.2 µg/ml (range 3.6–16); MES 1–7.35 µg/ml (range 3–16); MES 2–2.5 µg/ml (range 2–10) and MES 3–2.2 µg/ml (range 0.3–5.7), $p < 0.001$). Median IFX trough levels were significantly higher in patients with MH than without MH (6.5 µg/ml (3–16) vs 2.4 µg/ml (0.3–10), $p < 0.001$). The area under the curve of IFX to predict MH was 0.95 (95% CI 0.894–1.0, $p < 0.001$). A trough level of IFX ≥3.15 µg/ml presented high sensitivity (97.4%, 95% CI: 80.7–99.0) and high specificity (86.1%, 95% CI: 74.2–97.5) for MH. In multivariate regression analysis, only IFX trough level above the cut-off value was an independent predictor for MH ($p < 0.001$).
Conclusions: Higher IFX trough levels are significantly associated with MH in UC. IFX trough levels ≥ 3.15 µg/ml are required to achieve MH.

P421

Effects of combination therapy in inflammatory bowel disease: how long should we keep concomitant immunomodulators?

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Background: Combination therapy (CT) in inflammatory bowel disease (IBD) is considered to be superior to monotherapy. Reduction of biological immunogenicity is believed to be an advantage, especially in the first 6 months. Nonetheless CT may increase the risk of neoplasia and infection. The aim of this study was to evaluate the benefits of CT beyond 6 months.
Methods: Retrospective cohort-study, which included all IBD patients who underwent treatment with anti-TNF between 2003–2017 in our unit. Inclusion criteria: IBD patients submitted to CT (anti-TNF+immunomodulator) for at least 3 months. Patients who lost follow-up were excluded. Patients were divided in 2 groups, based on CT duration (≤6 months and >6 months). The main outcomes include time to biologic treatment failure (defined as need to dose increase, switch biologic or surgery) and immunomodulator-related adverse events. Long-term clinical remission (CR) as well as deep remission (DR) were the secondary outcomes. DR was defined

as CR (as described in medical records), endoscopic remission (absence of ulcers and erosions in endoscopy) and in ileal Crohn's disease as absence of radiologic activity.

Results: 136 patients were included, 90 of which underwent CT. Most patients had Crohn's disease (90%). Mean age was 38.3 years (SD 12.5) and 56% were females (n = 50). Median duration of combined therapy was 12-months (IQR 6), and most patients maintained combination therapy after 6-months (84.4%, n = 76). Adverse reactions were attributed to immunomodulator in 7.8% (n = 7), most of them (71.4%, n = 5) in the first 6-months of treatment. There was not a significant association between biologic treatment failure and duration of CT (p = 0.396). Time to relapse was not correlated to the duration of CT (p = 0.451). There was also no association between CT duration and need to escalate to a second (p = 0.352) or third biologic (p = 0.419). Longer CT was also not significantly associated with long-term clinical remission (p = 0.804) nor deep remission (p = 0.329).

Conclusions: There was no additional benefit in maintaining combination therapy beyond 6 months. Considering the long-time risks, namely infections and neoplasia, it is reasonable to consider that combined therapy for 6-months may be as effective as concomitant therapy for longer periods.

P422

Immunogenicity of a proposed adalimumab biosimilar, FKB327, and the reference product in patients with rheumatoid arthritis

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Background: The FKB327-002 double-blind (DB) study to compare the efficacy and safety of a candidate adalimumab biosimilar, FKB327, and the reference product (RP) in patients with rheumatoid arthritis also being treated with methotrexate (MTX)—the ARABESC trial—was presented previously. The FKB327-003 study, also known as the ARABESC-OLE trial, was a Phase 3 open-label extension (OLE) study to compare the long-term safety, efficacy, immunogenicity, and pharmacokinetics of FKB327 and RP. The immunogenicity of RP and FKB327 was examined across studies.

Methods: In the DB study, patients were randomised 1:1 to receive FKB327 or RP (40 mg subcutaneously) every other week for 24 weeks, with continuing MTX. In the OLE study, patients completing the DB study with clinical response and no safety concerns were immediately re-randomised to FKB327 or RP, so that two-thirds of patients remained on the same treatment as in the DB study and one-third switched to the alternate treatment for weeks 0 through 28 (Part 1), then all received FKB327 through Week 78 (Part 2). A total of 645 patients (FKB327, n = 324; RP, n = 321) who entered the OLE study were evaluated for immunogenicity during continuous treatment and across switching sequences in the studies. Immunogenicity was assessed by evaluation of antidrug antibodies (ADAs; proportion of patients ADA-positive, ADA-titre, and neutralising ADAs) using validated, high-sensitivity electrochemiluminescence assay and competitive ligand-binding assay. The impact of ADAs on efficacy and safety was also evaluated.

Results: The proportion of patients with positive ADA status was highest prior to dosing at week 0 in the OLE study, at 61.7% and 60.0% for FKB327 and RP, respectively. The proportion of patients with positive ADA status did not increase over time to Week 30 (the end of Part 1) and was similar for FKB327 and RP at all time points. The majority of ADAs were neutralising. At Week 78, the proportion of patients with positive ADA status was lower in all treatment sequences, at 51.1%, 54.4%, 48.1%, and 42.5% for the FKB327–FKB327–FKB327, FKB327–RP–FKB327, RP–FKB327–FKB327, and RP–RP– FKB327 treatment sequences, respectively. The scale of negative impact of ADA on efficacy was higher in the ADA high-titre category in FKB327 and RP to a similar degree. Incidence of hypersensitivity and injection-site reactions was low in both FKB327 and RP, with no apparent relationship to ADA-titre category.

Conclusions: The RP and FKB327 showed comparable immunogenicity in long-term administration. Treatment switching from RP to FKB327 or vice versa did not influence either immunogenicity or sustainability of efficacy or safety.

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Comparative efficacy of anti-tumour necrosis factor agents and vedolizumab in ulcerative colitis

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Background: Anti-tumour necrosis factor (TNF) agents and vedolizumab are used to treat UC but response is variable and there are little data on comparative efficacy of these agents. Apart from prior exposure to anti-TNF agents and concurrent immunomodulatory therapy, predictors of clinical response and remission to biologics have not been identified. We aimed to (i) compare the efficacy of anti-TNF agents and vedolizumab as induction and maintenance therapy in UC and (ii) investigate the utility of routinely used clinical and biochemical parameters in predicting clinical response and remission to biologics.

Methods: Patients who were commenced on any biological agent for ambulant UC were included in this single-centre cohort study. Disease activity was monitored serially by calculation of Simple Clinical Colitis Activity Index (SCCAI) for up to 12 months. Faecal calprotectin (FC) at baseline and subsequent visits were recorded if available. Clinical response was defined as decrease in SCCAI ≥3 and remission by SCCAI ≥2. We compared the efficacy of anti-TNF agents and vedolizumab for induction and maintenance of response on an intention-to-treat basis. We also examined the utility of FC and early normalisation of FC to predict response and remission at 6 and 12 months.

Results: Ninety-seven patients commencing anti-TNF and 42 commencing vedolizumab therapy were included. Vedolizumab-treated patients had greater rate of prior anti-TNF therapy (69% vs. 11.3%, $p = 0.001$) and a lower baseline FC (median 577µg/g, IQR 72–210 vs. 955µg/g, IQR 116–2100 vs. $p = 0.005$). Clinical response, remission and steroid-free remission rates were broadly comparable between anti-TNF and vedolizumab-treated patients at 6 weeks, 6 and 12 months. Clinical remission at 12 months was higher in the vedolizumab group (51.4% vs. 27.8%, 27.8%, difference 95% CI 4.8–42.4) but no difference was noted in steroid-free remission at 12 months. There was a significant weekly reduction in SCCAI for vedolizumab (–0.06, 95% CI –0.09 to –0.04, $p < 0.001$) and anti-TNF agents (–0.06, 95% CI –0.07 to –0.04, $p < 0.001$). Similarly, the weekly calprotectin dropped significantly for vedolizumab (–7.64 µg/g, 95% CI –12.82 to –2.45, $p = 0.004$) and anti-TNF agents (–17.43 µg/g, 95% CI –23.79 to –11.08, $p < 0.001$). The colectomy rate (9.5% vedolizumab, 4.1% anti-TNF) and treatment persistence rate at 12 months (73% vedolizumab, 71% anti-TNF) were comparable between the two groups. None of the clinical and biochemical variables including baseline and early normalisation of FC predicted remission at 6 and 12 months.

Conclusions: In a single-centre series of biologic-treated UC patients, the efficacy of anti-TNF and vedolizumab appear comparable. We could not identify any predictors of response and remission.

P424

Is the switch to a second thiopurine a safe strategy in elderly patients with inflammatory bowel disease? A multi-centre cohort study of the ENEIDA registry

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Background: Thiopurines are the most commonly used immunosuppressants in inflammatory bowel disease (IBD), but their main limitation is the high rate of drug-related adverse events (AE) and treatment discontinuation. Switching to a second thiopurine may be an alternative in these cases, but series published up to now, include a limited number of patients. In a previous study, we demonstrated that starting thiopurines in elderly age is associated with a higher incidence of AE. Our aim was to evaluate the tolerance of switch to a second thiopurine as well as the persistence of treatment and the factors associated with it.

Methods: Based on the ENEIDA registry (a large, prospectively maintained database of the Spanish Working Group in IBD—GETECCU), adult IBD patients that switch to a second thiopurine due to AE were identified. Two cohorts were selected regarding the age at the beginning of thiopurine treatment: between 18 and 50 years, and over 60 years. The rate and concordance of AE that occurred with the second thiopurine, treatment discontinuation due to AE and the overall persistence of the second thiopurine were evaluated.

Results: Of the 17371 patients who started a first thiopurine in these two cohorts, 3903 patients discontinued thiopurine treatment due to AE. In 1278 of them (32%) a switch to a second thiopurine was performed (93% to mercaptopurine, 7% to azathioprine), 1105 patients below 50 years of age and 173 over 60 years. The AE of the first thiopurine were: digestive intolerance 60%, hepatotoxicity 13%, myelotoxicity 6%, acute pancreatitis 2%, other 19%. The rate of post-switch AEs was 58%, leading to the discontinuation due to AE of the second-thiopurine in 46% of cases. In those patients who presented post-switch AE, the most likely AE was the same that occurred with the first thiopurine, particularly digestive intolerance (61%). The cumulative probability of post-switch treatment discontinuation due to AE was 40%, 43%, 47%, and 50% at 6 months, 1–3–5 years, respectively. The persistence of post-switch treatment was 44%, 40%, and 34% at 1–3–5 years, respectively. The multi-variate analysis showed that the only independent risk factors of treatment discontinuation due to AE were the switch over 60 years (53% vs. 45%, OR 1.5, 95% CI 1.1–2.1), having developed

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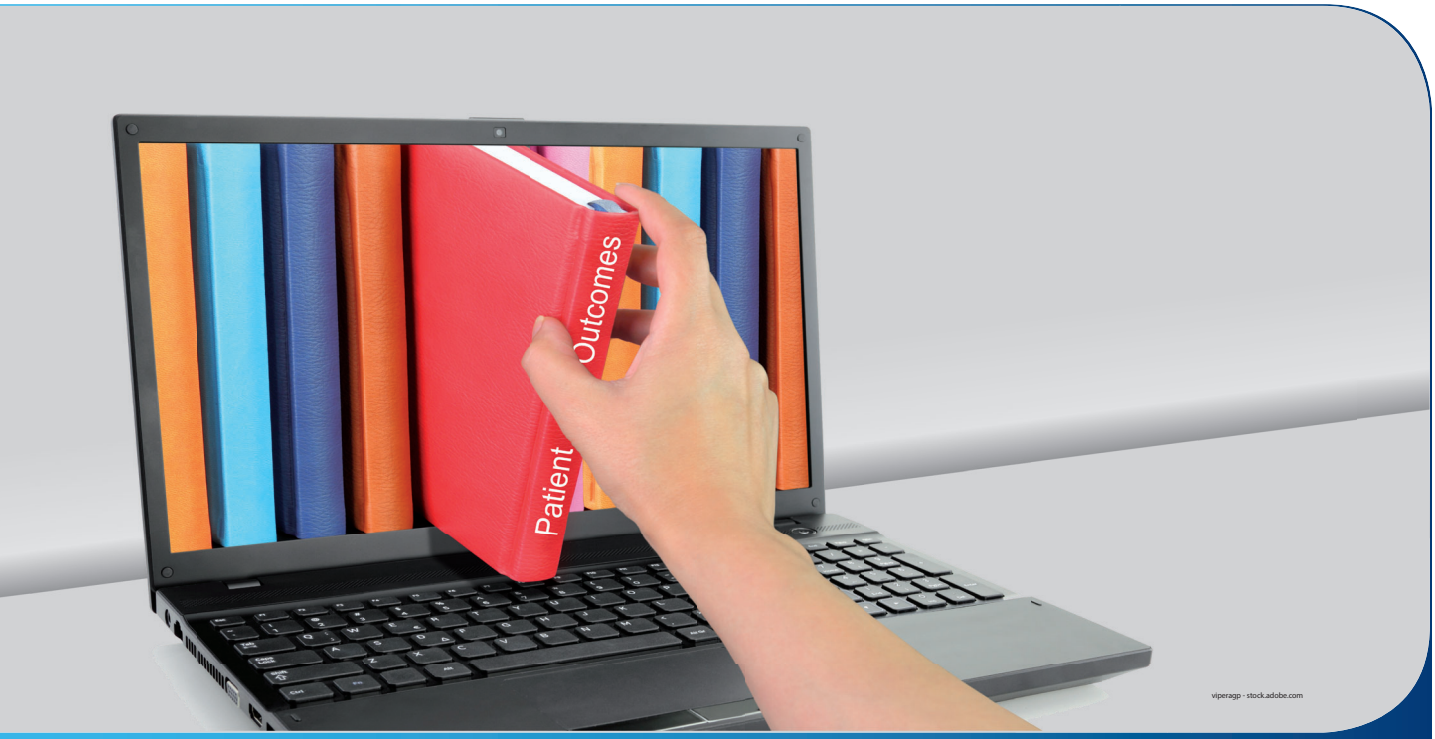

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digestive intolerance (48% vs. 41%, OR 1.4, 95% CI 1.1–1.8) or pancreatitis (83% vs. 45%, OR 6.8, 95% CI 2.6–18.2) with the first thiopurine.
Conclusions: In the largest series reported to date, we observed that switch to a second thiopurine is a valid strategy except in the case of pancreatitis. Close monitoring is advisable among elderly IBD patients switching to a second thiopurines because of AEs.

P425
Development of an enzyme-linked immunosorbent assay for therapeutic drug monitoring of ustekinumab

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Background: Ustekinumab is a monoclonal therapeutic anti-interleukin-12 and anti-interleukin-23 antibody approved for use in moderate to severe Crohn's disease (CD). Analysis of data from the Phase 3 induction trials, UNITI-1 and UNITI-2, demonstrated a significant exposure–response relationship of ustekinumab in CD. Interindividual differences in response to ustekinumab treatment may be explained in part by interindividual variability in pharmacokinetics. The aim of this work was to develop and validate an enzyme-linked immunosorbent assay (ELISA) to measure ustekinumab drug concentrations.
Methods: Samples diluted at 1:200 were added to microtiter plates coated with recombinant human antibodies against ustekinumab for binding. Mouse anti-human immunoglobulin G1 (HRP-anti h IgG1) was used to detect bound ustekinumab. Assay performance characteristics were determined according to the European in vitro diagnostic devices directive 98/79/EC.
Results: Both in serum and plasma, the method has been demonstrated to be linear from 1.10 to 37.35 ng/ml, showing a non-linear behaviour of less than ±20% in this interval. The limit of quantification (LoQ) for ustekinumab measurement in human serum samples was 0.953 ng/ml. Intra-assay variation (repeatability) was ≤9.5% (n = 23), while inter-assay variation (reproducibility) was ≤9.1% (n = 20). Linearity testing was performed by analysing three serially diluted samples spiked with ustekinumab; ustekinumab concentrations measured by the new assay were within 97%–117% of the expected concentrations. The assay detected no false-positive signals from the samples of untreated patients. The specificity of the antibody was tested by measuring the cross-reactivity against a range of compounds with structural similarity to ustekinumab. There was no cross-reactivity observed.
Conclusions: This newly developed ELISA offers a fast and accurate test with reproducible results. The specificity of the assay could be improved by the use of monoclonal antibodies to ustekinumab. This ELISA has potential utility in therapeutic drug monitoring of patients receiving ustekinumab, and additionally in pharmacokinetic/pharmacodynamic studies of the drug.

P426
Lympocytosis in patients with inflammatory bowel disease treated with anti-TNFa agents: is it significant?

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Background: True lymphocytosis has been sporadically reported to occur in rheumatology patients treated with anti-TNFa agents. Although it is generally considered as a benign, reactive and reversible phenomenon there is concern of a possible association with malignant lymphoproliferative disorders. Anti-TNFa-based immunosuppressive therapy has been implicated as a causal agent in patients with autoimmune diseases. Higher doses and combination with azathioprine in patients with inflammatory bowel diseases compared with other rheumatology patients could impact lymphocyte expansion more profoundly.
Methods: We evaluated peripheral blood lymphocyte levels in all IBD patients who initiated anti-TNF therapy in the outpatient IBD clinic during the last 3 years, with no evidence of lymphocytosis for at least 3 months prior to initiation of therapy. Lymphocytosis was defined as a lymphocyte count greater than 4000 per microlitre. In patients with lympocytosis peripheral blood T, B, and NK lymphocyte subpopulations were analysed using flow cytometry and lymphocyte levels were followed up for at least 6 months. We investigated possible associations with disease and patient characteristics, treatment, outcome and safety.
Results: We included a total of 62 patients: mean age 38.4 years, 30 males, 47 with Crohn's disease, 15 with ulcerative colitis, 27 on Infliximab, 35 on adalimumab, 2 on golimumab, 14 on combination with azathioprine. Lymphocytosis was observed in 16 patients (26.8%). Lymphocytosis significantly correlated with administration of infliximab: OR 5.02 (95% CI 1.2–17), p = 0.01, and combination therapy with azathioprine: OR 4.3 (95% CI 1.2–15.4), p = 0.024. Patients with lymphocytosis showed better treatment response: 15/16 (93.7%) vs. 28/46 (60.8%), p = 0.014. No difference in serious adverse events (infections, malignancies) was observed over a mean follow-up duration of 27.31 (22.2–32.3) months. Treatment interruptions and de-escalations led to disappearance and lesser degrees of lymphocytosis, respectively.
Conclusions: Lymphocytosis was observed in one-fourth of our cohort of IBD patients commenced on anti TNF-therapy. It was polyclonal, reversible, and dose related. It correlated with administration of infliximab and combination therapy with azathioprine. Patients with lymphocytosis were more likely to respond to therapy. Short-term safety was similar but long-term clinical significance remains unknown and should be further studied.

P427
Impact of curcuma longa on clinical activity and inflammatory markers in patients with active ulcerative colitis: a double-blind randomised placebo-controlled trial

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Background: Curcumin, biologically active substance of *Curcuma longa* (CL), has been shown to reduce disease activity in patients with ulcerative colitis (UC). However, role of natural CL in patients with active UC is not known. We conducted study to know the effect of CL in reducing clinical activity and inflammatory markers in patients with active UC.
Methods: The study was a single-centre, double-blind, randomised, placebo-controlled trial in which patients with active UC (UCDAI

≥3) were enrolled. The two arms of the study were mesalamine 2.4 g/day with powder of Curcuma longa 10 g/day (n = 28) (CL group) or with placebo (n = 25) (PL group) for 8 weeks. Primary outcome was clinical improvement at Week 8 as defined by decrease in UCDAI score by ≥3 points. Secondary outcomes at Week 8 were reduction in Faecal Calprotectin (FC) by ≥25 units from baseline and improvement in histological activity.
Results: Of 150 patients of UC screened, 53 patients fulfilled inclusion criteria and were randomised. Though more patients in CL group achieved primary outcome compared with placebo, it was not statistically significant [60.7% vs. 52%; p = 0.412]. Decrease in FC by ≥25 points was significantly more often in study group (83.3% vs. 50%; p = 0.034). Histological score decreased significantly in the study group (p = 0.022) compared with control group (p = 0.19). Epithelial injury score also decreased significantly in CL group (p = 0.02). Adverse drug reaction rate was similar in both the groups (28.7% vs. 32.0%; p = 0.786).
Conclusions: Curcuma longa can reduce the disease activity as assessed by UCDAI, FC, and histological examination when added to standard therapy. It is a low-cost, natural, and easily available add on therapy to reduce the disease activity.

P428

Long-term outcomes of endoscopic ballon dilation for small-bowl strictures using double balloon enteroscopy in patients with Crohn's disease

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Background: Crohn's disease (CD) often progresses to stricturing or penetrating type. Although the most common reason for intestinal resection is gastrointestinal stricture, endoscopic balloon dilation (EBD) is a useful procedure for relieving stricture and thereby allowing avoidance of surgery. However, only a few studies have examined the long-term usefulness of EBD for treating small-bowel stricture. Our present CD patients who had undergone EBD for small-bowel stricture (including ileocolonic anastomotic stricture) were retrospectively examined to determine the long-term usefulness of this procedure.
Methods: The subjects had undergone dilation of small intestinal and ileocolonic anastomotic strictures by double balloon enteroscopy at our department between 2005 and August 2015. EBD was indicated for patients with stricture symptoms or confirmed stricture precluding passage of an endoscope whose stricture sites were free of deep ulceration, abscess or fistula, and measured less than 5 cm. The data on short- and long-term outcomes were collected from the records of patients meeting the indications. Short-term success was defined as the passage of an endoscope through the stricture site or a combination of technical success of EBD and resolution of stricture symptoms. For long-term outcomes, cumulative surgery-free rates were analysed.
Results: This study included 111 patients who had met the indications and undergone EBD. The patient characteristics were a male-to-female ratio of 88:23, mean age of 35.6 years, and mean symptom duration of 12 years. The disease types were ileal in 57 patients and ileocolonic in 54. The short-term success rate was 72.1% (80/111). Overall, the cumulative surgery-free rates were 63.8% at 4 years and 52.8% at 8 years. Surgery was necessary for small-bowel stricture in 74.5% of the patients and for other reasons (eg, fistula formation) in 25.5%. When the cumulative surgery-free rates were compared between patients with and without short-term success, the rates were statistically significantly higher in those with success (p < 0.05).
Conclusions: In CD patients, EBD for small-bowel stricture achieved a high short-term success rate and was useful for long-term avoidance of surgery after such success.

P429

Factors associated with weight gain in patients treated with anti-TNF-α for inflammatory bowel disease: a cohort study

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Background: Previous studies have shown weight gain in patients with spondyloarthritis treated with anti-TNF. This weight gain could be explained by both the orexigenic effect of anti-TNF. However, other factors could be involved such as diet changes, limited physical activity, and socioeconomic deprivation. The aim of the study was to identify factors associated with weight gain in patients treated with anti-TNF for IBD.
Methods: Consecutive IBD patients treated with anti-TNF were included in a multi-centre study (Groupe Hospitalier Intercommunal de Montfermeil, Hôpital Cochin Paris, Centre Hospitalier de Dunkerque). Most of the patients were attending the outpatient clinic for anti-TNF infusion. They were asked to answer questionnaires about (1) disease activity; (2) quality of life (sIBDQ); (3) fatigue (FACIT); (4) physical activity; (5) socio-economic level (EPICES score); 6) anxiety and depression (HAD score). All the patients had an interview with a dietician. IBD's characteristics were extracted from the prospective data base Focus_MICI®, shared by the three centres. Patients were divided in two groups: (1) patients with more than 10% weight gain since anti-TNF initiation; (2) patients with less than 10% weight gain. The two groups were compared using univariate analysis.
Results: One hundred and thirteen patients [sex ratio (F/M) 51/62, mean age 41 years] were included from January to July 2018. Sixty-nine (61%) had Crohn's disease and 44 (38%) had ulcerative colitis. Mean disease duration was 10.3 years and mean anti-TNF duration was 3.8 years. Anti-TNF were given for luminal CD in 56% and refractory UC in 69%. Twenty-one (30%) patients had previous digestive surgery. Seventy-one (62%) patients had clinical remission. Thirty-nine (34%) patients had more than 10% weight gain since anti-TNF initiation. Patients with weight gain >10% were significantly more deprived (p < 0.02), more sedentary (p < 0.05) and had more high carbohydrate diets (p < 0.05). However, remission rate was higher in patients with less than 10% weight gain (p < 0.04). Age, sex ratio, tobacco use, first-degree relative history of obesity, corticosteroids for more than 4 weeks, mean CRP, levels of anxiety or depression, and fatigue were not statistically different between the two groups. Optimisation of treatment was not statistically different between the two groups.
Conclusions: In this study, one third of the patients had a weight gain of more than 10% since anti-TNF therapy initiation. Weight gain was associated with socioeconomic deprivation, limited physical activity, high-carbohydrate diet, and lower remission rates. These results should be confirmed but already suggest the need to include IBD patients into physical activity and nutrition education Programmes.

P430

European clinician perspective on withdrawing immunosuppression

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Background: Treating to target in inflammatory bowel disease is achieved through early immunosuppression with rapid escalation to combination therapy. Short-term studies support de-escalation to mono-therapy in certain contexts, however long-term outcomes of withdrawing immunosuppression are unknown.[1,2] We aimed to assess clinician perspective on, and current barriers to, withdrawing immunosuppression in European practice.
Methods: 500 questionnaires were distributed to workshop participants at the 11th Congress of European Crohn's and Colitis Organisation (ECCO). Likelihood of withdrawing IBD therapies, as well as clinician and patient factors associated with cessation, and barriers to withdrawal were recorded.
Results: Responses were obtained from 132 attendees. 108 clinicians [median age 37 (IQR33–46), 66.7% female] adequately completed surveys from 37 countries with varying levels of clinical experience [median years 6; IQR (3–15)]. Patient–clinician discussion around ceasing immunosuppressive therapy was infrequently raised by both clinicians and patients. The likelihood of ceasing mesalazine monotherapy was greater compared with any biologic agents ($p < 0.05$), in ulcerative colitis (UC) and Crohn's disease (CD). The likelihood of ceasing a thiopurine and anti-TNF was similar, however significantly different when compared with vedolizumab and ustekinumab ($p < 0.05$). The primary reason for ceasing mesalazine was to eliminate unnecessary medications, compared with malignancy and infection risk driving thiopurine and biologic agent cessation. For patients in long-term remission there was great variability in perceived barriers to stopping immunosuppression. Clinician's reported greater concern about relapse in patients being treated with anti-TNF, vedolizumab, or ustekinumab, compared with mesalazine or immunomodulators ($p < 0.001$). However, the majority of clinician's perceived high likelihood of 're-capture' above 50% for all medications.
Conclusions: A reluctance to both de-escalate and cease IBD therapy as part of routine practice prevails across Europe. Further long-term prospective studies are required to evaluate the outcomes of complete immunosuppression withdrawal.
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P431

Validation of a therapeutic drug monitoring test to measure the adalimumab biosimilar SB5 in comparison with the reference adalimumab

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Background: Validation of therapeutic drug monitoring (TDM) tests is an essential requirement for using these tools to help assess reasons for non-response. The arrival of biosimilars has prompted a need to validate that existing TDM tests are suitable to determine drug levels for all versions of a given molecule. The adalimumab (ADL) biosimilar SB5 (IMRALDI®, Biogen) was authorised by the European Commission in August 2017, and has recently become available for prescription in several European countries. Promonitor®-ADL test is routinely used to monitor IBD patients treated with ADL. In this study, we validated the suitability and performance of Promonitor-ADL CE-marked TDM test for quantifying SB5 serum concentrations in comparison to reference adalimumab (HUMIRA®, Abbvie).
Methods: The study evaluated imprecision and bias applied to the reference ADL and SB5 biosimilar. The validation study was in line with the design requirements established in the Clinical and Laboratory Standards Institute (CLSI) guideline EP10-A3 for the determination of imprecision and bias. Imprecision was evaluated using three replicates of five human serum sample matrices representative of clinically relevant ADL concentrations and spanning the measurement range of Promonitor-ADL.[1] Validations were ran on one instrument with one kit lot by one operator over six non-consecutive operating days and one run per testing day, with an acceptance criterium of CV% ≤20%. The Lower Limit of Quantification (LLOQ) of Promonitor-ADL was determined according to CLSI guideline EP17-A2.
Results: The imprecision of Promonitor-ADL was calculated by estimating the components of variance due to within-run and between-day factors meet the accuracy goals proposed at all concentration levels of SB5 vs. HUMIRA (CV% between 5% and 12%). The assessment of accuracy showed that Promonitor-ADL equally measures the active moiety of HUMIRA or SB5. The test is able to quantify SB5 in the measurement range of 0.9 to 10.9 µg/ml with a bias estimate of –0.124 (1%) to 0.897 (10%) µg/ml and an overall imprecision of 5% to 11%. The measurement range includes the recommended clinical decision points. LLOQ of the test to determine ADL was determined to be 0.36 µg/ml.
Conclusions: This study demonstrates that Promonitor-ADL test can measure either the reference ADL drug or the biosimilar SB5 (IMRALDI) with equivalent sensitivity, precision and accuracy.
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P432

Barriers to prescribing anti-TNF therapy in inflammatory bowel disease (IBD) across newly industrialised emerging market countries: an analysis of the 'EXPLORE' study

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Background: Physician challenges to prescribing anti-tumour necrosis factor (TNF) therapy among patients with ulcerative colitis (UC) and Crohn's disease (CD) in real-world clinical practice remains limited in the newly industrialised countries in APAC, Latin America (LatAm), and Russia, Middle East (RME) regions. We aimed to assess physician-perceived barriers to prescribing anti-TNF therapy in local settings.

Methods: The EXPLORE study is a chart review of IBD patients describing indicators and predictors of suboptimal response to anti-TNF therapy. It comprises a cross-sectional survey (completed during June 2017 till June 2018) of IBD specialists to identify local barriers to prescribing anti-TNF in real clinical practice, including those perceived to be faced by non- IBD GI specialists managing IBD patients.

Results: The survey was completed by 73 IBD specialists. In 2016, the median (min–max) number of biologic-naïve UC and CD patients referred to IBD specialist sites was 30 (1–811) and 40 (2–1000), respectively. Amongst IBD patients eligible for anti-TNF therapy who did not receive it, estimates were higher for CD (median [min–max]: 30% [0–100%]) compared with UC (20% [0–100%]). Among IBD specialists, 'patient affordability' (51%), 'patient fear of side effects' (47%), and the 'complex reimbursement process' (33%) were the three most frequent barriers to prescribing anti-TNF therapy. For non-IBD GI specialists, 'physician lack of experience with anti-TNF therapy' (48%), 'patient affordability' (47%), and 'patient fear of side effects' (45%) and 'perceived safety risk' (45%) were the three most common perceived barriers. Regional differences are shown in Table 1.

Table 1. The most common barriers to prescribing anti-TNF therapy by IBD specialists and non-IBD gastrointestinal (GI) specialists in the newly industrialised countries in Asia Pacific (APAC), Latin America (LatAm), and Russia, Middle East (RME) regions.

	IBD specialists	%	Non-IBD GI specialists	%
APAC* N=33	1. Patient affordability	73%	1. Patient affordability	64%
	2. Patient fear of side effects	64%	2. Physician lack of experience	61%
	3. Complex reimbursement process	49%	3. Patient fear of side effects	52%
LaTAm* N=15	1. Patient affordability	27%	1. Late diagnosis of IBD	40%
	1. Late referral to IBD specialist	27%	2. Physician lack of experience	33%
			2. Perception that only IBD specialist can prescribe	33%
			2. Late referral by primary care physician	33%
			2. Complex reimbursement process	33%
			2. Patient affordability	33%
RME* N=25	1. Fear of side effects	44%		
	2. Late referral to IBD specialist	40%	1. Perceived safety risk	52%
	3. Complex reimbursement process	36%	2. Patient fear of side effects	48%
	3. Patient affordability	36%	3. Physician lack of experience	40%

*APAC (South Korea, China, Taiwan and Singapore), LatAm (Argentina, Colombia and Mexico) and RME (Russia, Saudi Arabia and Turkey).

Hospitals were the most common setting to administer anti-TNF therapy for 78%, 67%, and 46% of patients in APAC, RME, and LatAm, respectively; however, 'lack of staff in infusion centres' (36%) and 'low numbers of infusion centres' (32%) were frequently reported challenges.

Conclusions: EXPLORE is one of the first IBD studies of its kind conducted in the newly industrialised countries. The conducted physician's survey within this study identified key barriers to prescribing anti-TNF therapy. This analysis highlighted an unmet medical need, where a large proportion of IBD patients eligible for biologic therapy did not receive it. Better biologic reimbursement coverage, physician education strategies, along with availability of safer biologic therapies and greater infusion capacity, may be required in these countries to improve IBD patient management.

P433

Aetiologies of iron deficiency-related anaemia in German patients with inflammatory bowel disease

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Background: Iron deficiency (ID) is a common manifestation of IBD but frequently overlooked, even if anaemia is present. Causes of anaemia in IBD include intestinal bleeding, reduced iron intake, and impaired iron absorption due to acute inflammation. Thus, anaemia in patients with IBD is most commonly iron deficiency anaemia (IDA), anaemia of chronic inflammation (ACI), or a combination of both aetiologies (MIX). Anaemia can seriously impact quality of life, morbidity and hospitalisation rates and therefore requires prompt diagnosis and treatment with intravenous (IV) or oral iron preparations, depending on its severity and causes. We aimed to determine and compare the prevalence of different types of anaemia in patients with ulcerative colitis (UC) and Crohn's disease (CD).

Methods: Baseline data from IBD patients (n = 192) with iron deficiency-related anaemia enrolled in a prospective observational study of IV iron therapy performed in 98 centres in Germany were assessed to identify aetiologies of anaemia. Demographic and biochemical parameters were documented. Anaemia was diagnosed as defined by the WHO (Hb: males <13 g/dl; females <12 g/dl) and sub-classified as IDA (ferritin <30 ng/ml, TSAT < 20%), ACI (ferritin >100 ng/ml, TSAT< 20%, CRP >5 mg/l) or MIX (ferritin >30 and <100 ng/ml, TSAT<20%). Anaemia not fitting these categories was defined as 'unclassified anaemia'.

Results: In total, 192 (71/37% male, 121/63% female) patients were enrolled, 55.2% (106/192) with CD and 44.8% (86/192) UC. Mean age was 37.9 ± 13.5 years; mean Hb was 9.4 ± 1.9 g/dl (CD, 9.3 ± 1.8 g/dl; UC, 9.5 ± 1.9 g/dl; p = 0.567). Anaemia was severe (Hb <10 g/dl) in 55.7% of CD and 53.3% of UC patients (p = 0.665). Overall, IDA was the most common type of anaemia (80.2%). Frequencies of ACI, MIX, and unclassified anaemia were 3.6%, 9.4%, and 6.8%, respectively. IDA was the predominant form of anaemia independent of disease phenotype, with a prevalence of 74.5% and 87.2% in CD and UC, respectively. CD patients tended to have more ACI and MIX (4.7%, 12.3%, respectively) than UC patients (2.3%, 5.8%, respectively).

Conclusions: Iron deficiency anaemia was found to be the predominant aetiology of anaemia in patients with both UC and CD, with

a slightly higher relative prevalence in UC. Patients with CD tended to have a higher probability of ACI, either alone or in combination with IDA. Besides effective iron therapy, inflammation management is therefore an important prerequisite for effective anaemia therapy in patients with IBD and iron-related anaemia.

P434

Surgery management of Crohn's disease in children: our experience

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Background: Classically, surgical treatment in paediatric Crohn's disease (CD) was the last option after the failure of available medical treatments. Currently, surgery is offered in patients with localised inflammatory activity despite optimised medical treatment or in patients with complications of the disease in early stages. The aim of our study is to review our experience to know the phenotype of patients who need surgery, surgical technique used and short- and medium-term results.
Methods: Retrospective cohort study of patients with paediatric CD who underwent surgery (excluding surgery of perianal disease) between 2012 and 2017 in a tertiary paediatric hospital. Epidemiological, clinical, analytical, radiological, endoscopic and surgical variables were collected and analysed.
Results: Twenty-five patients had required surgical treatment (52% males). Mean age at diagnosis was 11.6 ± 2.5 years, with a median (IQR) from the onset of symptoms to diagnosis of 0.74 (1) years. Mean time from diagnosis to the date of surgery was 2.5 ± 2 years. Forty per cent had a structuring behaviour at debut, 4% penetrating and 12% both of them. The most frequent location was ileocolonic (60%). Regarding the treatments received before surgery, 68% had received exclusive enteral nutrition and immunosuppressives, 20% corticosteroids and immunosuppressives, 20% anti-TNF-α treatment in monotherapy and 84% biological treatment (anti-TNFα/vedolizumab/ustekinumab) with immunosuppressives. The most frequent surgical indication was recurrent intestinal obstruction (84%). All interventions were initiated by laparoscopy although 12% were converted to laparotomy. Eighty-four per cent of the patients had a single resection, 8% multiple resections, and in the remaining an ileostomy without resection was performed. Ileocaecal area was resected in 78.3% of the patients and in 2 patients a single strictureplasty was performed. Mean surgical time was 3.8 ± 1.2 h and the average number of days of admission was 8.2 ± 3.3. There were no cases of surgical wound infection or postoperative ileus. For prevention of postoperative recurrence, 96% of patients received biological treatment (anti-TNF-α, ustekinumab) ± immunosuppressives. To date, endoscopic control has been performed in 13 patients (between 6 and 12 months after surgery) with the following Rutgeerts index: i0 46.1%; i1 30.8%; i2 15.4%; i4 7.7%. At follow-up, one patient required surgical re-intervention.
Conclusions: Although new biological treatments has reduced the need of surgery in paediatric Crohn's disease, a surgical approach by experienced teams, could be an effective and safe alternative in selected cases with complicated disease or unresponsive to medical treatment.

P435

Rapidity of symptomatic and inflammatory biomarker improvements following upadacitinib induction treatment: data from the U-ACHIEVE study

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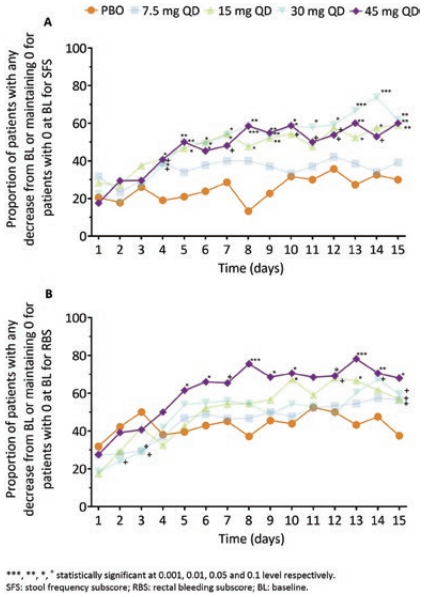
Background: Upadacitinib (UPA), an oral, selective Janus Kinase 1 inhibitor, demonstrated improved efficacy compared with placebo (PBO) in a Phase 2b induction study in patients with moderately-to-severely active ulcerative colitis (UC).[1] This analysis assessed the time to onset of symptomatic improvement, clinical response, and improvement in biomarkers during the induction phase of U-ACHIEVE.
Methods: Adult patients with moderately to severely active UC were randomised to double-blind therapy with extended-release UPA 7.5, 15, 30, 45 mg once daily (QD) or PBO for 8 weeks. Data from patient daily diary (as observed) on Mayo stool frequency subscore (SFS, 0–3) and rectal bleeding subscore (RBS, 0–3), as well as bowel urgency (BU, Y/N) and abdominal pain (AP, 0–3) were examined daily in the first 15 days of therapy. The proportion of patients with clinical response per partial Mayo score (decrease from baseline [BL] in Partial Mayo score ≥ 2 points and ≥ 30%, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1), and the change from BL in high-sensitivity C-reactive protein (hs-CRP) and faecal calprotectin (FC) were evaluated at Week 2. Comparisons between each UPA dose with PBO for proportions was assessed by Cochran–Mantel–Haenszel tests and mean change from BL by analysis of covariance with treatment and randomisation factors as covariate.
Results: A total of 250 patients were randomised. The mean SFS was 2.7 and RBS was 1.7 at BL. Trends of higher proportion of patients achieving symptom improvement in SFS and RBS were observed in the UPA 45 mg group than PBO as early as Day 4 (figure) and reached statistical significance ($p < 0.05$) by Day 8 in SFS, RBS, BU, and AP (Table 1).

Figure. Proportion of patients with (A) any decrease from baseline or maintaining 0 for patients with 0 at baseline for SFS and (B) any decrease from baseline or maintaining 0 for patients with 0 at baseline for RBS.



***, **, *, ˚ statistically significant at 0.001, 0.01, 0.05 and 0.1 level respectively.
SFS: stool frequency subscore; RBS: rectal bleeding subscore; BL: baseline.

Table 1. Proportion of patients with SFS =1, RBS = 0, AP =1, and no BU at Day 8.

	PBO	UPA 7.5 mg QD	UPA 15 mg QD	UPA 30 mg QD	UPA 45 mg QD
Proportion of patients with SFS ≤ 1	6/43 (14.0)	14/45 (31.1)*	12/44 (27.3)	15/46 (32.6)*	21/53 (39.6)**
Proportion of patients with RBS = 0	9/43 (20.9)	16/45 (35.6)	19/44 (43.2)*	21/46 (45.7)*	33/53 (62.3)***
Proportion of patients with no BU	2/41 (4.9)	6/40 (15.0)	11/40 (27.5)**	9/42 (21.4)*	19/50 (38.0)***
Proportion of patients with AP ≤ 1 [a]	11/20 (55.0)	11/23 (47.8)	8/21 (38.1)	15/23 (65.2)	23/28 (82.1)*

***, **, *, * statistically significant at 0.001, 0.01, 0.05 and 0.1 level respectively.
PBO: placebo; UPA: upadacitinib; QD: once daily; SFS: stool frequency subscore; RBS: rectal bleeding subscore; BU: bowel urgency; AP: abdominal pain.
[a] The analyses were conducted among patients with AP >1 at BL.

At Week 2, the proportion of patients with clinical response and the median change from BL in hs-CRP was statistically significantly greater in the UPA 15, 30, and 45 mg QD groups vs. the PBO group (Table 2).

Table 2. Clinical and biomarker outcomes at Week 2.

Endpoints	Placebo n=46	UPA 7.5 mg QD n=47	UPA 15 mg QD n=49	UPA 30 mg QD n=52	UPA 45 mg QD n=56
Clinical response per partial Mayo score[a], n (%)	7 (15.2)	11 (23.4)	18 (36.7)*	19 (36.5)*	31 (55.4)***
Mean change from baseline in hs-CRP (mg/L)[b] Median (range)	0.095 (-15.98, 30.10)	-2.150*** (-20.58, 4.30)	-5.275** (-115.37, 36.84)	-4.950*** (-45.00, 2.93)	-3.090*** (-61.73, 19.69)
Mean change from baseline in FC (mcg/g)[b] Median (range)	-365.0 (-11820, 8522)	-382.5 (-6593, 13420)	-662.0 (-15174, 25639)	132.0 (-17838, 5341)	-659.0 (-16528, 11610)

***, **, * statistically significant at 0.001, 0.01, and 0.05 levels, respectively.
[a] non-responder imputation analysis; [b] last observation carried forward analysis.
UPA: upadacitinib; QD: once daily; hs-CRP: high sensitivity C-reactive protein; FC: faecal calprotectin.

Conclusions: Early symptomatic improvement, as early as Day 4, was observed with UPA treatment in patients with active UC, concurrent with a rapid decrease in markers of inflammation.

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P436

Darvadstrocel treatment outcomes in Crohn's disease patients with complex perianal fistulas: the role of TNFi co-treatment in ADMIRE CD

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Background: Darvadstrocel (DVS) is an expanded, allogeneic, adipose-derived, mesenchymal stem cell therapy indicated in the treatment of complex perianal fistulas (CPAF) in patients with Crohn's disease (CD).[1,2] In ADMIRE CD (NCT01541579), a pivotal Phase 3, double-blind, randomised study, more patients who received DVS in addition to standard of care achieved combined remission at Weeks 24 and 52 compared with standard of care with placebo (PBO).[1,2] This post-hoc analysis assessed the role of co-treatment with tumour necrosis factor inhibitors (TNFi) on the outcomes for DVS therapy in treatment-refractory patients with CPAF in CD.

Methods: In ADMIRE CD patients were randomised to receive DVS or PBO. Allowed co-treatments were TNFi or immunomodulators (IMM). Randomisation was stratified by co-treatment received at baseline. This analysis was performed on the modified intent-to-treat population (mITT) (received study treatment and had at least one post-baseline efficacy assessment). Two subgroups were examined: TNFi co-treatment (with or without IMM); and no co-treatment. The outcomes examined were combined remission (clinical assessment of closure of all treated external openings draining at baseline, and the absence of collections >2 cm confirmed by MRI) and clinical remission (closure of all treated external openings that were draining at baseline despite gentle finger compression) at Weeks 24 and 52.

Results: In both subgroups at Weeks 24 and 52, the proportion of patients achieving combined and clinical remission in the DVS arm was greater than with PBO. TNFi with DVS achieved and sustained greater clinical remission compared with TNFi with PBO at Week 24 (58.7% vs. 50.0%) and Week 52 (61.9% vs. 43.5%). In the TNFi subgroup, the number of treatment-emergent adverse events related to study treatment was greater in the PBO arm than in the DVS arm, the most frequent being anal abscess.

Conclusions: In patients not receiving TNFi co-treatment, at Week 52 DVS compared with PBO had a benefit of similar magnitude compared with patients receiving concomitant TNFi. At Week 52, only the DVS groups achieved >60% clinical remission regardless of TNFi use. In summary, with or without TNFi, DVS consistently provided greater benefit than PBO alone. Further studies with larger cohorts are needed to confirm these post-hoc observations.

Table 1. Combined and clinical remission at Week 24 by TNFi co-treatment (mITT population). *LOCF rules applied. **No TNFi or IMM co-treatment at baseline. ***Patients co-treated with IMM only.

	Combined remission,* 24 weeks			Clinical remission,* 24 weeks		
Co-treatment	DVS *n*, % (95% CI)	PBO *n*, % (95% CI)	Treatment difference (p.p.) (95% CI)	DVS n, % (95% CI)	PBO n, % (95% CI)	Treatment difference (p.p.) (95% CI)
TNFi (with or without IMM) *n* = 125	35, 55.6 (43.3 to 67.8)	26, 41.9 (29.7 to 54.2)	13.6 (–3.7 to 31.0)	37, 58.7 (46.6 to 70.9)	31, 50.0 (37.6 to 62.4)	8.7 (–8.7 to 26.1)
No co-treatment** *n* = 43	13, 54.2 (34.2 to 74.1)	4, 21.1 (2.7 to 39.4)	33.1 (6.0 to 60.2)	14, 58.3 (38.6 to 78.1)	5, 26.3 (6.5 to 46.1)	32.0 (4.1 to 60.0)
Full mITT population*** *n* = 204	53, 51.5 (41.8 to 61.1)	36, 35.6 (26.3 to 45.0)	15.8 (2.4 to 29.2)	57, 55.3 (45.7 to 64.9)	43, 42.6 (32.9 to 52.2)	12.8 (–0.8 to 26.4)
Confidence interval [CI]	Percentage points (p.p.)					

Table 2. Combined and clinical remission at Week 52 by TNFi co-treatment (mITT population). *LOCF rules applied. **No TNFi or IMM co-treatment at baseline.***Patients co-treated with IMM only.

	Combined remission, * 52 weeks			Clinical remission,* 52 weeks		
Co-treatment	DVS *n*, % (95% CI)	PBO *n*, % (95% CI)	Treatment difference (p.p.) (95% CI)	DVS *n*, % (95% CI)	PBO *n*, % (95% CI)	Treatment difference (p.p.) (95% CI)
TNFi (with or without IMM) *n* = 125	38, 60.3 (48.2 to 72.4)	25, 40.3 (28.1 to 52.5)	20.0 (2.8 to 37.2)	39, 61.9 (49.9 to 73.9)	27, 43.5 (31.2 to 55.9)	18.4 (1.1 to 35.6)
No co-treatment** *n* = 43	14, 58.3 (38.6 to 78.1)	6, 31.6 (10.7 to 52.5)	26.8 (–2.0 to 55.5)	16, 66.7 (47.8 to 85.5)	7, 36.8 (15.2 to 58.5)	29.8 (1.1 to 58.6)
Full mITT population*** *n* = 204	58, 56.3 (46.7 to 65.9)	39, 38.6 (29.1 to 48.1)	17.7 (4.2 to 31.2)	61, 59.2 (49.7 to 68.7)	42, 41.6 (32.0 to 51.2)	17.6 (4.1 to 31.1)
Confidence interval [CI]	Percentage points (p.p.)					

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P437

Risk of immunomediated adverse events or secondary loss of response to infliximab in elderly patients with inflammatory bowel disease: a cohort study of the ENEIDA registry

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Background: Infliximab is one of the most used biological drugs in inflammatory bowel disease (IBD). Immunomediated adverse events (IAE) are of the most frequent reported infliximab-related adverse events. Elderly patients have differential pharmacodynamic and pharmacokinetic characteristics. We recently reported an increased risk of thiopurine-related AEs in this population; hence, it would be relevant to ascertain if combined treatment is adequate in this

population. Our aim was to evaluate the rate of infliximab-related IAE in elderly IBD patients.

Methods: All adult patients in the ENEIDA registry (a large, prospectively maintained database of the Spanish Working Group in IBD–GETECCU) who received a first course of infliximab treatment were identified. Patients were selected in two cohorts regarding the age at the beginning of infliximab treatment: over 60 years, and between 18 and 50 years of age. The rates of IAE recorded in the ENEIDA database (infusion reactions, delayed hypersensitivity, oedema, allergy, anaphylaxis, psoriasis, lupus-like syndrome) were compared, as well as the rate of secondary loss of response (SLR).

Results: We included 939 (12%) patients who started infliximab over 60 years and 6844 (88%) patients below 50 years. The rate of IAE (15% vs. 15%, ns) and treatment withdrawal due to IAE (13% vs. 12%, ns) was similar in both groups. Neither differences were observed according to IAE: infusion reactions (8.3% vs. 8.2%), late hypersensitivity (1.4% vs. 1.2%), paradoxical psoriasis (0.9% vs. 1.4%) and drug-induced lupus erythematosus (0.7% vs. 0.6%). Patients below 50 years were significantly more often treated with concomitant immunosuppressants (57% vs. 48.1% >60 years, $p < 0.05$). In the multi-variate analysis, combination with immunosuppressants (OR 0.741; 95% CI 0.64–8.5, $p < 0.05$) and female sex (OR 1.8; 95% CI 1.6–2.1, $p < 0.05$) were the only independent predictors to develop IAE. The rate of SLR was also similar in both study groups (20% vs. 21%). Combination therapy with immunosuppressants was the unique risk factor to develop SLR (OR 0.85; CI 95% 0.73 to 0.98, $p = 0.021$).

Conclusions: Elderly IBD patients who start treatment with infliximab have a similar risk of developing IAE and SLR than younger patients. From this point of view, elderly would benefit from combination therapy.

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Lupus-like reactions in patients with inflammatory bowel disease treated with anti-TNFs are rare but insidious adverse events: data from a large single-centre cohort

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Background: The occurrence of lupus-like reactions (LLRs) may complicate the management of patients with inflammatory bowel disease (IBD) treated with anti-TNFs. However, very few data on the incidence, predictors, and clinical outcomes of LLRs have been reported. We aimed to describe all these features in a large cohort of IBD patients treated with anti-TNF drugs

Methods: All records of consecutive patients who started a treatment with an anti-TNF from January 2006 to June 2018 were retrospectively reviewed. Patients were defined as having LLR by the presence of immunologic abnormalities (positivity for ANA and/or anti-ds-DNA), along with clinical features that included at least two of the following: arthralgia, fatigue, fever, cutaneous manifestations, or serositis, which had a clear temporal association with exposure to the anti-TNFs, and resolved without recurrence once the drug was discontinued. Univariable and multiple Cox proportional hazard models were used to estimate the association between all variables at baseline and occurrence of LLRs.

Results: In total, 760 patients (1059 total treatments with anti-TNFs) were included. Participants contributed a total of 2863.5 person-years of follow-up, during which 16 cases of LLRs (2.1% of patients) were reported, with an incidence rate of 5.6 per 1000 person-years. Female gender and being former smokers were more prevalent in the LLR group (75.0% vs. 44.1%, $p = 0.02$; and 18.8% vs. 5.4%, $p = 0.037$, respectively), with a hazard ratio of 3.86 (95% CI: 1.21–12.38; $p = 0.023$) and 4.42 (95% CI: 1.20–16.24; $p = 0.025$), respectively, at Cox regression analysis adjusted for possible confounders. LLRs occurred after a mean of 12.0 ± 9.7 months of therapy with anti-TNFs. Antinuclear antibodies were universally positive, and 10 out 16 (62.5%) patients had also anti-ds-DNA. Arthropathy was the most frequent symptom (87.5%), followed by fatigue (81.2%), and fever (31.2%). Three cases presented with a concomitant autoimmune hepatitis-like syndrome. The diagnosis of LLR was further confirmed by a re-challenge with the culprit agent in half of the cases. All LLRs resolved following discontinuation of the drug after a mean of 8.1 ± 4.2 weeks, even if 10 patients required corticosteroids for the control of symptoms. Five patients (31.2%) were switched to a second anti-TNFs, and one of them developed a second LLR.

Conclusions: In this very large cohort of patients treated with anti-TNFs, LLRs were rare adverse events, more common in women and former smokers. Clinical features are non-specific and insidious. All LLRs resolved following discontinuation of the drug, but the use of corticosteroids was required in most of the cases.

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Effectiveness and safety of the sequential use of a second and third anti-TNF agent in patients with inflammatory bowel disease: results from the ENEIDA registry

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Background: The aim of the present study was to investigate the efficacy and safety of the sequential use of a second and a third anti-TNF agent after failing or developing intolerance to an anti-TNF drug.
Methods: Patients diagnosed with Crohn's disease (CD) or ulcerative colitis (UC) from ENEIDA registry (a prospectively maintained registry from GETECCU) who switched to another anti-TNF drug after failure or intolerance to a previous anti-TNF, were included. Efficacy, loss of response, and safety of the second and third anti-TNF were evaluated by logistic regression, Kaplan–Meier and Cox regression analyses.
Results: In total, 1122 patients that switched to a second anti-TNF were included (50% men, mean age at diagnosis 31 years, 73% CD). The reasons for withdrawal the first anti-TNF were: primary failure (22%), secondary failure (51%), and intolerance (27%). Remission was achieved with the second anti-TNF drug in 45% of patients in the short-term. The rate of remission was similar between CD and UC patients (46% vs. 41%, $p = 0.06$). There was no difference in remission rates according to the sequence of the anti-TNF administration: infliximab–adalimumab or adalimumab–infliximab (42% vs. 48%, $p = 0.07$). The factors associated with a lower probability of achieving remission after a second anti-TNF were: combo therapy (OR = 0.5 95% CI = 0.4–0.8), to withdraw the first anti-TNF due to a primary failure (vs. intolerance; OR = 0.6, 95% CI = 0.4–0.9), and to withdraw the first anti-TNF due to secondary failure (vs. intolerance) (OR 0.6, 95% CI = 0.5–0.9). The cumulative incidence of loss of response after achieving remission with the second anti-TNF (median follow-up of 19 months) was 45%: 23% at 1 year and 62% at 5 years. The incidence of loss of response to the second anti-TNF was 19% per patient-year of follow-up. The factors associated with a higher risk of loss of response were: UC vs. CD (HR = 1.6; 95% CI = 1.1–2.1, $p = 0.005$) and combo therapy (HR = 2.4; 95% CI = 1.8–3, $p < 0.0001$). Adverse events occurred in 15% of the patients who switched to a second anti-TNF (10% stopped the treatment). Seventy-one patients switched to a third anti-TNF and 55% achieved remission. The incidence of loss of response to a third anti-TNF was 22% per patient-year (median follow-up of 9 months). Seven patients (11%) had adverse events, but only one discontinued the therapy.
Conclusions: Almost half of the patients who switched to a second anti-TNF achieved remission; however, a high proportion of them subsequently lost response. Factors associated with loss of response were type of inflammatory bowel disease and combo therapy. Approximately 50% of patients who received a third anti-TNF achieved remission; however, again, a high proportion of them lost response subsequently.

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Comparison of infliximab serum levels between venous and capillary blood in paediatric IBD patients using novel blood sampling technology

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Background: Infliximab (IFX) enormously changed the treatment of inflammatory bowel disease (IBD) in paediatric patients over the last years. To optimise IFX treatment outcome, therapeutic drug monitoring is important. Measurements are typically taken by venipuncture. Dried blood sampling (DBS), using capillary blood obtained from a finger prick, may also be used to measure IFX blood levels. For paediatric patients, the latter is less invasive and can be done outside of the hospital, facilitating a more personalised treatment. The aim of this study was to compare IFX blood level measured by venipuncture vs. DBS in paediatric IBD patients.
Methods: This prospective clinical pilot study included 20 paediatric IBD patients (aged 6–16 years). Before IFX infusion, blood was collected simultaneously through venipuncture as well as a DBS from a finger prick, using Mitratips© (Neotyrex). The IFX levels were assessed by ELISA (Sanquin, Amsterdam). IFX levels measured in DBS eluates were converted to serum values by making use of a fixed haematocrit value of 0.42. Spearman's correlation coefficient was calculated to examine the correlation between venous IFX serum level and DBS. The Bland–Altman analysis was used to measure limits of agreement.
Results: Twenty patients were included, median age 12.1 year [range 8–16 year], two patients with ulcerative colitis, 1 with IBD-Unclassified, and 17 with Crohn's disease. Four patients were excluded from the analysis, since IFX level was below detection level in venepuncture serum and/or DBS. There is significant strong correlation between venous IFX serum levels and DBS (r = 0.997, p = 0.0001) in the included patients. The mean difference between the two methods is –0.266 (95% CI: –0.592; 0.059) as calculated with Bland–Altman plot. There is no statistical significant difference between venous IFX serum levels and DBS. The limits of agreement are between –1.464 (95% CI: –2.029; –0.900) and 0.932 (95% CI: 0.367; 1.496) (Figure 1). It is worth noting that when using a limited number of patients, as done during this pilot study, the limits of agreement are typically wider.

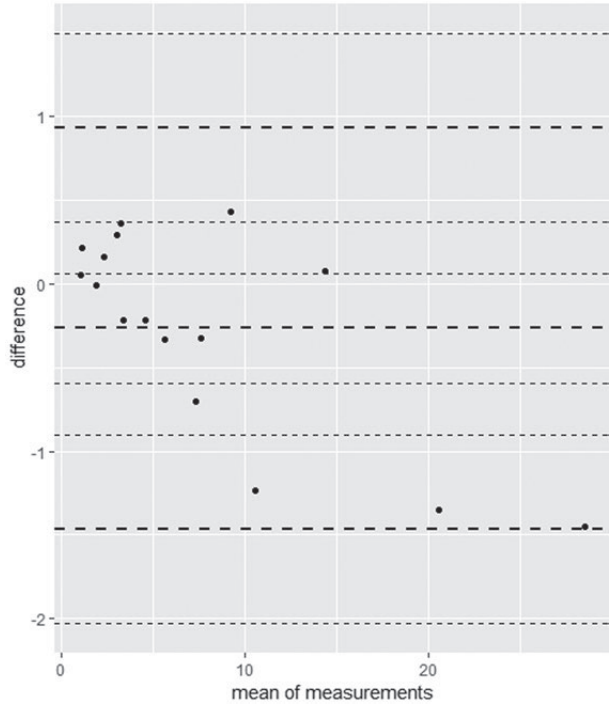

Figure 1. Bland–Altman scatterplot showing difference between venous and DBS IFX levels.

Conclusions: This is the first study comparing venous and capillary infliximab serum levels with novel blood sampling technology in paediatric IBD. There is strong correlation between the methods and acceptable limits of agreement. As such the bloodspot technology could be a good candidate for an alternative method to measure IFX blood levels in paediatric patients and facilitate therapeutic drug monitoring.

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Long-term immunogenicity of vedolizumab in ulcerative colitis and Crohn's disease (GEMINI Programme)

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Background: As previously reported in the pivotal GEMINI 1 (NCT00783718) and 2 (NCT00783692) trials, vedolizumab therapy for ≤ 52 weeks induced low rates of immunogenicity in patients with ulcerative colitis (UC) or Crohn's disease (CD), respectively. [1] [2] We report long-term immunogenicity in patients enrolled in GEMINI 1 (UC) or 2 (CD) followed by the GEMINI long-term safety (LTS) study (NCT00790933/EudraCT 2015-000480-14), including patients on placebo re-treated with vedolizumab in GEMINI LTS.
Methods: GEMINI 1 and 2 patients received vedolizumab 300 mg intravenously at Weeks 0 and 2 as induction therapy; Week 6 responders were randomised to vedolizumab every 8 or 4 weeks or placebo for ≤ 52 weeks. All GEMINI 1 or 2 patients were eligible to enrol in GEMINI LTS and receive vedolizumab every 4 weeks until study completion or withdrawal. Blood samples for immunogenicity determination were collected every 16 weeks. Immunogenicity (anti-vedolizumab antibody [AVA] status) was determined using an enzyme-linked immunosorbent assay; AVA-positive samples were characterised using a neutralising assay.
Results: Among 1966 patients receiving continuous vedolizumab, 74 (4%) were AVA-positive during GEMINI (11 persistently positive; 42 neutralising AVA-positive). Among 240 patients who received 2 doses of vedolizumab as induction therapy and were randomised to placebo during maintenance in GEMINI 1 or 2 and who were subsequently re-treated with vedolizumab in GEMINI LTS, 42 (18%) were AVA-positive (27 persistently positive; 23 neutralising AVA-positive). Immunogenicity rates were higher during GEMINI 1 and 2 (first 52 weeks of treatment) than GEMINI LTS. Overall, 114 (5%) patients developed an infusion reaction. No patients on continuous vedolizumab with an infusion reaction (n = 101) were persistently AVA-positive. Two of 13 (15%) patients re-treated with vedolizumab in GEMINI LTS who had an infusion reaction were persistently AVA-positive.
Conclusions: Long-term treatment with vedolizumab was associated with low immunogenicity rates consistent with results from GEMINI 1 and 2, even in patients initially treated with vedolizumab induction followed by placebo maintenance in GEMINI 1 and 2 who were subsequently re-treated with vedolizumab in GEMINI LTS. No relationship was observed between immunogenicity and safety.

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Strictureplasty for Crohn's disease of the small bowel in the biological era: long-term outcomes and risk factors for site specific recurrence

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Background: Patients affected by Crohn's disease (CD) often require multiple surgeries and are at higher risk of short bowel syndrome. While bowel-sparing techniques should still have an indication in these patients, a considerable reduction of the use of strictureplasty has been observed, especially since the introduction of biological drugs.

Methods: Patients undergoing strictureplasty for small bowel CD from 2002 were included.

Risk factor for recurrence of CD were analysed through a multi-level logistic regression analysis, considering the hierarchical structure of the data. Level-2 variables were related to patient, level-1 to strictureplasty. A model without predictors was run to calculate the intraclass correlation coefficient to evaluate the degree of homogeneity of the outcome within patients; an intermediate model adding level-1 and level-2 variables and testing all intra-level interactions was subsequently performed. The estimated residual standard deviation and the estimated residual intraclass correlation of random-intercept logistic model were calculated. All p values refer to two-tailed tests of significance. A p-value of <0.05 was considered significant.

Results: A total of 266 patients were included in the study. Overall, 718 strictureplasties were performed. Median follow-up time was 96 months (6–209). Site specific recurrence rate was 1.6% at 2 years, 12.7% at 5 years, and 25.7% at 10 years.

	Number, mean or median	%, standard deviation or range
Total number of patients	266	
Mean number of strictureplasties/patient	1.95	±2.85
Median age of patients (years)	39.5	18–76
Median years of disease	8.2	0.1–37
Number of additional resections	196	73.7%
Smoking after strictureplasty	68	25.6%
Biologics after strictureplasty	79	29.7%
Biologics before strictureplasty	72	27.1%
Previous surgery for Crohn's disease	85	32.0%

Characteristics of patients undergoing strictureplasty for Crohn's disease

	N	%
Total number of strictureplasty	718	
Ileum	440	61.3
Jejunum	135	18.8
Terminal ileum	143	19.9
Conventional strictureplasty	643	89.6
Nonconventional strictureplasty	75	10.4
New stricture	651	90.7
Recurrence on strictureplasty	36	5
Recurrence on anastomosis	31	4.3

Characteristics of the strictureplasties performed

Variables	Odd ratio	Standard error	p-value
Ileum location	1.49	0.35	0.091
Nonconventional strictureplasty	3.57	1.72	0.008
Strictureplasty on previous anastomosis	13.59	11.18	0.002
Age	0.98	0.01	0.246
Total number of strictureplasties	1.13	0.08	0.088
Use of biologics after strictureplasty	4.75	2.25	0.001
Duration of disease	1.26	1.04	0.776

Results of the multi-level regression logistic analysis of risk factors for site specific recurrence.

Conclusions: Strictureplasty is a safe procedure and is correlated with acceptable recurrence-free rates also after a very long follow-up time. Despite nonconventional strictureplasties are associated with a significantly higher risk of site specific relapse, whenever possible a bowel sparing technique should be performed, especially in the presence of long strictures. In case of a recurrence of a previous anastomosis, a resection should be preferred. The use of biologics after surgery identifies patients at higher risk of recurrence. The effect of biological drugs on long-term outcome after bowel sparing technique should be assessed in future prospective trials.

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Clinical features, therapeutic requirements, and evolution of patients with Crohn's disease and upper digestive tract involvement (CROHNEX study)

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Background: Patients with upper (L4) and diffuse (L1 + L4) Crohn's disease (CD) may have a more aggressive and refractory disease course. However, evidence on this particular sub-type of patients is scarce. Clinical guidelines do not offer specific protocols on how to manage them.

Methods: To identify the clinical characteristics, therapeutic requirements and complications that are independently associated with an upper digestive tract CD involvement.

METHODS: Retrospective study of cases and controls matched (1: 2) by sex and age in patients with CD (L4 or L1 + L4: cases; L1 or L3: controls) of the ENEIDA database (49 hospitals). The small intestine was evaluated with radiologic and/or endoscopic examination, and complex perianal disease was excluded. Clinical variables: pattern, severity, anaemia; Complications: stenosis, fistula, abscess, perforation and digestive bleeding; Therapeutic requirements: use of 1 anti-TNF, more than 1 ant-TNF, anti-TNF intensification, second-line biologic drug, iv iron, blood transfusions, enteral nutrition, endoscopic/radiological treatments, surgeries and hospitalisations were investigated. A logistic regression analysis with those significant variables in univariate analysis (SPSS) was performed.

Results: In total, 919 cases and 1838 controls were identified. Multivariate analysis showed that cases were independently associated to stricturing pattern at diagnose (OR: 1.2, 95% CI: 1–1.5; $p = 0.048$), iron deficient anaemia (OR: 2.3, 95% CI: 1.6–3.4; $p < 0.0001$), more extensive involvement (> 30 cm) (OR: 2.7, 95% CI: 2.3–3.3; $p < 0.0001$), and the use of second-line biologics during follow-up (OR 1.6, CI 95% 1–2.4; $p = 0.04$). In contrast, they exhibit less abscesses (OR 0.6, 95% CI: 0.5–0.8; $p = 0.001$) and have less familial history of inflammatory bowel disease (OR 0.7, 95% CI: 0.6 –0.9; $p = 0.008$).

Conclusions: In the most extensive series of upper digestive tract involvement in CD, it is shown that they present a more advanced disease at CD diagnosis, suggesting either a late diagnosis or different physiopathologic pathways for L4 involvement. Consequently, they are more refractory to treatments, requiring more frequently second-line biologics. A specific diagnostic and therapeutic strategy must be considered for these patients. This includes consider signs that allow a high rate of suspicion such as iron deficient anaemia in patients with normal upper and lower endoscopy.

P444

Post-induction Infliximab trough levels in severe and moderate paediatric ulcerative colitis: preliminary data of a retrospective, population cohort-based study

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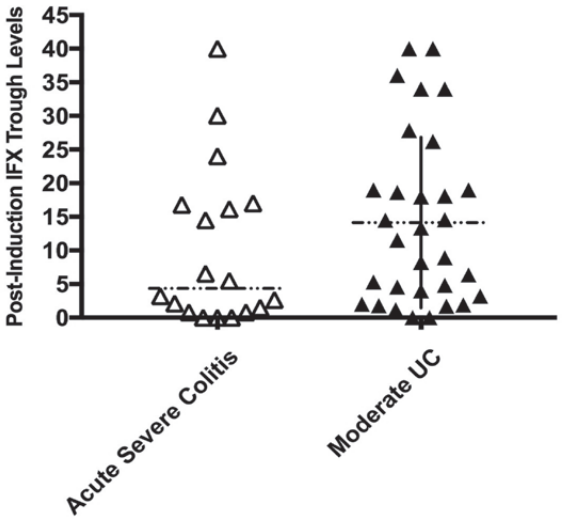
Background: Recent adult evidences suggest that Infliximab (IFX) trough levels (TL) in acute severe colitis (ASC) patients may be decreased due to a higher faecal loss and severe tissue damage. The aims of this study were to evaluate post-induction trough levels (TL) in severe and moderate UC children and to compare disease outcomes.

Methods: This was a single-centre, retrospective study involving the IBD unit of the Children Hospital of Philadelphia. Children aged from 6 to 21 years with a confirmed diagnosis of UC, starting IFX with a PUCAI ≥35 and with available post-induction TL between July 2012 and July 2018 were recruited. The following information were recorded: age at diagnosis; disease extent, and clinical activity index based on PUCAI before IFX starting; therapeutic history, IFX dosage, timing between infusions, primary non-response (PNR), loss of response (LOR), and surgery after IFX starting. Post induction TL and laboratory evaluations including complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and albumin at the moment of IFX starting were also collected.

Results: Fifty-two UC children were included in this preliminary analysis. Of these, twenty-one (38.5%) had a PUCAI ≥ 65, while 31 (61.5%) showed PUCAI values ≥35 < 65. When compared with moderate UC children, patients affected by ASC presented significant lower median values of haemoglobin ($p = 0.05$), while showing significant higher values of ESR ($p = 0.04$). The median IFX dosage at the induction was significantly higher in the ASC group when compared with the moderate UC (10 vs. 5 mg/kg; $p = 0.03$). Median post-induction TL were lower in patients with ASC when compared with moderately severe UC with a trend towards statistical significance [4.35 (0–40) vs. 11.5 (0–40); $p = 0.07$) (Figure 1).



Antibody-to-IFX formation rate did not differ between the two groups after the induction. PNR was observed in 6 out of 21 (28.6%) children with ASC vs. 2/31 (6.5%) patients with moderate UC (p = 0.04). Overall, at 12 months of follow-up, 8 out of 21 (38.1%) ASC children interrupted IFX therapy for PNR or LOR vs. 5/32 (16.1%) children with moderate UC (p = 0.05). Three out of 21 (14.3%) children with ASC underwent surgery within 12 months from IFX starting, compared with 2/31 (6.5%) patients with a PUCAI ≥35<65 (p = 0.3).

Conclusions: ASC children at IFX starting showed lower post-induction trough levels and more severe disease outcomes at 12 months including PNR, LOR and a higher risk of surgery.

P445

Prevalence rates of biosimilar discontinuation and switchback to originator biologics following non-medical switching: a meta-analysis of real-world studies

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Background: To optimise clinical outcomes of biologics for autoimmune conditions, continued treatment of the same agent is critical, particularly for stable patients. The introduction of biosimilars to originator biologics has prompted non-medical switching (NMS) which may interrupt treatment consistency. This study examined prevalence rates of biosimilar discontinuation and switchback to originator following NMS.

Methods: Real-world studies between January 2012 and August 2018 were identified through a systematic literature review. Discontinuation and switchback rates were extracted. A meta-analysis (MA) estimated the annualised discontinuation and switchback rates. A subsequent MA assessed annualised incremental discontinuation rate among studies that reported discontinuation for both cohorts: patients underwent NMS (switchers) and patients remained on originators (non-switchers).

Results: A total of 62 studies were identified: 34 in gastroenterology, 31 in rheumatology, and 3 for both. Half reported switchback; only 9 reported discontinuation for both switchers and non-switchers. Mean/range sample size of NMS cohorts was 136/9–1641; mean/range follow-up was 10/3–24 months. Annualised discontinuation rate (95% Confidence Interval) was 21% (18%, 25%); switchback rate was 14% (10%, 17%) in all NMS patients and 62% (44%, 80%) in discontinuers. Mean sample size of switchers and non-switchers was 344/89–1621 and 768/19–2870, respectively; mean follow-up was 11/6–18 and 12/6–18 months. Annualised incremental discontinuation rate was 18% (4%, 31%), indicating a significantly higher rate in switchers.

Conclusions: Biosimilar discontinuation is prevalent in the real world among patients who underwent NMS. Furthermore, switchback to originators is common following biosimilar discontinuation. Careful consideration is necessary when switching patients who are already on an originator to a biosimilar.

P446

Dose escalation with originator infliximab is more common than standard dosing in paediatric IBD: the DEVELOP experience

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Background: DEVELOP is a multi-centre, prospective, observational registry of the long-term safety and clinical status of 6070 paediatric patients with inflammatory bowel disease (IBD; Crohn's disease [CD]: 4122, ulcerative colitis [UC]: 1643, and IBD-unclassified[IBD-U]: 305; median age at enrolment 13.0 years) treated with originator infliximab (REM) and/or other medical therapies for IBD as part of routine clinical care. DEVELOP has sites in the US, Canada and the EU and enrolled patients from 2007 to 2017. The labelled maintenance dose and interval of REM for treatment of paediatric CD or UC is 5 mg/kg IV every 8 weeks. Our aim was to assess how frequently providers needed to escalate this dose.

Methods: Enrolment was targeted such that half of the enrolled patients had been exposed to REM at baseline. The treating physicians then continue to prescribe IBD treatments based on their usual clinical practice and standards of care. Patients are categorised into cohorts according to their prevalent or incident IBD medication exposure, including patients receiving therapy prior to enrolment and patients receiving therapy during registry follow-up. The last data cut available (30 June 2018) assessed 33 586 patient-years (PY) of follow-up.

Results: Among all patients (Table 1), the median average maintenance dose of REM thus far during the registry period is 6.5 mg/kg (CD: 6.1 mg/kg, UC: 7.5 mg/kg and IBD-U: 8.0 mg/kg). In the most recent 12-month follow-up period, the median maintenance dosing frequency was 8 weeks for CD patients, 7 weeks for UC patients and 6 weeks for IBD-U patients. The median total number of REM infusions was 17.0, with a median duration of REM exposure of 32.3 months and a mean duration of 38.9 months. During the entire registry follow-up period, 27% of patients who had been receiving REM discontinued the drug. The median interval between first dose and discontinuation was 20.9 months and the most common reasons for discontinuation were loss of efficacy (47% of discontinuations), adverse events (17%) and administration reactions (13%).

Conclusions: In the international DEVELOP paediatric IBD registry, standard dosing of REM is the exception rather than the rule. The median maintenance doses used in CD, UC and IBD-U are all higher than the labelled dose of 5 mg/kg. In UC and IBD-U, the median maintenance interval is also shorter than the labelled interval of q8 weeks. Further analysis will examine clinical measures before and after dose escalation.

Table 1. Remicade exposure during registry participation: all IBD patients

	CD	UC	IBD-U	All patients
Total patients, N	4122	1643	305	6070
Ever (includes prior to enrollment), n (%)	2902 (70.4%)	1002 (61.0%)	203 (66.6%)	4107 (67.7%)
Exposed prior to baseline	1956 (47.5%)	763 (46.4%)	165 (54.1%)	2884 (47.5%)
First dose on or after baseline	946 (23.0%)	239 (14.5%)	38 (12.5%)	1223 (20.1%)
Initiated Remicade during registry follow-up	828 (20.1%)	196 (11.9%)	32 (10.5%)	1056 (17.4%)
Initiated Remicade at baseline	118 (2.9%)	43 (2.6%)	6 (2.0%)	167 (2.8%)
Average dose during registry (mg/kg)				
Number of patients	2528	798	174	3500
Mean (SD)	6.7 (2.64)	7.7 (2.54)	8.1 (3.72)	7.0 (2.72)
Median	6.1	7.5	8.0	6.5
IQ range	(5.0; 8.1)	(5.6; 9.3)	(5.8; 9.5)	(5.0; 8.6)
Range	(0; 61)	(4; 41)	(1; 41)	(0; 61)
Duration of exposure during registry (months) *				
Number of patients	2576	814	175	3565
Mean (SD)	44.5 (29.66)	24.3 (20.06)	24.8 (21.05)	38.9 (28.81)
Median	41.6	19.1	18.3	32.3
IQ range	(18.1; 69.0)	(8.6; 32.9)	(9.5; 32.4)	(13.9; 59.4)
Range	(3; 126)	(0; 109)	(3; 108)	(0; 126)
Exposure During Last Registry Follow-up Interval				
Maintenance dosing frequency (weeks)				
Number of patients	1455	474	117	2046
Mean (SD)	7.3 (1.30)	6.8 (1.38)	6.2 (1.59)	7.2 (1.37)
Median	8.0	7.0	6.0	8.0
IQ range	(6.0; 8.0)	(6.0; 8.0)	(5.0; 8.0)	6.0; 8.0)
Range	(4; 12)	(3; 12)	(2; 10)	(2; 12)

Note: Last registry follow-up interval is defined as the last 6-month interval for patients with at least 1 post-baseline visit.
* Duration of Remicade exposure was calculated by considering each administration of Remicade exposure as 91 days of exposure. If 2 dose intervals overlapped, then the intervals were collapsed. Remicade dose (mg/kg) could not be computed if a patient did not report Remicade dose or body weight.
Key: CD = Crohn's disease; IBD = inflammatory bowel disease; IBD-U = IBD-unclassified; IQ = interquartile range; SD = standard deviation; UC = ulcerative colitis.

P447

The impact of therapeutic drug monitoring during biosimilar infliximab switch in inflammatory bowel disease

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Background: Therapeutic drug and antibody monitoring (TDM) is now an established strategy to manage patients with inflammatory bowel disease being treated with biologic agents. Biosimilar switching of originator infliximab (IFX) is recommended by ECCO and BSG. The role of TDM during biosimilar infliximab switch is not well studied. This study aimed to analyse and compare IFX drug and antibody levels before and after switch. The aim of our study was to study the impact of TDM on biosilimar infliximab switching by detecting the proportion of patients who have sub-therapeutic drug levels and/or anti-IFX antibodies either before or 3 months after the switch, who would be considered as secondary loss of response (LOR).
Methods: All patients with either Crohn's disease (CD) or ulcerative colitis (UC) who were switched to Remsima, a biosimilar infliximab in 2017 at the two hospital sites were included. Disease activity was assessed using Harvey–Bradshaw Index (HBI) or Simple Clinical Colitis Activity Index (SCAI). The most recent colonoscopy/radiological imaging and faecal calprotectin (FCP) was recorded. Pre- and post- switch infliximab and antibody levels were obtained. Concomitant use of immunomodulators (azathioprine, mercaptopurine or methotrexate) was noted.
Results: 119 patients had IFX Remicade® switch to Biosimilar Inflectra® or Remsima®. Eighty-six patients had CD and 32 had UC. In total, 110 patients had pre-switch therapeutic drug and antibody monitoring, and 115 had post switch monitoring as well within 3 months. Sixty-seven patients had sub-therapeutic but detectable IFX drug levels prior to the switch with either mild or inactive clinical scores for both CD and UC. SCAI ranged between 0–9, mean 1.433 and HBI ranged between 0–12, mean 2, indicating that majority of patients were in clinical remission. Nineteen patients had undetectable IFX drug levels, and post switch continued to have undetectable levels. Sixteen of these 19 patients had high anti-IFX antibodies suggesting that these patients were secondary loss of response who needed a change of their biologic to another agent. Of 86 patients, 11 had dose escalation to 10 mg/kg and then attained therapeutic levels. SCAI ranged between 0 and 9, mean 1.433, and HBI ranged between 0 and 12, mean 2, indicating that majority of patients were in remission. Post switch matched FCP showed 60 patients in remission with FCP < 200 μg/g and 22 patients with FCP > 250 μg/g.
Conclusions: Therapeutic drug and antibody monitoring before and 3 months after Biosimilar switch detects secondary loss of response in patients maintained on scheduled IFX treatment in clinical and biochemical remission. It should be recommended over blanket switching as it may prevent un-necessary switching for some patients who are no longer responding the IFX or those who may merit a drug withdrawal.

P448

Cannabis and cannabinoids for the treatment of inflammatory bowel disease: a systematic review and meta-analysis

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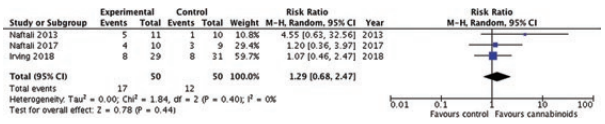
Background: Inflammatory bowel disease (IBD) patients increasingly use complementary and alternative medicine such as cannabis and/or cannabinoids. Cannabinoids may have anti-inflammatory properties through interaction with the endocannabinoid system. We performed a systematic review with meta-analysis to assess the efficacy of cannabi(noid)s in treating IBD.
Methods: We included randomised controlled trials (RCTs) and non-randomised studies (NRSs) analysing IBD patients of any age using cannabi(noid)s. Two reviewers searched MEDLINE, Embase and CENTRAL until 19 July 2018. A data extraction sheet included study characteristics, patient characteristics, intervention details, and disease activity scores. We assessed risk of bias with the Cochrane Risk of Bias tool and the Newcastle-Ottawa Quality Assessment Scale. Revman 5.3 computed relative risks (RR), mean differences (MD), and standardised mean differences (SMD) with a 95% confidence interval (95% CI) using the random-effects model. For the meta-analyses, only RCTs were included.
Results: The search identified 571 records of which 9 NRSs and 4 RCTs were eligible for inclusion. The meta-analysis included 100 randomised participants. Risk of bias was moderate to high. Cannabi(noid)s were not effective in inducing remission (RR = 1.29, 95% CI = 0.68–2.47; see figure). Statistical heterogeneity was low (I^2 = 0%, p = 0.40). However, average disease activity score in the intervention group (SMD = 1.47, 95% CI = 1.00–1.94) was significantly different from the average disease activity score in the control group (SMD = 0.71, 95% CI = 0.31–1.15; p = 0.02, I^2 = 81%).

Effect on CRP and calprotectin was not significant (MD=0.50, 95% CI = −1.87–2.86; MD=−31, 95% CI = −162–101). Abdominal pain, general well-being, nausea, diarrhoea and poor appetite all improved with cannabi(noid)s on Likert-scales. Baseline quality of life was lower in patients using cannabis amongst cohort studies (MD = −0.64; 95% CI = −0.92 to −0.36) but improved significantly with cannabi(noid)s in a prospective NRS and two RCTs.

Conclusions: Cannabi(noid)s seem ineffective in inducing remission in patients with IBD. However, IBD patients may benefit from cannabi(noid)s by improvement of symptoms and quality of life. Although statistical heterogeneity was low, studies were heterogeneous regarding patients and intervention and mostly included small numbers of patients. Larger uniform studies are needed. Additionally, the most effective formulation and dose as well as safety of cannabi(noid)s have to be further elucidated.



P449

Selective depletion of LAG3+ cells in T-cell-driven inflammation: a randomised, double-blind, placebo-controlled, FTIH phase I/Ib clinical trial

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Background: The temporal cell surface expression of lymphocyte activated gene 3 (LAG3) on recently activated T cells presents an opportunity for targeted therapy in certain inflammatory diseases. LAG3$^+$ cells are enriched in inflamed lesions in ulcerative colitis,[1] Crohn's disease and psoriasis. GSK2831781 is a highly potent, humanised IgG1, antibody-dependent cellular cytotoxicity-enhanced monoclonal antibody that depletes LAG3$^+$ cells.

Methods: A single escalating intravenous dose of GSK2831781 or placebo was administered to 40 healthy volunteers (up to 0.15 mg/kg). Three cohorts of nine patients with mild–moderate psoriasis were randomised to GSK2831781 (0.5, 1.5, or 5 mg/kg) or placebo in a 2:1 ratio. Safety, tolerability, pharmacokinetics (PK), and immunogenicity were evaluated. Circulating LAG3$^+$ T cells were quantified using flow cytometry. LAG3$^+$ and CD3$^+$ cell counts and transcriptomics were assessed in psoriatic skin biopsies acquired prior to dosing and at Day 29. Psoriasis activity severity indices (PASI) and plaque lesion severity scores (PLSS) were profiled.

Results: GSK2831781 was well-tolerated with no safety concerns identified. PK was non-linear, partly explained by target-mediated drug disposition; the non-linear process was saturated at doses ≥0.5 mg/kg. Dose-dependent depletion of circulating LAG3$^+$ memory T cells was observed for 6–8 weeks following a single 5 mg/kg dose. LAG3$^+$ and CD3$^+$ (Figure 1) cells were reduced in psoriasis skin biopsies at 1.5 and 5 mg/kg. Preliminary analysis showed down-regulation of pro-inflammatory mRNA transcripts (*IL-17F*, *IFN-γ*, and *S100A12*) and up-regulation of those associated with epithelial integrity (*CDHR1*) which met the threshold of ≥1.5-fold change in median values vs. placebo at 5 mg/kg. There was no apparent decrease to Treg-associated transcripts (*IL-10* and *FOXP3*). GSK2831781 improved PASI and PLSS (Figure 1) at all doses (difference of estimated mean change from baseline in PLSS vs. placebo for 5 mg/kg, on Day 29 was −2.01 [95% CI: −3.57, −0.44]). The per cent change from baseline PLSS mean for 5 mg/kg, Day 29 was −30.9% (SD: 13.41) vs. placebo −1.9% (SD: 22.40).

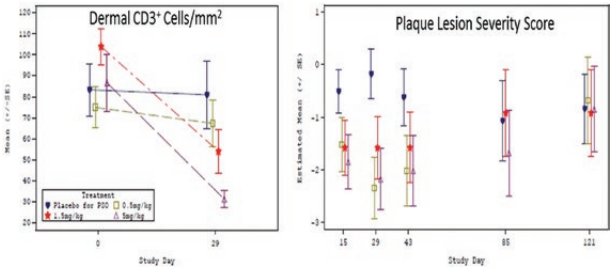

Figure 1

Conclusions: GSK2831781 effected dose-dependent depletion of LAG3$^+$ T cells in blood, reduced LAG3$^+$ and CD3$^+$ cells in psoriatic skin and exhibited encouraging effects on pro-inflammatory and epithelial integrity transcripts, which translated into clinical improvements. These data are supportive of Phase II studies in other T-cell-related diseases, including inflammatory bowel disease.

Reference

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P450

Association of Infliximab trough levels and transmural healing in Crohn's disease

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Background: As new and more effective therapies become available, more objective and rigorous therapeutic outcomes in Crohn's disease (CD) are demanded including mucosal healing (MH) and perhaps transmural healing (TH). Several studies have shown a positive correlation between infliximab (IFX) trough levels and favourable outcomes. Nevertheless, the therapeutic range to achieve such demanding endpoints is still unknown. We aimed to assess the association between IFX trough levels and MH, magnetic resonance enterography (MRE) healing, and TH in CD.

Methods: Retrospective cohort study. Patients with CD with ileal or ileocolonic location receiving IFX treatment with an MRE, ileocolonoscopy and IFX trough level performed within a 2.8 ± 1.9-month interval were included. Active MRE was defined by a bowel wall thickening >3 mm, increased contrast enhancement, and presence of complications; MH was defined as the absence of mucosal ulceration. The presence of inactive MRE and MH defined TH. IFX trough levels were measured using a drug-sensitive assay (Theradiag®).

Results: Ninety-three patients were included; 50.5% were male with a median age of 24 (range 9–64); 83.9% of patients were under concomitant immunomodulator therapy. MH, MRE healing, and TH were present in 64.5%, 57%, and 61.3% patients, respectively. Median IFX trough levels were significantly higher in patients with MH (7.25 µg/ml (1.9–14) vs. 2.9 µg/ml (0.03–7), $p = 0.034$), MRE healing (7.25 µg/ml (3.75–14) vs. 2.14 µg/ml (0.03–7); $p < 0.001$) and TH (7.5 µg/ml (3.75–14) vs. 2.6 µg/ml (0.03–7.66), $p = 0.015$) with respective ROC curves for MH (0.83 (95% CI 0.682–0.978, $p = 0.003$), MRE healing (0.95 (95% CI 0.865–0.985, $p < 0.001$)) and TH (0.875 (95% CI 0.749–1.0, $p < 0.001$). An IFX level ≥5.2 µg/ml, ≥5.7 µg/ml and ≥5.2 µg/ml was predictive of MH (sensitivity 85%; specificity 72.7%), MRE healing (sensitivity 75.5%; specificity 90.2%) and TH (sensitivity 89.5%, specificity 75%).
Conclusions: There is a significant association between higher IFX trough levels and MH, MRE healing and TH in CD. IFX trough levels ≥ 5.2 µg/ml are required to achieve TH, suggesting that IFX levels may differ based on the treatment goal.

P451

Safety and efficacy of ferric carboxymaltose (FCM) for the treatment of iron deficiency anaemia in paediatric patients affected by inflammatory bowel disease (pIBD)

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Background: Iron deficiency anaemia (IDA) is a common complication of pIBD affecting cognitive development and quality of life, and its oral treatment might be is hampered by as poor compliance and efficacy. Intravenous FCM has been shown to be effective and safe for IDA in adult patients, but paediatric studies are limited. Aim: To study the safety and efficacy of FCM in the treatment of IDA in pIBD.
Methods: Retrospective review of all pIBD patients with IDA treated with FCM between 2013 and 2018 in two tertiary care paediatric IBD centres. IDA was diagnosed by combining haemoglobin (HB), haematocrit (HCT), mean cell volume (MCV), iron levels, total iron binding capacity (TIBC), transferrin saturation (TSAT), and ferritin. Inflammatory biomarkers (C-reactive protein [CRP] and faecal calprotectin [FC]) were also assessed. Patients received 500–1500 mg of FCM according to body weight. Bloods were repeated 4–6 weeks after each infusion. Patient and disease characteristics are expressed as percentage and mean ± SD. Paired samples *t*-test was used for statistical analysis, and significance was set at the $p < 0.05$ level.
Results: A total of 213 infusions were administered to 132 pIBD patients with IDA, 70 males (53%), Crohn's disease = 90 (68.2%), ulcerative colitis = 25 (18.9%), inflammatory bowel disease unclassified = 17 (12.9%). Mean age at the first injection was 12.53 years (SD 3.811, range 3–18). Four–six after first FCM injection, a significant improvement was found in HB (107.36 ± 15.899 vs. 122.34 ± SD, $p < 0.001$), HTC (0.333 ± 0.4 vs. 0.375 ± 0.375; $p < 0.001$), MCV (75.94 ± 6.8 vs. 80.35 ± 6.82, $p < 0.001$), iron (7.37 ± 5.03 vs. 11.96 ± 7.21 µmol/l, $p < 0.001$), TIBC (63.71 ± 18.02 vs. 54 ± 49.80 µmol/l, $p < 0.001$) TSAT (12.16 ± 8.14 vs. 24.19 ± 13.64%, $p < 0.001$) and ferritin (64.32 ± 168.45 vs. 215.77 ± 195.43 µg/l, $p < 0.001$) was shown. No statistical difference was observed pre and post infusion for CRP and FC. Only 3 patients showed an adverse reaction: one developed an anaphylactic reaction, the remaining 2 itch and transient fever. No adverse events were recorded in patients under 6 years old ($n = 11$).
Conclusions: FCM administration is safe and effective for routine management in children with IBD, including those who are under 6 years old

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Impact of implementing a rapid access clinic in a high-volume inflammatory bowel disease centre: accessibility, resource utilisation and outcomes

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Background: Emergency situations in inflammatory bowel diseases (IBD) put significant burden on the patient and healthcare system as well. We aimed to prospectively measure indicators of quality-of-care, after implementation of a new rapid access clinic (RAC) at the McGill University Health Centre (MUHC) tertiary care IBD centre.
Methods: The RAC provides patients an opportunity to be evaluated by IBD specialists urgently without having to present to the emergency department. RAC was structured by providing an emergency contact email address to the patients, with a specific document explaining the pertinent symptoms that merit utilisation of this access avenue. Each email was read and reviewed by a specialised IBD nurse or physician. Patient access, resource utilisation and outcome parameters were collected from MUHC IBD Center Rapid Access clinic including consecutive patients who contacted the RAC via email between July 2017 and September 2018.
Results: 261 patients (44.1% men, mean age: 39 years, CD: 64% [L3: 46.2%, B2–3: 31.8%], UC: 32% [extensive colitis: 56.6%], biological therapy: 61.6%, previous surgery: 20.4%) were included. 85.7% of requests were deemed appropriate for a rapid appointment. The reason for RAC appointment was potential disease flare in 62.5% of patients. The median time to RAC visit was 3 days (IQR: 1–6 days) from the first point of contact (email/phone) by the patient. Patients had a fast track evaluation with optimised resource utilisation in the majority of cases. CRP and faecal calprotectin were the most common measures of disease severity performed, 85.2% and 62.5%, respectively. Clostridium difficile stool test and stool culture test were performed in 43.8% and 42.4% of the patients. The frequency of colonoscopy and flexible sigmoidoscopy following the RAC visit were 22.9% and 6.7%. Only a minority of patients underwent CT (7.1%) and MR (1%) imaging. A change in therapy promptly occurred in 57.0% of patients. Within 30 days from the index visit, 21 patients (19 patients with IBD-related symptoms) required ER visit and 9 patients hospital admission. 9 ER visits were initiated during the RAC visit, 7 other patients had unplanned ER visit due to continuous IBD activity. Only 5 patients who were screened by the RAC physician and deemed not to require an urgent consultation presented at the ER (unplanned ER visit rate were 1.8%, no patient required admission).
Conclusions: Implementation of an RAC improved healthcare delivery by avoiding unnecessary ER visits and by increasing access to an IBD centre. Patients had a fast track evaluation with optimised resource utilisation. Data presented here can serve as example for a more optimal cost utilisation for future IBD centres.

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Golimumab in real-world practice in patients with ulcerative colitis: 2-year interim results from a non-interventional trial in Germany

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Background: Prospective data evaluating work productivity and activity in real-world practice are available in patients with moderate to severe ulcerative colitis (UC) treated with Golimumab (GLM) are rare. The aim of this study was to assess the change of work productivity, activity and quality of life (QoL) in UC patients treated with GLM for 2 years in an observational real-world setting in Germany.
Methods: The WPAI-questionnaire (Work Productivity Activity Impairment Questionnaire) was used for the primary analysis. The change of work productivity and ability for daily activities at 3 months and 24 months vs. baseline visit was evaluated. The four subscores of WPAI were assessed: absenteeism, presenteeism, total work productivity impairment (TWPI), and activity impairment. Change in TWPI at Month 3 was the primary endpoint. To assess quality of life the IBDQ (Inflammatory Bowel Disease Questionnaire) and SF12v2 were used. Analysis population included all patients treated with GLM and who did have data for at least two visits (*n* = 282).
Results: A total of 287 UC patients were enrolled. Analysis population included 282 patients. Slightly less than half of the analysis population were male (47%). At baseline, 61% had moderate UC, 17% had severe UC by global physician's assessment. Concomitant steroids were used in 44% of patients. In total, 212 patients were analysed for the primary endpoint, as these were employed at baseline. 24 months after start of treatment all WPAI subscores showed significant improvements compared with baseline. Significant improvements were detected in the IBDQ and SF12v2 (Table 1).

	Change from BL Mo 3(%)	Change from BL Mo 24 (%)
WPAI		
TWPI [mean ± SD]	-17.3 ± 32.3 (N=103) *	-25.5 ± 30.2 (N=46) *
Absenteeism [mean ± SD]	-13.8 ± 38.8 (N=138) *	-23.7 ± 41.8 (N=61) *
Presenteeism [mean ± SD]	-14.9 ± 28.8 (N=105) *	-23.8 ± 27.4 (N=48) *
Activity impairment [mean ± SD]	-14.4 ± 28.5 (N=156) *	-30.7 ± 30.9 (N=72) *
	Change from BL Mo 3	Change from BL Mo 24
IBDQ	26.5 ± 36.4 (N=201) *	42.6 ± 40.6 (N=98) *
SF12v2 (PCS-12)	3.3 ± 8.3 (N=194) *	6.5 ± 9.4 (N=94) *
SF12v2 (MCS-12)	4.2 ± 10.1 (N=194) *	5.5 ± 10.6 (N=94) *

*comparison vs baseline: p<0.001

Conclusions: GLM treatment results in significant improvement of work productivity and daily activities in patients with UC up to 24 months after start of treatment.[1] Patients also experience a significant and clinically meaningful improvement in their QoL in terms of IBDQ[2] and SF12v2.[3]

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P454

Prediction of endoscopic activity in patients with Crohn's disease: systematic review and external validation of published prediction models

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Background: Endoscopic healing (EH) is associated with an improved long-term prognosis and is therefore considered a key target in the treatment of Crohn's disease (CD). Assessment of EH requires ileocolonoscopy, which is a costly and burdensome procedure. A non-invasive index, combining several predictors, to predict EH would simplify and improve management of CD in clinical practice. Published non-invasive models predicting EH often lack external validation. We reviewed the current literature for prediction models for ileocolonic endoscopic activity and subsequently compared their discriminatory abilities using two datasets.
Methods: We systematically searched PubMed, Embase, and the Cochrane libraries until 14 February 2018 for all published diagnostic models based on a combination of at least three predictors, for example, symptoms, serological, or faecal parameters, for ileocolonic endoscopic activity or EH in CD assessed by ileocolonoscopy. We subsequently evaluated the discriminatory value (area under the receiver-operating characteristic curve [AUC]) of the identified models in two separate cohorts, that is, the TAILORIX study[1] (346 colonoscopies in 155 patients), and the development dataset of the Utrecht Activity Index (UAI)[2] (93 colonoscopies in 82 patients). We corrected for clustering per patient employing the Obuchowski method.
Results: After screening 5303 titles, 21 studies reporting on 27 models with ≥3 predictors were identified. The most commonly used predictors, alongside other predictors in the models, were C-reactive protein (*n* = 18 [67%]) and faecal calprotectin (*n* = 13 [48%]). Twelve models were reported in sufficient detail for validation; of these, 8 models could be validated: 6/8 in the TAILORIX and 6/8

in the Utrecht Activity Index dataset. For a threshold of endoscopic activity measured by the CD Endoscopic Index of Severity (CDEIS) ≥3, the AUCs of the published models ranged from 0.55 to 0.85 in the TAILORIX dataset, and from 0.59 to 0.77 in the UAI development dataset (figure). When considering the discriminative ability of continuous values of faecal calprotectin the AUC was 0.82 and 0.79, in the TAILORIX and UAI dataset, respectively, and for CRP: 0.75 and 0.80, respectively.

Conclusions: Based on the discrimnatory ability published prediction models display limited benefit over faecal calprotectin or CRP in prediction of endoscopic activity in CD.

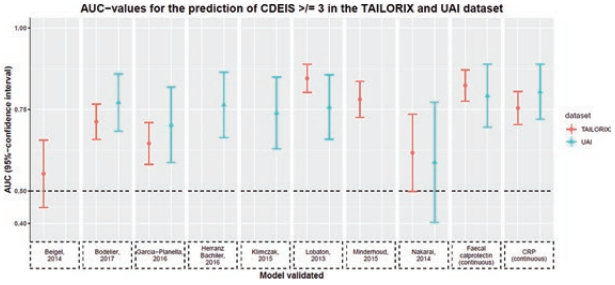

Figure. Discriminative ability of published prediction models, faecal calprotectin and CRP for CDEIS ≥3 as tested in the TAILORIX and UAI development dataset. If no AUC is indicated for a model, it was not validated in that particular dataset, because the predictors were not available. Beigel (2014) was only validated within the colonoscopies performed after the baseline colonoscopy in the TAILORIX dataset. Minderhoud (2015) was not validated in the UAI development dataset, because it was developed in that dataset. The model of Nakarai (2014) was only developed and thus validated for patients with a low CRP value. AUC, area under the receiver operating characteristic curve; CRP, C-reactive protein, UAI, Utrecht Activity Index development dataset.

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P455

Evaluation of the optic nerve function in patients with ulcerative colitis and Crohn's disease

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Background: The purpose of our study was the evaluation of optic nerve function using conventional visual evoked potentials (cVEP) and multi-focal visual evoked potentials (mfVEP) in patients with ulcerative colitis and Crohn's disease without known ophthalmological disease.

Methods: Twenty-six patients with ulcerative colitis and Crohn's disease under treatment with anti-TNFa agent and normal visual acuity, and 36 healthy controls were examined with cVEP and mfVEP in both eyes. The potential and latency of P100 wave of cVEP and the maximum potential density and latency of the three most central rings of mfVEP and also their total values were studied by specialised ophthalmologists.

Results: As for the right eyes (OD) of the patients, there was no statistically significant difference for cVEP, in comparison with controls. As for mfVEP, there was a statistically significant difference between patients and controls to the mean value of potential density in ring 1 (p = 0.019, with mean value 228.77 ± 138,67 nV/deg^2) and ring 3 (p = 0.016, with mean value 12.08 ± 8.50 nV/deg^2) and to latency in ring 3 (p = 0.017, with mean value 180.80 ± 58.63 ms). Also a statistically significant difference was found in the total potential value (p = 0.021, with a value of 140.88 μV).

As for the left eye (OS), there were no statistically significant differences in cVEP between patients and controls. In the mfVEP, a statistically significant difference between patients and controls was revealed in the latency (p = 0.038, with latency mean value 166.07 ± 38.41 ms). Potential density in ring 2 was very close to in the statistical significance (p = 0.053).

Conclusions: The mfVEP method revealed disturbances in optic nerve function, in patients with Crohn's disease or ulcerative colitis under biologic treatment without obvious ophthalmologic problems. These functional disorders are likely to be related to the disease and its treatment, so further research on the subject is warranted taking into account disease course.

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Quality of life is associated with wearable-based physical activity in patients with inflammatory bowel disease: a prospective, observational study

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Background: Inflammatory bowel disease (IBD) patients are at risk for an impaired quality of life, for example, due to the chronic relapsing character of the disease. Even though there a numerous emerging IBD therapies these days, a cure of the disease is still not offerable. So, patient-reported outcomes such as quality of life are gaining importance in the assessment of patients. The association of objectively measured physical activity and quality of life in IBD patients has not been studied in depth. The present prospective, observational study was devised to analyse habitual physical activity in IBD patients and further investigate the link between physical activity and disease-specific quality of life.
Methods: 91 IBD patients were stratified into 4 groups (Crohn's disease (CD) and ulcerative colitis (UC), in remission and with moderate–severe activity, respectively), and evaluated with respect to disease-specific quality of life (IBDQ), habitual physical activity (accelerometry), body composition (bioelectrical impedance analysis, BIA), as well as clinical (HBI, SCCAI) and biochemical (CRP, faecal calprotectin) parameters of disease activity.
Results: In patients with moderate–severe disease activity, IBDQ was significantly lower when compared with patients in remission (Mann–Whitney *U* test and Kruskal–Wallis test, $p < 0.001$). The physical activity level (PAL) was higher in remission than in active disease (Mann–Whitney *U* test, $p < 0.05$). IBDQ was significantly correlated to the duration of strenuous physical activity per day ($p = 0.029178$, $r = 0.235$), skeletal muscle mass ($p = 0.033829$, $r = 0.229$), and biomarkers of inflammation (CRP: $p < 0.005$, $r = -0.335$, faecal calprotectin: $p < 0.005$, $r = -0.385$). Furthermore, patients with active disease had a significantly lower sleep efficiency.
Conclusions: In this prospective, cross-sectional study, disease-specific quality of life was significantly associated with accelerometrically determined habitual physical activity as well as disease activity in patients with inflammatory bowel disease. This may be related to a reciprocal impact of these factors. Habitual physical activity, IBD-disease activity as well as health-related quality of life closely correlate with each other and should be taken in account during doctors' visits to further improve patients general well-being and establish a system of quality of life modifiers next to medical therapies.

P457

Influence of concomitant immunomodulators during maintenance therapy with Adalimumab in inflammatory bowel disease: looking for the ideal patient to use monotherapy

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Background: Adalimumab (ADL) is widely used in in patients with inflammatory bowel disease (IBD), both Crohn`s disease (CD) or ulcerative colitis (UC). High serum ADL levels are associated with better outcomes. Although concomitant immunosuppressants (IS) are often added to ADL to prevent the formation of antibodies, addition of an immunomodulator in patients receiving ADL is still a matter of debate. Some authors suggest that ADL can be use in monotherapy to avoid some potential adverse effects (infections or tumours). The aim of this study was to assess the association of random serum ADL levels with the concomitant use of IS and other relevant clinical variables to be able to indetify the ideal candidates to be treated in monotherapy.
Methods: We conducted a prospective study in IBD patients (CD or UC) who received maintenance therapy with ADL. All patients received induction with ADA (160 mg and 80 mg at Weeks 0 and 2) and were maintained on either 40 mg every week or every other week. All ADA samples were drawn after patients had been receiving their maintenance dose for at least 12 weeks. Studied variables were gender, UC or CD, Body Mass Index (BMI), smoking habit, extra intestinal manifestations (EIMs), previous Infliximab (INFX) treatment, concomitant IS or prednisone (PDN), faecal calprotectin, albumin levels and C reactive protein (CRP.
Results: Data were available for 642 serum samples from 228 patients (45 UC and 183 CD), median age 41 years (range 14–74). Of them 110 (48%) were treated with IS and 17 (7.5%) were under PDN, 114 (50%) were male, 53 (23%) smokers, 59 (26%) had EIMs and 96 (42%) had received IFX previously. Median BMI was 24.2 (range 16–48). Median serum ADL were 8.5 μg/ml (range 0–24). Univariate analysis showed significant association between gender ($p = 0.004$), IS treatment ($p = 0.001$), PDN treatment (0.001), EIMs (0.03), UC ($p = 0.001$), BMI ($p = 0.001$), CRP levels ($p = 0.001$), albumin levels ($p = 0.03$) and faecal calprotectin ($p = 0.001$) with serum ADL levels. Multi-variable analysis showed significant association between serum ADL levels and the use of IS (OR = 0.52; CI 95% 0.036–0.24), CD (OR = –0.18; CI 95% –0.018 to –0.08), BMI (OR = –0.18; CI 95% –0.03 to –0.01) and faecal calprotectin (OR = –0.16; CI 95% –0.00 - 0.00)
Conclusions: There is an inverse relationship between absence of IS treatment, CD, BMI and faecal calprotectin with serum ADL levels. Therapeutic drug monitoring should be done more often in these group of patients. In case of combo therapy, the withdrawal of immunomodulators as an adjuvant therapy should be conscientiously weighed in obese patients with CD and with elevation of faecal calprotectin.

P458

Effect of cognitive behavioural therapy on clinical disease course in adolescents and young adults with inflammatory bowel disease and subclinical anxiety and/or depression: results of a randomised trial

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Background: Anxiety and depressive symptoms are prevalent in patients with inflammatory bowel disease (IBD) and may negatively influence disease course. We investigated the effect of cognitive be-

havioural therapy (CBT) on clinical disease course in 10- to 25-year-old IBD patients with subclinical anxiety and/or depression.
Methods: In this multi-centre parallel group randomised controlled trial, patients were randomised to disease-specific CBT in addition to standard medical care (CBT + Care us usual [CAU]) or CAU only. Primary outcome was relapse rate in the first 12 months after randomisation. Secondary outcomes were clinical disease activity, faecal calprotectin and C-reactive protein (CRP). χ^2-test and linear-mixed models were performed to compare groups.
Results: Seventy patients were randomised (mean age 18.3 years (±50% < 18 years), 31.4% male, 51.4% Crohn's disease, 78.6% quiescent disease). After 12 months, relapse rate did not differ between patients in the CBT+CAU (n = 37; 43.2%) vs. CAU (n = 33; 48.5%) group (p = 0.66). Furthermore, clinical disease activity, faecal calprotectin and CRP, did not significantly change over time between and within both groups. Exploratory analyses in 10- to 18-year-old patients showed a different course of faecal calprotectin (p = 0.008) between both groups, with a 9% increase/month in the CAU (p = 0.004). In addition, in the same exploratory analysis for CRP, the difference between both groups approached significance (p = 0.054), with a 7% increase/month in the CAU group (p = 0.022).
Conclusions: CBT did not influence disease course in young IBD patients with subclinical anxiety and/or depression. However, exploratory analyses showed a possible positive effect of CBT on CRP and faecal calprotectin levels in children.

P459

Vedolizumab for the treatment of chronic pouchitis: the Edinburgh experience

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Background: Pouchitis is the most common complication following ileal pouch-anal anastomosis (IPAA) formation for medically refractory UC. Despite most patients responding to antibiotics, 10–15% of patients will develop chronic debilitating pouchitis that becomes antibiotic dependant or refractory to antibiotics and immunosuppressive therapy. Vedolizumab is a gut selective a4b7 anti-integrin biologic that offers a potential new mechanism for the treatment of chronic pouchitis. Therefore, the aim of this study was to evaluate the effectiveness of vedolizumab for the treatment of chronic pouchitis
Methods: This was a retrospective case series performed at a tertiary IBD centre in Edinburgh, UK. All patients started on vedolizumab for the indication of antibiotic dependant or treatment refractory (failed antibiotic therapy ± immunomodulator or anti-TNF) pouchitis following IPAA for active UC were included. All patients had active pouchitis, defined by a pouchitis disease activity index (PDAI) >7. Baseline characteristics were collected via review of electronic medical records. Assessment of improvement was determined by the treating physician at last follow-up (score: '0' no improvement; '1' mild; '2' moderate; '3' excellent). Differences in the PDAI clinical subscore and faecal calprotectin levels between baseline and last follow-up were also analysed using the Wilcoxon signed rank test.
Results: Seven patients were included (4 females, 3 males; median age 51 years [IQR 48–59]) with a median follow-up of 46 weeks (IQR 29–106). Of these, 6 patients were started on vedolizumab for the treatment of refractory pouchitis whilst 1 patient was started for antibiotic dependant disease. All patients remained on vedolizumab at the end of follow-up. Median PDAI at baseline was 9 (8–10). At last follow-up 0%, 42.9% (n = 3/7), 14.3% (n = 1/7) and 42.9% (n = 3/7) were deemed to have no, mild, moderate and excellent improvement, respectively. The mean PDAI clinical sub-score fell significantly from 5 to 2 (Figure 1A). The mean faecal calprotectin levels also fell significantly from 618 µg/g to 129 µg/g (Figure 1B). At last follow-up, 85.7% (n = 6/7) required no further antibiotic treatment since initiating vedolizumab including the patient with previously antibiotic dependant disease. Arthralgia was the only reported adverse event (n = 2).

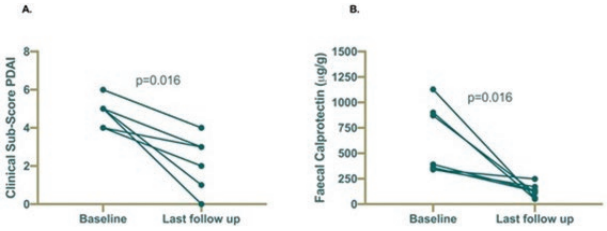

Figure 1.

Conclusions: Vedolizumab is an effective and well-tolerated treatment option for chronic refractory pouchitis.

P460

Efficacy of ustekinumab in patients with anti-TNF refractory Crohn's disease: data from a real-world study in Brazil

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Background: Ustekinumab (UST) is a fully human monoclonal antibody against IL-12/23. UST induced a clinical response and maintained a higher rate of response than placebo in patients with Crohn's disease (CD). UST was approved in Brazil in November 2017. Real-world data regarding efficacy and safety to UST in CD is lacking in our country. We report our experience of UST use in patients with CD refractory to anti-TNF therapy.
Methods: An open-label prospective not controlled study was performed including patients from five academic medical centres with severely active, refractory CD starting on UST (IV infusions followed by scheduled subcutaneous [SC] injections) between November 2017 and October 2018. All patients signed the informed consent form. We evaluated clinical response and remission (based on Harvey–Bradshaw index [HBI]), C-reactive protein (CRP) and faecal calproprotectin (FC) levels. Clinical response and clinical remission were defined by HBI decrease ≥3 and HBI ≤3, respectively. Patients were evaluated by HBI from baseline until Week 44. CRP and FC were evaluated from baseline and at Week 16.
Results: Forty-four patients were treated with UST during the study period. The mean age was 37.1 years (IQR: 18–68), disease duration 9.8 years (IQR: 1–29), mean age at diagnosis was 26.9 (IQR: 6–66). Seventy-five per cent of patients had previous surgeries, 54.5% had historical of perianal disease and 63.6% had anaemia at baseline. Mean HBI at baseline was 10.4 (IQR: 5–19). At baseline mean CRP was 29.1 mg/l (IQR: 0.60–125) and mean FC was 1210 mg/kg (IQR:

150–3157, *n* = 29). The majority of patients received SC injections every 8 weeks. At Week 8, 84.1% achieved clinical response and 38.6% achieved clinical remission. Clinical remission at second, third, fourth and fifth SC injection (from Week 16 to 44) was 60.5% (23/38), 63.0% (17/27), 60.9% (14/23) and 75% (15/20), respectively. CRP decreased to 18.4 mg/l at Week 8 and to 14.6 mg/l at Week 16. Mean FC at Week 16 was 1011.1 mg/kg (IQR: 5–3077), exhibiting a decrease of 198.9 mg/kg after induction. Two patients stopped UST due to non-response. No new safety signals were observed.

Conclusions: UST therapy was successful for inducing clinical remission and improving laboratory biomarkers of disease activity in patients with refractory CD. Both UST induction and maintenance regimens until Week 44 were well tolerated. This results support a favourable safety profile.

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Endoscopic features for loss of response in patients with Crohn's disease who were treated with infliximab by top-down strategy

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Background: The top-down strategy of treatment with anti-TNF agents showed the potentials for improved efficacy and outcomes in patients with Crohn's disease (CD), especially those suspected to have a poor prognosis. However, few studies have evaluated clinical and endoscopic features associated with secondary loss of response (LOR) in CD cases treated with infliximab by the top-down strategy.

Methods: We treated 410 CD patients with infliximab (IFX) from December 2004 to May 2010 in our hospital. Among these CD cases treated with IFX, those receiving the top-down regimen were defined by a disease duration of less than 2 years, no treatment history of steroid/immunomodulator/biologics, and no history of surgery. Effectiveness of IFX was defined on the basis of a more than 70-point decrease in the Crohn's disease activity index (CDAI). Endoscopic effectiveness was defined as a more than 50% decrease in the simple endoscopic score for Crohn's disease (SES-CD). LOR was defined as a more than 50-point increase, requiring additional or increasing doses of concomitant therapy.

Results: We retrospectively investigated 58 CD cases treated with infliximab by the top-down strategy. The cumulative remission rate was 86.1% at 1 year, 70.0 at 2 years and 61.0% at 4 years. The LOR group (*n* = 24, 10.9 ± 8.8 months) had a significantly longer disease duration than the non-LOR group (*n* = 34, 9.9 ± 18.8 months) (*p* = 0.04). The other factors at baseline including concomitant immunomodulator administration, albumin level, CDAI, whole SES-CD and segmental SES-CD of 5 sections each did not differ between the 2 groups. Among the changes in segmental SES-CD at Week 52 from week 0 as the index of endoscopic improvement, the scores for the caecum and ascending colon (–2.0 ± 2.0), the descending and sigmoid colon (–1.0 ± 1.9) and the rectum (+0.4 ± 2.4) in the LOR group were significantly lower than those in the non-LOR group (–4.3 ± 0.5, $p < 0.01$; –5.3 ± 2.4, $p < 0.01$; –2.6 ± 1.8, $p < 0.02$), while endoscopic improvements of the other segments were observed in both groups. Especially, longitudinal ulceration in the descending and sigmoid colon in the LOR group was not significantly improved as compared with that in the non-LOR group (positive rate: 62.5% vs. 71.4% at week 0, 62.5% vs. 14.3% at Week 52; $p = 0.05$).

Conclusions: LOR occurrence rate in CD patients treated with IFX by the top-down strategy was similar to that in CD patients treated with IFX by the conventional strategy. The existence of an active lesion in the ileocaecum or distal colon, especially a highly active lesion (eg, longitudinal ulcer) in the distal colon, at baseline might predict LOR endoscopically.

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Dietary restrictions on inflammatory bowel disease

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Background: Patients with inflammatory bowel disease (IBD) have symptoms associated with inflammation of the gastrointestinal tract that can lead to changes in their dietary habits to control their symptoms. The objective of this study was to demonstrate that there is an excessive food restriction in this group of patients.

Methods: Prospective study evaluating the eating habits of 34 patients with IBD in the symptomatic and asymptomatic phases of the disease.

Results: Of the 34 patients, 38.2% were male and 61.8% female. 73.5% had Crohn's Disease (CD) and 26.5% ulcerative colitis (UC) with a mean of 13.2 years of disease duration. The mean body mass index (BMI) was 22.8 kg/m^2. In the symptomatic phase of the disease, 97.1% of the patients stated that they had food restrictions, avoiding 3.4 food groups, more frequent abstain of vegetables and dairy products. In the asymptomatic phase, 79.4% of the patients made restrictions, avoiding 2.2 food groups, with milk products being the most exclude. Patients with a history of small and/or large intestine removal were twice as restrictive in the symptomatic phase of the disease (7.5 food groups). Thirty per cent of patients maintained the same restrictions in the symptomatic and asymptomatic phase of the disease. Analysing the restrictions by IBD type, they were similar in both phases of the disease. Patients with a higher educational level restricted an average of one more food group in the symptomatic phase of the disease. In addition to food groups, restrictions on confection methods were observed both in the symptomatic and asymptomatic phases, being more evident in the first one, with fried being the most avoided.

Conclusions: There is an excessive food restriction in both phases of the disease, although exclusion diets are not recommended and there is little evidence of their role in symptom relief. Creating a multi-disciplinary consultation of IBD with the presence of a nutritionist would bring benefits to combat myths and adjust the diet individually to avoid unnecessary restrictions that may bring future complications.

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Factors to determine prognosis of intestinal cancer associated with Crohn's disease

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Background: Patients with Crohn's disease (CD) have increased risk of developing intestinal cancer (IC). However, the factors to deter-

mine the prognosis of such cancer have not been revealed yet. The aim of this study was to clarify the factors to determine prognosis of IC in CD.

Methods: We searched for IC cases associated with CD from a Japanese medical database (Ichushi) between 1983 and 2015, using two keywords (Crohn's disease and malignancy), picking up only IC, and arranging duplicates. The total number of cases were 271, and the prognosis was described in 141. The patients were classified to two groups: Survival group (n = 51; observation time = 16 (3–132) months (median (range)) and Death-Recurrence (DR) group (n = 93: observation time = 10 (0.6–72) months), where the latter includes patients with advanced disease, residual cancer after surgical treatment. or recurrence after curatively intended operation.

Results: The age at IC diagnosis is younger in DR group (39.5 (25–84) vs. 46 (27–73); $p < 0.01$). The age at Crohn's disease was also younger in DR group (27 (14–69) vs. 24 (6–69); $p < 0.05$), and the durations of each group were similar (15 years vs. 16.5). Penetrating disease behaviour was more frequent in DR group (60% vs. 39%), but the difference did not reach statistical significance ($p = 0.08$). The proportion of fistula-originated cancer was similar (48% vs. 16%; $p < 0.01$). In DR group, the cancer was located more frequently around the rectum (rectum and anus; 68% vs. 51%; $p < 0.05$). Preoperative diagnosis was achieved less frequently in DR group (58% vs. 67%) without statistical significance. The histology of cancer was 10%:19%:11%:7%:49% (well differentiated: moderately differentiated: poorly differentiated: signet ring cell: mucinous) in DR group and 52%:14%:2%:0%:26% in Survival group, and the proportion of well differentiated adenocarcinoma was significantly lower in the former ($p < 0.01$). IC stage at diagnosis was 1%:3%:23%:35%:38% (stage 0:1:2:3:4) in DR group and 10%:30%:50%:10%:0% in Survival group, and the proportion of Stage 3 was higher in the latter ($p < 0.01$).

Conclusions: In conclusion, young IC and CD diagnosis, fistula-originated cancer, cancer around rectum, Stage 3 or more advancer, and histology other than well differentiated carcinoma were risk factors for poorer prognosis in IC associated with CD.

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Study of the usual aetiologies of methotrexate and azathioprine discontinuation in inflammatory bowel disease

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Background: A significant number of patients with inflammatory bowel disease (IBD) have to interrupt azathioprine and sometimes subsequently methotrexate too. We aimed to investigate the common reasons of the interruption of both these important immunomodulators at a tertiary referral IBD centre.

Methods: We performed a retrospective analysis of 852 IBD patient records in our department following a predefined investigation protocol.

Results: We identified 57 patients who received or were currently on MTX and 45 patients who interrupted AZA before the introduction of biologics. In total, 38 patients (21 males, 17 females) aged 39 ± 11 years (range 20–84 years) interrupted MTX subsequently to AZA interruption. Twenty-nine of these patients were diagnosed with Crohn's disease (CD) and 9 with ulcerative colitis (UC). In total 7 CD patients (30.3%) and 2 UC patients (22.2%) had been operated with major surgery at the time of MTX interruption. The reasons that patients interrupted both AZA and MTX are listed in Table. Thirteen of the 38 patients (34.2%) had common reasons to interrupt both AZA and MTX. The most frequent common reason was ineffectiveness/non-response (7 out of 13 patients) gastrointestinal intolerance (3 out of 13 patients) and bone marrow toxicity (2 out of 13 patients). Most patients with AZA and MTX intolerance were subsequently started on biological agents.

Reasons to stop AZA or MTX	PRE-AZA patients (n=38)	%	PRE-MTX patients (n=38)	%
Ineffective/non-response	15	39.5	20	52.6
Pancreatitis	7	18.4	-	-
Liver toxicity	3	7.9	5	13.2
Gastrointestinal intolerance	4	10.5	6	15.8
Flu-like syndrome	1	2.6	1	2.6
General/non-specified intolerance	1	2.6	-	-
Leucopenia	2	5.3	1	2.6
Severe infection	1	2.6	-	-
Skin allergy	1	2.6	-	-
Bone marrow toxicity	2	5.3	2	5.3
Pregnancy/breast feeding	1	2.6	-	-
Long-term disease remission	-	-	-	-
Rare causes (oral ulcer, MS)	-	-	2	5.3
Maximal MTX dose >1.3gr	-	-	1	2.6

Conclusions: A significant number of IBD patients who interrupt AZA due to ineffectiveness/non-response and are subsequently switched to MTX will discontinue MTX also for the same reason. Ineffectiveness and gastrointestinal intolerance for AZA makes the patient prompt to interrupt also MTX for the same reason.

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UC trial designed more than 5 years ago in the light of the EMA guideline on the development of new medicinal products for the treatment of ulcerative colitis

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Background: Developing a new drug in ulcerative colitis (UC) is challenging. More challenging is the clinical trial design. We highlight, here, the Phase 3 trial design of a new 5ASA drug (TP0503) and compare it to the current EMA 'guideline on the development of new medicinal products for the treatment of ulcerative colitis'.

Methods: Each item in the EMA guideline was compared with the TP0503 protocol (Asacol 1600 mg vs. Asacol 400 mg) and GEMINI1 trial (vedolizumab). This comparison will cover the patient selection (section 4), efficacy assessment (section 5), study design (section 6). Safety aspects (section 7) and the risk management plan (section 8) were well-respected by both trials.

Results: As per the EMA guideline, patient selection in TP0503 and GEMINI1 was based on symptoms, endoscopic and histological findings. Patients with malignancy and Clostridium D. infection were excluded. TP0503 was also in line with the Jairath et al. recommendation concerning the endoscopic severity of disease at entry. All TP0503 patients had a Mayo Endoscopic Score (MES) ≥2. MES was assessed by one central reader. This is one of the first trials that used central reading for inclusion and efficacy assessments. In the efficacy assessment, TP0503 respected each item of the guideline looking at the symptomatic and endoscopic remission as a treatment goal for induction and maintenance of remission in UC. In TP0503, the primary endpoint was a co-primary endpoint at Week 8 of clinical remission and endoscopic remission as defined by MAYO ≤2 without any subscore >1, whilst GEMINI trial used the total MAYO response. Remission was only secondary endpoint, not in line with EMA guideline. For the study design, TP0503 respected each item of the guideline except for two. For ethical reasons, it was not possible to randomise UC patients

to a placebo arm therefore TP0503 trial was a non-inferiority trial. Nor where they stratified according to prior treatment.
With regards to missing data, TP0503 considered all missing data as failures, unlike the GEMINI trial where the LOCF was used to manage some missing data. Patients on topical co-medication were excluded from both trials. Looking at safety aspects, beside the exclusion of acute severe colitis and patients with pouchitis, which are not part of the mesalazine indications, TP0503 respected all other criteria.
Conclusions: TP0503 trial was designed to insure the most objective evaluation of efficacy in UC patients. The most stringent criteria were used to include and assess patients with mild and moderate UC patients.

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Tofacitinib for the treatment of ulcerative colitis: Up to 5.4 years of safety data from global clinical trials

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Background: Tofacitinib is an oral, small-molecule Janus kinase inhibitor approved in several countries for the treatment of ulcerative colitis (UC). The efficacy and safety of tofacitinib as UC induction and maintenance therapy were evaluated in Phase (P) 2[1] and P3[2] randomised, placebo-controlled studies, and in an ongoing, open-label, long-term extension (OLE) study.[3] We report updated tofacitinib safety analyses from the UC programme, with exposure up to 5.4 years.
Methods: Patients who received placebo, tofacitinib 5 or 10 mg twice daily (BID) were analysed as two cohorts: Maintenance (P3 maintenance, *n* = 592) and Overall (patients receiving tofacitinib 5 or 10 mg BID in P2, P3 or the OLE study, *n* = 1157; 2050.5 patient-years' exposure; data at November 2017). Proportions and incidence rates (IR; unique patients with events per 100 patient-years) were evaluated for adverse events (AEs) of special interest. Opportunistic infections, malignancies, major adverse cardiovascular events (MACE) and gastrointestinal perforations were reviewed by independent adjudication committees. Results in the overall Ccohort based on the previous December 2016 data cut are presented for context.
Results: In total, 1157 patients received ≥1 dose of tofacitinib 5 or 10 mg BID. Demographics and disease characteristics were generally similar among treatment groups across cohorts. For the Overall Cohort, most patients (*n* = 956, 83%) received an average tofacitinib dose of 10 mg BID. IR for AEs of special interest were: death, 0.2; serious infection, 1.9; herpes zoster, 3.8; opportunistic infection, 1.2; malignancy (excluding non-melanoma skin cancer [NMSC]), 0.6; NMSC, 0.8; MACE, 0.3; and gastrointestinal perforation, 0.1.
Conclusions: The safety profile of tofacitinib in patients with UC was manageable, and similar to the tofacitinib rheumatoid arthritis programme and that of other UC therapies including biologics. IR for AEs of special interest did not increase with longer exposure relative to previously reported analyses from the OCTAVE programme. A dose-dependent risk of herpes zoster was observed.

Table. Baseline demographics and disease characteristics, and IR (unique patients with event per 100 pt-years) for AEs of special interest in the tofacitinib UC programme, for each cohort

	Maintenance Cohort						Overall Cohort – Dec 2016 (Induction + Maintenance + OLE)		Overall Cohort – Nov 2017 (Induction + Maintenance + OLE)	
	Placebo (N=198)		Tofacitinib 5 mg BID (N=198)		Tofacitinib 10 mg BID (N=196)		Tofacitinib All (N=1157)		Tofacitinib All (N=1157)	
Age (years), mean (SD)	43.4 (14.0)		41.9 (13.7)		43.0 (14.4)		41.3 (13.9)		41.3 (13.9)	
Female, %	41.4		48.0		43.9		41.3		41.3	
Race, n % White Asian	155 (78.3) 26 (13.1)		164 (82.8) 23 (11.6)		153 (78.1) 25 (12.8)		927 (80.1) 144 (12.4)		927 (80.1) 144 (12.4)	
Total Mayo score at baseline, mean (SD)	3.3 (1.8)		3.3 (1.8)		3.4 (1.8)		8.6 (2.0)		8.6 (2.0)	
Disease duration (years), mean (SD)	8.8 (7.5)		8.3 (7.2)		8.7 (7.0)		8.2 (7.0)		8.2 (7.0)	
Total pt-years' exposure	100.4		146.2		154.3		1612.8		2050.5	
Treatment duration (days), median (range)	138 (14–382)		363.5 (22–420)		368 (1–399)		514 (1–1606)		609 (1–1961)	
Pts with AEs, n (%)	149 (75.3)		143 (72.2)		156 (79.6)		950 (82.1)		969 (83.8)	
Pts with SAEs, n (%)	13 (6.6)		10 (5.1)		11 (5.6)		169 (14.6)		189 (16.3)	
	n (%)	IR (95% CI)	n (%)	IR (95% CI)	n (%)	IR (95% CI)	n (%)	IR (95% CI)	n (%)	IR (95% CI)
Death	0 (0.0)	0.0 (0.0, 3.6)	0 (0.0)	0.0 (0.0, 2.5)	0 (0.0)	0.0 (0.0, 2.4)	4 (0.3)	0.2 (0.1, 0.6)	5 (0.4)[a]	0.2 (0.1, 0.6)
Serious infection	2 (1.0)	1.9 (0.2, 7.0)	2 (1.0)	1.4 (0.2, 4.9)	1 (0.5)	0.6 (0.0, 3.5)	33 (2.9)	2.0 (1.4, 2.8)	39 (3.4)	1.9 (1.3, 2.5)
Herpes zoster	1 (0.5)	1.0 (0.0, 5.4)	3 (1.5)	2.1 (0.4, 6.0)	10 (5.1)	6.6 (3.2, 12.2)	65 (5.6)	4.1 (3.1, 5.2)	76 (6.6)	3.8 (3.0, 4.7)
Opportunistic infection[b]	1 (0.5)	1.0 (0.0, 5.4)	2 (1.0)	1.4 (0.2, 4.9)	4 (2.0)	2.6 (0.7, 6.7)	21 (1.9)	1.3 (0.8, 2.0)	25 (2.2)	1.2 (0.8, 1.8)
Non-herpes-zoster opportunistic infection[b]	0 (0.0)	0.0 (0.0, 3.6)	0 (0.0)	0.0 (0.0, 2.5)	0 (0.0)	0.0 (0.0, 2.4)	4 (0.4)	0.2 (0.1, 0.6)	4 (0.4)	0.2 (0.1, 0.5)
Malignancy (excl. NMSC)[b,c]	1 (0.5)	1.0 (0.0, 5.4)	0 (0.0)	0.0 (0.0, 2.5)	0 (0.0)	0.0 (0.0, 2.4)	8 (0.7)	0.5 (0.2, 1.0)	13 (1.2)	0.6 (0.3, 1.1)
NMSC[b]	1 (0.5)	1.0 (0.0, 5.4)	0 (0.0)	0.0 (0.0, 2.5)	3 (1.5)	1.9 (0.4, 5.6)	11 (1.0)	0.7 (0.3, 1.2)	16 (1.4)	0.8 (0.4, 1.3)
MACE[b]	0 (0.0)	0.0 (0.0, 3.6)	1 (0.5)	0.7 (0.0, 3.8)	1 (0.5)	0.6 (0.0, 3.5)	4 (0.4)	0.2 (0.1, 0.6)	6 (0.5)	0.3 (0.1, 0.6)
Gastrointestinal perforation[b,d]	1 (0.5)	1.0 (0.0, 5.4)	0 (0.0)	0.0 (0.0, 2.5)	0 (0.0)	0.0 (0.0, 2.4)	3 (0.3)	0.2 (0.0, 0.5)	3 (0.3)	0.1 (0.0, 0.4)

Adjudicated data do not include data from the Phase 2 Study (A3921063; NCT00787202)
[a]Causes of death were one case each of aortic dissection, pulmonary embolism, hepatic angiosarcoma, acute myeloid leukaemia and malignant melanoma
[b]Adjudicated events. Percentage (%) was calculated based on the number of pts in studies in which adjudication was performed
[c]One case of breast cancer in the Maintenance Cohort (placebo arm), and, in the Overall Cohort, one case each of cervical cancer, hepatic angiosarcoma, cholangiocarcinoma with metastases to peritoneum, leiomyosarcoma, Epstein-Barr-virus-associated lymphoma, malignant melanoma, renal cell carcinoma, lung cancer, invasive ductal breast carcinoma, adenocarcinoma of the colon with metastases to the liver, essential thrombocythaemia, acute myeloid leukaemia and adenocarcinoma of the colon
[d]Gastrointestinal perforation excludes fistulae and abscesses below peritoneal reflection
AE, adverse event; BID, twice daily; CI, confidence interval; IR, incidence rate; MACE, major adverse cardiovascular events; N, number of patients in the treatment group; n, number of unique patients with a particular adverse event; NMSC, non-melanoma skin cancer; OLE, open-label, long-term extension; pt, patient; SAE, serious adverse event; SD, standard deviation; UC, ulcerative colitis

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Circulating CD8 α4β7+ and CD8b7+ memory T cells as early biomarkers of clinical response to vedolizumab in ulcerative colitis

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Background: Vedolizumab (VDZ) is a humanised monoclonal antibody targeting the α4β7 integrin us in ulcerative colitis (UC). So far, no biomarker of response to VDZ has been identified.
AIM: To assess whether circulating CD4+ and CD8+ α4β7+/ α4β7- memory T lymphocytes are molecular markers of response to VDZ treatment in patients with UC.
Methods: Prospective study, 15 patients with active UC (Ulcerative Colitis Disease Activity Index (UCDAI) >3, Mayo endoscopic subscore >1, faecal calprotectin >250 µg/g) and with prior failure to anti-TNFα therapy, starting treatment with VDZ (300 mg iv, standard induction regime). Peripheral blood sample obtained just before first dose of VDZ, purification of circulating memory T cells (CD45RO+) and simultaneous analysis of CD CD4+ and CD8+ limphocitic subpopulations (α4β7+/–, HLA-DR+/–, CD25+/–, IL23R+/–, CCR9+/–, IL17A+/–, IL-23R+/–, IL-9+/–, β7 +/–) by flow citometry. Clinical

response and remission (UCDAI clínic) and faecal calprotectin levels were evaluated at Weeks 6 and 14.
Results: Eight females, age 46 ± 16 years extent (Montreal E1: 2 patients, E2: 8 patients, and E3: 5 patients), 7 severe colitis (UCDAI > 9). At Week 6: 9 patients were in clinical response, 7 patients were in clinical remission and 8 patients had faecal calprotectin levels <250 µg/g. At Week 14 : 10 patients remained in clinical response , 8 were in clinical remission and 10 patients had faecal calprotectin levels <250 µg/g. Patients with clinical response, clinical remission and faecal calprotectin levels < 250 µg/g at Week 6; and clinical remission and faecal calprotectin levels < 250 µg/g at Week 14, presented an absolute account of CD8 α4β7+ and CD8b7+ memory T cells at baseline significantly higher when compared with patients with no VDZ response (Table 1). No differences were identified according to the severity of the flare or the extent of the disease. No statistically significant differences were identified in the other lymphocyte subpopulations included in the study.

Wk 6	CD8 α4β7+	p	CI (95%)	CD8b7+	p	CI (95%)
Clinical response (yes/no)	23.10/9.63	**0.005**	6.80-20.16	21.57/12.8	0.11	3.10-14.40
Clinical remission (yes/no)	23.10/10.01	**0.006**	7.99-17.59	21.56/13.64	0.017	2.41-13.45
Fecal calprotectin < 250 mcg/g (yes/no)	22.9/12.04	0.036	3.25-18.47	21.12/14.91	0.09	-0.23-12.65
Wk 14	**CD8 α4β7+**	**p**	**CI (95%)**	**CD8b7+**	**p**	**CI (95%)**
Clinical response (yes/no)	19.91/10.31	0.18	3.37-15.80	19.75/13.38	0.05	-0.36-13.10
Clinical remission (yes/no)	21.86/9.63	**0.004**	5.84-18.62	21.16/12.80	**0.008**	3.09-13.63
Fecal calprotectin < 250 mcg/g (yes/no)	22.50/12.20	**0.042**	2.68-17.90	22.30/13.98	**0.029**	2.64-14

Conclusions: The absolute account of CD8 α4β7+ and CD8b7+ memory T cells before starting VDZ treatment could be early biomarkers of clinical response, allowing to select a subset of patients that are more likely to respond to VDZ.

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Long-term function after transanal vs. transabdominal ileal pouch-anal anastomosis for ulcerative colitis: a multi-centre cohort study

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Background: The transanal approach has been introduced in ileal pouch-anal (IPAA) surgery to gain better exposure for the rectal dissection. It has been shown to be safe with lower morbidity than the trans-abdominal approach. The aim of this study was to compare functional outcome of transanal ileal pouch-anal anastomosis (ta-IPAA) with transabdominal (abd-IPAA) approach for ulcerative colitis (UC) using the Cleveland Global Quality of Life (CGQL).
Methods: This is a multi-centre cohort of consecutive patients undergoing abd-IPAA or ta-IPAA for UC prospectively registered in the databases of three tertiary referral institutions between March 2002 to September 2017. Patient characteristics, surgical details and postoperative outcomes were retrieved. The primary end-point was pouch function determined by CGQL score. The questionnaire was administered to all patients with a functioning pouch for 12 months.
Results: Ninety-nine patients with ta-IPAA were compared with 274 patients with abd-IPAA. A defunctioning stoma was created at the time of pouch construction in 46 (46%) patients undergoing ta-IPAA and in 130 (47%) patients with abd-IPAA (p = 0.90). Thirty-day postoperative complications according to Clavien-Dindo classification (p = 0.22) as well as anastomotic leak rates (13% vs. 6%), abd-IPAA and ta-IPAA, respectively, were comparable (p = 0.09). Time to stoma closure did not differ between the two groups (abd-IPAA- 6 ± 7 vs. ta-IPAA- 5 ± 4 months; p = 0.72). Twelve months CGQL score was obtained for 251 patients in the abd-IPAA group and for 97 in ta-IPAA cohort. The CGQL index was comparable between the two groups (0.72 ± 0.15 vs. 0.75 ± 0.12; p = 0.07). Quality of health and energy level components were statistically higher for ta-IPAA (7.30 ± 1.53 vs. 7.73 ± 1.19, p = 0.01; 6.68 ± 1.74 vs. 7.17 ± 1.54, p = 0.01) while no difference was found for quality of life item (7.63 ± 1.52 vs. 7.62 ± 1.30, p = 0.73). Pouch failure (including defunction and excision) was reported in 40 of 298 (12%) patients undergoing abd-IPAA and in 1 patient (1%) having ta-IPAA during the follow-up period.
Conclusions: ta-IPAA produces functional result comparable to transabdominal approach at 12 months after surgery.

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Effectiveness of dose optimisation by pre-genotyping NUDT 15 R139C on reducing thiopurine-induced leucopoenia in Chinese patients with Crohn's disease: a randomised controlled trial

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Background: More than 20% Chinese patients with IBD develop thiopurine-induced leucopoenia. Recent retrospective studies have confirmed that NUDT15 R139C variant is a reliable marker of thiopurine-induced leucopoenia in Asian population. Thus we conduct this prospective study to explore whether an optimising strategy based on NUDT15 R139C genotypes affect outcomes of Chinese patients with Crohn's disease (CD).
Methods: A prospective, randomised study was conducted in two tertiary hospitals in China (NCT02929706). CD patients (18–65 years old) with indication of the use of thiopurine were included. The exclusion criteria were: Contraindication of thiopurine, previous use of azathiopurine and co-treatment with 5-ASA or allopurinol. The Patients were randomly assigned to the intervention group (pre-genotyping NUDT 15 R139C) or control group (receive standard dosage of azathiopurine with a target dosage of 2–2.5 mg/kg/day). Patients in the intervention group found to be wild-type carriers were prescribed with standard dose of azathiopurine, while the heterozygotes received 50% of the standard dosage. Considering all the variant of homozygotes develop leucopoenia in the previous study, these patients in the intervention group did not receive thiopurine. NUDT15 R139C genotypes were determined with PCR-RFLP

and sequencing. Patients were followed for 48 weeks. The primary endpoint was the differences of incidence of leucopoenia (white blood cell <3500 mm^{-3}).The secondary outcomes were other adverse events and the efficacy (evaluated by CDAI, CRP, and mucosal healing) between the two optimisation strategies.

Results: A total of 400 Chinese CD patients were randomised. The frequency of NUDT15 R139C variant, sex, age, baseline CDAI were similar in the two groups. The rate of thiopurine-induced leucopoenia is significantly lower in the intervention group (20.8% vs. 29.7%; p = 0.041; relative risk = 0.619; 95% confidence interval (0.389–0.982).The difference is more significant in patients with NUDT15 variant [29.6 vs. 65.7 (RR 0.220, 95% CI 0.07–0.65)]. The patients develop leucopoenia in the intervention group seems milder the control group (Grade 1; 68.6% vs. 45.8%, p = 0.04). No differences of other adverse events were found. We compare the efficacy in patients treated with corticosteroids and maintain remission with AZA only. One hundred and twenty-one patients were included and no differences were found in CDAI, CRP level, and the rate of mucosal healing at the 48th week.

Conclusions: Pre-genotyping NUDT15 R139C before starting thiopurine could be a promising strategy to reduce the rate of leucopoenia. This optimisation strategy does not seem to influence the clinical efficacy in 48 weeks of follow-up.

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DUBLIN (Degree of Ulcerative colitis Burden of Luminal INflammation) score, a simple method to quantify inflammatory burden in ulcerative colitis

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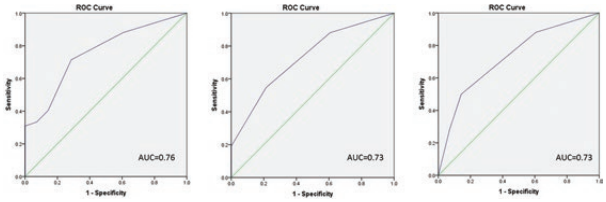
Background: Endoscopic scores of local severity do not reflect disease extent or disease burden. The DUBLIN score is a simple bedside clinical score that estimates inflammatory burden using both disease severity and extent. As the need to personalise therapy for UC patients increases, a score to accurately assess disease burden will be of great relevance. The aim of this study was to assess the clinical utility of the DUBLIN score by comparing its performance with objective biomarkers.

Methods: DUBLIN score was calculated as a product of Mayo Endoscopic Score (0–3) and disease extent (E1-E3). Correlation with objective biomarkers was performed in a retrospective 'discovery cohort'. A validation cohort was recruited from a single-centre, where clinical outcomes, colectomy rate, and biochemical data were collected prospectively.

Results: The discovery cohort included 70 patients with UC.

DUBLIN score correlated significantly with faecal calprotectin levels. (r = 0.394; p < 0.01). ROC analysis using FCP >50 μg/g showed a higher AUC with DUBLIN score (AUC = 0.76) than Mayo Score (AUC 0.73).



Receiver-operating characteristic (ROC) curves constructed using a faecal calprotectin measurement of >50 μg/g as the threshold to define disease activity. DUBLIN score (AUC = 0.76) (Panel A) was greater than either Mayo score or extent alone.

The validation cohort included 41 patients. Patients with high inflammatory burden (DUBLIN >3) had higher C-reactive protein and faecal calprotectin, and lower albumin than low inflammatory burden patients.

DUBLIN score	<3 (n = 18)	≥3 (n = 23)	p-value
Age (median; IQR)	47 (36–69)	39 (27–46)	0.07
Gender (male; n(%))	11 (61.1)	15 (65.2)	0.79
Disease duration (years) (median; IQR)	10 (1–13)	10 (3–16)	0.39
Faecal calprotectin (μg/g) (median; IQR)	185 (19–1060)	1222 (381–3000)	0.03*
Albumin (g/l) (median; IQR)	40 (37.5–41)	34 (28.75–39.25)	0.003*
C-reactive protein (mg/l) (median; IQR)	3 (1–6)	13 (2.75–36.75)	0.002*

Patient demographics and biochemical data based on 'high' (Dublin score ≥3) and 'low' inflammatory burden (Dublin <3) in the 'validation' cohort.High DUBLIN score was associated with an increased risk of treatment failure (introduction/escalation of biologic agents, introduction of immunomodulators, use of oral steroids or surgery). (HR 2.98; 95% CI 1.002–8.87; p = 0.049).

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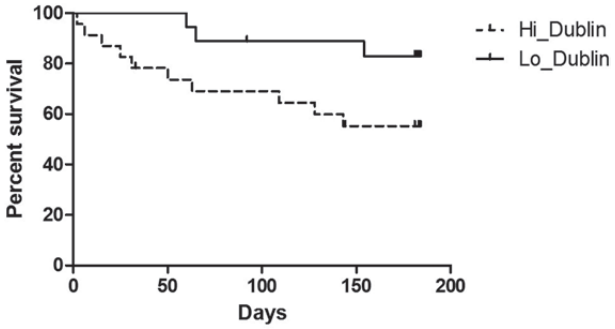
Age (median; IQR)	36.5 years (26–47.25)			DUBLIN Score (n = 70)	
Gender (male; n; %)	37 (52.8)				16 (23%)
C-reactive protein (median; IQR)	2 (IQR 1–7.25)			1	16 (23%)
Albumin (median; IQR)	37 (IQR 35–39)			2	17 (24%)
Faecal calprotectin (median; IQR)	94.5 (15.75–1142.25)			3	5 (7%)
Extent		Mayo Endoscopic Score		4	3 (4%)
E0 (no active disease)	16 (23%)	Mayo 0	16 (23%)	6	9 (13%)
E1	29 (41%)	Mayo 1	25 (36%)	9	4 (6%)
E2	11(16%)	Mayo 2	21 (30%)		
E3	14 (20%)	Mayo 3	8 (11%)		

Patient characteristics, disease extent, Mayo endoscopic score, and DUBLIN score calculated in the discovery cohort. (n = 70).



High inflammatory burden is associated with a significantly higher risk of treatment failure in the validation cohort.

Conclusions: The DUBLIN score is a simple measure of inflammatory burden which correlates with objective inflammatory markers and is associated with clinical outcomes such treatment failure. DUBLIN score has the potential to assist in personalising therapy for patients with UC.

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Association of vedolizumab levels with clinical and biochemical markers of inflammation during maintenance therapy in inflammatory bowel disease

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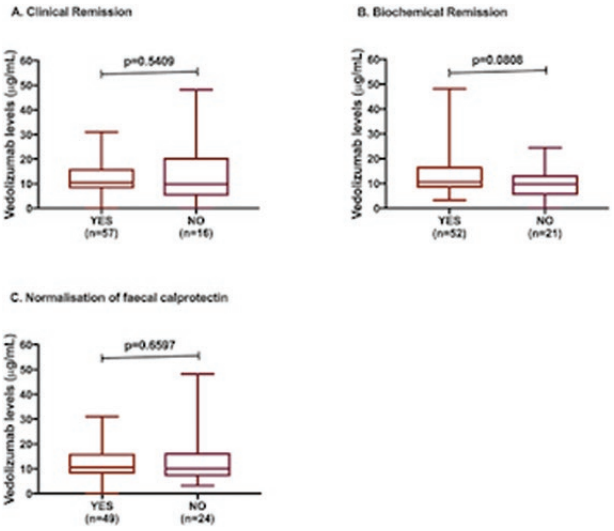
Background: The role of TDM in the context of vedolizumab therapy remains unclear. Initial studies have shown a relationship between post induction levels andlong-term outcomes. However, the clinical utility of measuring levels during maintenance treatment remains to be elucidated. Therefore, we aimed to establish the relationship between trough vedolizumab levels and clinical remission, biochemical remission, and faecal biomarker remission during maintenance therapy.

Methods: We performed a prospective cross-sectional service evaluation of IBD patients receiving maintenance vedolizumab. All patients had received a minimum of 12 weeks therapy following standard induction (0, 2, 6 ± 10 week dosing). Over a 16 week period, data on clinical activity (HBI or Partial Mayo score), CRP, vedolizumab levels and faecal calprotectin were collected at patients infusions. Clinical remission was defined as HBI <5 or partial Mayo <2; biochemical remission as CRP <5 g/l; and faecal biomarker remission as faecal calprotectin (FC) <250 µg/g. Vedolizumab levels were processed using the Immundiagnostik monitor ELISA.

Results: Seventy-three patients (30 UC, 43 CD; median age 36 years [IQR 29–56]) fulfilled inclusion criteria and had vedolizumab levels matched with clinical activity scores, CRP and faecal calprotectin. Median disease duration was 12 years (IQR 7–19) with a median vedolizumab duration of 1.6 years (IQR 0.8–2.2). 20.5% of the cohort were receiving a concomitant immunomodulator. The majority of patients had detectable levels (n = 71/73, 97.3%) with a median vedolizumab level of 10.6 µg/ml (IQR 7.9–16.1). No significant difference was observed in median levels between UC and CD patients (11.1 µg/ml vs. 10.4 µg/ml, p = 0.54). Individuals on 4-weekly therapy had higher median levels than those on 8- weekly (16.1 µg/ml vs. 10.4 µg/ml, p = 0.02). A correlation was observed between vedolizumab levels and albumin (Spearman's r = 0.25, p = 0.03) as well as BMI (Spearman's r = –0.40, p < 0.01). Clinical remission, biochemical remission and faecal biomarker remission was present in 78.1%, 71.2% and 67.1%, respectively. No difference was observed in vedolizumab levels in patients in clinical remission, biochemical remission or with faecal biomarker remission (Figure 1). Area under the ROC curve for predicting clinical remission, biochemical remission and biomarker remission was 0.55 (p = 0.54), 0.63 (p = 0.08) and 0.53 (p = 0.66), respectively.



Conclusions: Vedolizumab trough levels are not associated with outcomes during maintenance therapy.

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Efficacy of intravenous ustekinumab re-induction in patients with Crohn's disease with a loss of response

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Background: Ustekinumab (UST) has been shown to be effective in inducing and maintaining remission in patients with Crohn's disease (CD). However, a significant number of patients do not respond or experience a secondary loss of response (LOR). We assessed the utility of UST intravenous (IV) re-induction (~6 mg/kg) to achieve clinical and endoscopic response or remission in patients with active CD on UST maintenance therapy.

Methods: A multi-centre retrospective cohort study was performed. Adult patients (>18 years old) who received an IV re-induction dose of UST for either partial response or secondary LOR to UST, based on clinical, biochemical or endoscopic criteria, were identified at two Canadian academic centres. Post-reinduction, clinical remission was defined as an HBI < 5 off corticosteroids. Biochemical response and remission were defined as ≥ 50% decrease and normalisation, respectively, of faecal calprotectin (FCP) and/or CRP. Endoscopic remission was defined as a SES-CD score of < 3 and endoscopic response was defined as a decrease in SES-CD ≥ 50%. Adequate drug concentrations were defined as a UST level of ≥ 1 µg/ml. The primary outcome of interest was complete clinical, biochemical and

endoscopic remission. Secondary outcomes included clinical remission, biomarker response, and safety.

Results: Twenty-eight patients (median age 35.5 years, 46% women) underwent IV reinduction between January 2017 and July 2018. The indication for re-induction was partial response in 43% (n = 12) and LOR in 57% (n = 16). The majority of patients (89%) received re-induction while receiving UST maintenance q 4 weeks. The median time to re-induction was 18.5 months (interquartile range [IQR]: 13.0–34.8). Clinical outcomes were assessed at a median of 14 weeks (IQR: 13–17) post re-induction. The primary outcome was achieved in 28.6% (n = 8). Clinical remission with biochemical response was achieved in 53.8% of patients (n = 14). Therapeutic drug monitoring for UST was performed in 10 patients prior to reinduction, and 18 patients post-reinduction. Pre-reinduction UST concentrations were ≥ 1 µg/ml (mean 3.8 ± 3.5 µg/ml) in 80%, compared with 100% of post-reinduction UST concentrations (mean 6.4 ± 4.2 µg/ml). The mean UST concentration post-reinduction was significantly higher in patients having achieved the primary outcome compared with those who did not (9.7 ± 4.1 vs. 4.8 ± 3.1 µg/ml, p = 0.01). No serious adverse events were reported following UST re-induction.

Conclusions: Ustekinumab IV reinduction can be used safely to induce complete remission and response in patients with Crohn's disease with partial response or losing response, even in the context of previously defined adequate UST drug concentrations. Further studies evaluating this strategy are warranted.

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Cumulative histological inflammation predicts colorectal neoplasia in ulcerative colitis

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Background: Chronic inflammation in ulcerative colitis (UC) is associated with the development of subsequent colorectal neoplasia (CRN). The group at St. Mark's Hospital (London) previously reported a novel 'cumulative inflammatory index' that predicted development of CRN in patients with UC.[1] In this analysis, we sought to validate these findings.[2]

Methods: A previously described cohort of UC patients with and without CRN from the University of Chicago were matched for age at diagnosis, histological extent and disease duration (within 5 years).[2] Disease severity was defined using a 6-point histology inflammatory activity (HIA) score. HIA scores were calculated for each colonoscopy by taking the mean or maximum score, respectively, of all biopsy fragments. Per the St. Mark's scoring, cumulative burden for a patient was calculated by summing each HIA score multiplied by the length of the surveillance interval in years. Persistency was defined by the number of surveillance episodes with a severity score greater than 2 divided by the total number of surveillance procedures. *T*-tests compared mean and maximum HIA score, assessing mean and maximum severity, cumulative burden, and persistency of inflammation in UC patients.

Results: Sixty-two UC patients (26 cases with CRN, 36 controls without CRN) were analysed. Fifty-five per cent were male, the mean disease duration was 20.6 years, the mean age at CRN diagnosis was 43.9 years (Table 1). Of the 26 cases, 6 (23%) patients had colorectal cancer, 16 (62%) had low-grade dysplasia, and 4 (15%) were indefinite for dysplasia. Using mean HIA scores we found cumulative burden to be statistically higher in patients who developed CRN (p = 0.04). Using maximum HIA scores we found cumulative burden, mean severity, and persistency to be significantly higher in cases compared with controls (p = 0.02, p = 0.03, and p = 0.01, respectively). Maximum severity was numerically larger in cases for both mean and maximum HIA scores, but did not reach significance (Table 2).

Conclusions: Cumulative histological inflammation is significantly associated with development of CRN in patients with UC. These findings support a management strategy of inflammatory disease control over time to reduce risk of CRN, and may influence selection of surveillance intervals.

Table 1. Demographics of study population (n = 62).

Characteristic	Cases (n=26)	Controls (n=36)
Male sex (n,%)	21, 80.8%	13, 36.1%
Age (mean, range)	42.9, 19-65	44.7, 23-69
Age at ulcerative colitis diagnosis (mean, range)	23.2, 4-40	23.2, 5-42
Disease duration in years (mean, range)	19.7, 5-37	21.4, 3-42
Disease extent (n,%)		
Pancolitis	22, 84.6%	29, 80.6%
Left sided	4, 15.4%	7, 19.4%
Smoking status (n,%)		
Non-Smoker	19, 73.1%	29, 80.6%
Ex-Smoker	4, 15.4%	2, 7.7%
Current Smoker	3, 11.5%	5, 13.9%
Family history of colorectal cancer (n,%)		
No	24, 92.3%	34, 94.4%
Yes	2, 7.7%	2, 5.6%
Primary sclerosing cholangitis (n,%)	4, 15.4%	2, 5.6%
Mean HIA score (median, range)	1.58, 0.29-5	1.33, 0.29-4
Maximum HIA score (median, range)	3, 1-5	3, 1-5
Number of colonoscopies (median, range)	3, 2-8	2, 2-9
Surveillance interval in months (median, IQR)	25.3, 14.1-49.5	25.6, 14.9-35.3

Table 2. Case–control inflammation severity score.

	Cases (n=26)	Controls (n=36)	p-value
Mean HIA Scores			
Cumulative Burden	12.63	7.98	0.03919*
Mean Severity	1.82	1.58	0.1525
Maximum Severity	2.42	1.94	0.06182
Persistency of Inflammation	0.31	0.27	0.5815
Maximum HIA Scores			
Cumulative Burden	22.63	13.93	0.0206*
Mean Severity	3.36	2.80	0.0266*
Maximum Severity	4.15	3.64	0.0643
Persistency of Inflammation	0.93	0.76	0.009193*

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Analysis of UC colectomy rates in pre- and post-biologic era in South-East Scotland

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Background: Anti-TNF treatment reduces requirement for surgical resection in CD; but whether biologic agents reduce colectomy rates in UC is not clear. Between February 2015 and June 2015, NICE and the Scottish Medicines Consortium approved the use of infliximab, adalimumab, golimumab and vedolizumab for medically refractory UC. Prior to this date biologic use in UC across Scotland was restricted to infliximab rescue therapy. We therefore aimed to describe UC colectomy rates before and after the advent of biologic use for moderately to severely active UC.
Methods: We performed a retrospective analysis of UC colectomy rates in a single Scottish health board (NHS Lothian) from January 2009 to December 2017. Surgical resections for UC were identified from the Lothian Pathology database and/or theatre record. Electronic medical records were screened to describe UC phenotype and operation details. Colectomies were termed 'elective' if operative decision was made prior to admission, 'emergency' if colectomy occurred during admission and 'fulminant' if within 3 months of diagnosis. Biologic prescriptions details for all UC patients from January 2009 to June 2017 were retrieved from the Edinburgh Biologics Registry. Extent and severity of disease were defined using the Montreal classification at colectomy or at initiation of biologic for those who did not undergo colectomy. Linear regression was used to assess change in rates of colectomy and biologic use over the study period.
Results: There was a reduction in annual colectomy rate during the overall study period (p = 0.028) (Figure 1), with 39 (30–44) median (IQR) colectomies between 2009 and 14 and 25 (23–26) between 2014 and 17. This was driven by a reduction in non-fulminant colectomy rate (p = 0.028); there was no change in the rate of fulminant colectomies. Over the same time, in keeping with national guidelines in Feb 2015, there was a significant increase in biologic prescribing (p < 0.001). In total, 296 patients underwent colectomy consisting of 193 (65%) emergency and 97 (33%) elective operations (Table 1). The first age pouch operation has seen a significant decline over the study period.

Figure 1. Colectomy rate per year divided by 'fulminant' cases performed within 3 months of diagnosis vs. 'non-fulminant' cases performed after 3 months of diagnosis. p denotes significance for the trend during follow-up.

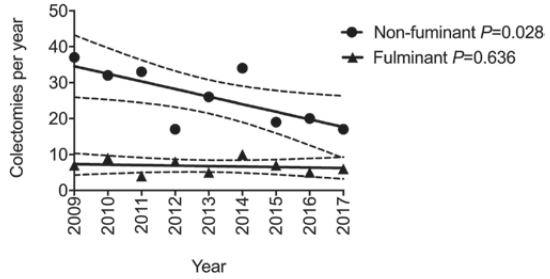

Table 1. Details of colectomy procedures performed for UC per year from 2009 to 2017.

Situation	Year									Pre-2015 (Median,IQR)	Post-2015 (Median,IQR)
	2009	2010	2011	2012	2013	2014	2015	2016	2017		
Elective	9	14	14	6	16	11	8	5	3	13 (8-15)	5 (3-8)
Emergency	34	27	23	19	15	26	17	19	16	25 (18-29)	17 (16-19)

Conclusions: Increased use of biologics has been matched by an overall reduction in colectomy rates. However, this has been driven by fewer operations in those who have established UC with fulminant colectomy rates unchanged over time.

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Rapid point-of-care anti-drug antibodies measurement correlates with standardised T tests and facilitate a proactive therapeutic drug monitoring approach in IBD patients on anti-TNF-α maintenance therapy

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Background: Therapeutic drug monitoring (TDM) for anti-TNF α agents has emerged as a strategy to optimise treatment in IBD patients and involves measurements of drug levels and anti-drug antibodies (ADI). ADI detection has been associated with loss of response and infusion reactions. Current techniques to measure ADI require multiple samples and patient appointments; reporting takes several weeks delaying the decision-making process. We aimed to compare the performance of a point-of-care (POC) test with the ELISA assay in a group of IBD patients treated with infliximab (IFX).
Methods: In this pilot, feasibility, double-centre study, a group of patients with Crohn's disease (CD) or ulcerative colitis (UC) referred to the of IBD Unit of Azienda Ospedaliera di Padova and Gastroenterology Unit di Feltre (BL) under Infliximab maintenance therapy were enrolled. Patients were evaluated immediately before the IFX-infusion and analysed for the presence of ADI with the POC-test (Promonitor Quick®, Progenika Biopharma-Grifols) and the well-established ELISA assay (Promonitor® anti-IFX and Promonitor IFX). Infliximab trough-levels (IFX-TL) were also analysed. According to the manufacturer, the lower limits of quantification were: POC = 23AU and ELISA-assay = 5AU. Clinical activity was defined according to Harvey–Bradshow Index (HBI) and partial Mayo score (pMS) in CD and UC patients, respectively; faecal calprotectin (FC) was also analysed.
Results: A total of 30 patients (mean age 46 ± 13,5; M/F 21/9; CD/UC 15/15) were tested. The POC-test found ADI in 11 (36.6%) patients, whereas the ELISA was positive for ADI in 12 (40%) patients; all patients positive for ADI showed low IFX TL according to published cut-off values (TL<3 μg/ml). No technical problems occurred during testing with both tested kits. The POC-test showed a good agreement with the comparative ELISA test. Overall, positive and negative per cent agreements between ELISA and POC test were 96.67%, 91.67% and 100% (Table 1), respectively. We also evaluated the relationship between clinical and biochemical activity with ADI presence according to POC test. No correlation was found between clinical activity (FC, HBI, and pMs) and presence/absence of ADI (Table 2)

Table 1. Promonitor Quick ANTI-IFX(serum) and Promonitor ANTI-IFX ELISA (serum) comparison

TABLE 1: Promonitor Quick ANTI-IFX(serum)and Promonitor ANTI-IFX ELISA (serum) comparison		ELISA (serum, n. samples)		
		Pos	neg	Total
POC(serum, n. samples)	pos	11	0	11
	neg	1	18	19
	Total	12	18	30
		PPA	NPA	OA
Agreement		91,67%	100%	96,67%
CI95%		76,03%-100%	100%	90,24%-100%

PPA, Positive Percent Agreement; NPA, Negative Percent Agreement; OA Overall Agreement

Table 2

TABLE POC(serum)	FC<150	FC>150	HBI<5	HBI>5	pMayo<2	pMaio>2
pos	6	5	6	2	3	0
neg	6	13	6	2	6	5
Total	12	18	12	4	9	5
PA	50%	27.78%	50%	50%	66.67%	/
CI95%	21.71%-78.29%	7.09%-48.47%	21.27%-78.29%	1.0%-99.0%	35.87%-97.47%	/

PA; percent agreement with the clinical scores

Conclusions: POC can reliably detect the presence of ADI in high agreement with the ELISA tests. Indeed, ADI measurement by POC was also able to identify patients with low IFX-TL. POC testing allows immediate management of patients requiring Infliximab dose adjustment and should be implemented in daily clinical practice.

P476

Combined therapy with adalimumab and mesenchymal stromal cells contributes to reduction in the degree of inflammation in ulcerative colitis

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Background: One of the new promising methods of treatment of patients with ulcerative colitis (UC) is biological therapy using bone marrow mesenchymal stromal cells (MSC). In some cases, simultaneously with MSC, patients receive concomitant anticytokine therapy. Currently, a new strategy for UC therapy is to achieve a deep remission of the disease. To compare the level of immunobiological and histological markers of inflammation—C-reactive protein (CRP), the Geboes Score (GS) and faecal calprotectin (FCP)—in patients with UC receiving cell therapy MSC, anti-cytokine therapy with adalimumab (ADA), and combined therapy of bone marrow MSC and ADA.

Methods: Sixty patients with total ulcerative colitis of moderate severity were divided into groups depending on the therapy. The first group of patients with UC aged from 19 to 56 years (Me-29) (n = 20) received anti-inflammatory therapy with the use of the culture of 2 million MSC/kg according to the scheme the second group of patients with UC (n = 20) aged 23 to 62 years (Me-41) received ADA in accordance with the recommended scheme, the third group of patients with UC (n = 20) aged 20 to 59 years (Me-33) received the MSC+ADA. The level of CRP, PCF and is was assessed 26 weeks after initiation of therapy. The baseline CRP was 25.0 ± 1.9; 26.5 ± 2.1 and 24.0 ± 2.4 mg/l, respectively. Baseline GS in the groups of patients was 4.4 ± 0.2; 4.35 ± 0.2 and 4.5 ± 0.3 points, respectively. The initial level of the FCP made 890.8 ± 88.8; 850.3 ± 83.9 and 910.5 ± 120.5 µg/g, respectively.

Results: After 26 weeks from the start of therapy in the first group of patients, the level of CPP was 6.8 ± 1.1 mg/l, in the second group 7.4 ± 1.3 mg/l, in the third group 7.9 ± 1.0 mg/l ($p > 0.05$). After 26 weeks from the start of therapy in the first group of patients, the level of FCP was 108.8 ± 9.3 µg/g, in the second group 90.6 ± 6.5 µg/g, in the third group 96.8 ± 6.3 µg/g ($p < 0.05$ compared with the first and second groups). After 26 weeks from the start of therapy in the first group of patients with GS was 0.7 ± 0.1 points, in the second group 0.65 ± 0.1 points, in the third-0.5 ± 0.06 points ($p < 0.001$ compared with the first and second groups).

Conclusions: Combined mesenchymal stromal cells and anti-cytokine therapy with adalimumab contributes to a more pronounced reduction in the degree of inflammation of the intestinal mucosa.

P477

Clinical remission by legacy vs. FDA definitions: definition justification and results from UNIFI Study

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Background: Ustekinumab (UST), an interleukin-12/23 blocker, was evaluated as induction and maintenance for moderate–severe ulcerative colitis (UC). Clinical remission was analysed using a US-specific definition (FDA) excluding the PGA (Physician's Global Assessment) and the legacy definition which includes the PGA to accommodate regional regulatory preference.

Methods: Patients (pts) were randomised to receive a UST intravenous (IV) induction dose (either 130 mg [n = 320] or approximating 6 mg/kg [n = 322]), or PBO (n = 319). Responders to UST IV induction were randomised to SC maintenance of 90 mg UST (either every 12 weeks [n = 172] or every 8 weeks [n = 176]), or PBO (n = 175). The primary endpoint for induction (Week 8) and maintenance (Week 44) was clinical remission. In a prior UC induction study with golimumab, 87.5% had >3 stools per day at baseline and stool number ≤3 aligned with what approximately 98% of patients reported as normal. FDA clinical remission definition was developed after FDA requested PGA removal (ie, absolute stool number ≤3 [aligned with upper limit of normal stool number in the general population], Mayo rectal bleeding subscore 0, and Mayo endoscopy subscore 0/1). This differed from the legacy definition (total Mayo score ≤2 points, with no individual subscore >1). Using golimumab and infliximab UC study data, FDA definition was assessed for agreement with legacy definition, treatment effect, and clinical meaningfulness using the Inflammatory Bowel Disease Questionnaire and the 36-item short form health survey as anchor variables. UNIFI remission was analysed using both definitions.

Results: The FDA definition demonstrated high concordance, specificity and sensitivity with the legacy definition with a similar treatment effect, and defined patients who had clinically meaningful benefit. In the UNIFI study, Week 8 clinical remission rates among patients receiving IV UST at either 130 mg or ~6 mg/kg were significantly higher than PBO patients by both legacy (15.6%, 15.5%, and 5.3%, respectively $p < 0.001$ for both doses) and FDA definitions (16.6%, 18.9%, and 6.3%, respectively; $p < 0.001$ for both doses). Week 44 clinical remission rates among patients randomised to q12wk or q8wk UST were significantly higher than PBO patients by both legacy (38.4%, 43.8%, and 24.0%, respectively; $p = 0.002$ q12wk and $p < 0.001$ q8wk) and FDA definitions (39.5%, 42.6%, and 24.6% respectively; $p = 0.002$ q12wk and $p < 0.001$ q8wk).
Conclusions: Using either legacy or FDA remission definition, IV UST induced remission and SC UST maintained remission in UST induction responders with moderately-to-severely active UC. Importantly, the FDA definition with absolute stool number ≤3 is clinically meaningful, easily understood by physicians and patients, and is not based on patients' distant recall of normal stool pattern.

P478

Immunogenicity is not the driving force of treatment failure in vedolizumab-treated inflammatory bowel disease patients

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Background: The pivotal GEMINI trials reported low immunogenicity (4%) of vedolizumab during treatment. However, 16 weeks after treatment discontinuation, 10% of patients were anti-vedolizumab antibody (AVA) positive using a drug-sensitive assay. AVA are frequently underestimated since most assays are not drug-tolerant and unable to detect anti-drug antibodies while there is drug in the circulation. This study aimed to explore which anti-drug antibody assay is best suited to detect AVA and investigated immunogenicity of vedolizumab in inflammatory bowel disease (IBD) patients discontinuing vedolizumab therapy.
Methods: A drug-tolerant assay was developed for the measurement of AVA in the presence of vedolizumab and compared with the previously established drug-sensitive (lower limit of quantification (LLOQ) = 5 ng/ml) and drug-resistant (LLOQ = 3800 ng/ml) assay by application on samples of IBD patients with proven AVA levels (Bian et al., IBD 2017). After selection of the most suitable assay, vedolizumab and AVA were measured at Week 6, at the last infusion and 12–20 weeks after treatment discontinuation in a cohort of 40 vedolizumab-treated IBD patients who stopped treatment due to primary non-response ($n = 23$), loss of response ($n = 8$), adverse events ($n = 7$), or a combination ($n = 2$).
Results: The drug-tolerant assay had an LLOQ of 350 ng/ml and could detect AVA in 20 samples compared with 1 and 10 samples with the drug-sensitive and drug-resistant assay, respectively. Using the drug-tolerant assay, three (8%) out of 40 vedolizumab-treated IBD patients who discontinued therapy were AVA positive at Week 6. All three patients also had AVA at least at one other time point. These three patients, as well as the other 37 did not have AVA at the time of the last infusion nor after treatment discontinuation. The median Week 6 vedolizumab concentration of 40 patients who discontinued therapy was 23.2 μg/ml (IQR 14.7–31.9 μg/ml). Primary non-responders had numerically lower median vedolizumab concentrations at Week 6 compared with patients with loss of response (20.3 vs. 30.7 μg/ml, respectively, $p = 0.0570$). Vedolizumab Week 6 concentrations of patients who stopped therapy due to adverse events were comparable to those of patients with loss of response.
Conclusions: Immunogenicity of vedolizumab is not the driving force of treatment failure and AVA do not increase upon treatment discontinuation in vedolizumab-treated IBD patients. We hypothesise that clinicians can stop and restart vedolizumab without the risk of adverse events or a diminished clinical response due to anti-drug antibodies. Additionally, our data suggest that underexposure during induction might partially be responsible for primary non-response.

P479

Analysis of haematological changes in tofacitinib-treated patients with ulcerative colitis across Phase 3 induction and maintenance studies

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Background: Tofacitinib is an oral, small-molecule JAK inhibitor approved in several countries for the treatment of ulcerative colitis. Changes in haematological parameters in participants of OCTAVE Induction 1 and 2 (NCT01465763 and NCT01458951) and OCTAVE Sustain (NCT01458574)[1] were evaluated.
Methods: In OCTAVE Induction 1 and 2, patients received either placebo (PBO) or tofacitinib 10 mg twice daily (BID) for 8 weeks; clinical responders were re-randomised into OCTAVE Sustain for 52 weeks (received PBO, tofacitinib 5 or 10 mg BID). Mean absolute lymphocyte count (ALC), absolute neutrophil count (ANC), platelet count (PC) and haemoglobin (Hgb) level changes were analysed. Haematological adverse events (AEs) were evaluated.
Results: Following 8 weeks of treatment (PBO or tofacitinib 10 mg BID) in OCTAVE Induction 1 and 2, Hgb levels, ALC and ANC were stable, while PC declined from baseline (Table). Up to Week 52 of OCTAVE Sustain, Hgb levels increased and ALC, ANC and PC declined in all groups (table). During OCTAVE Induction 1 and 2, AEs of anaemia were reported in 22 (2.4%) tofacitinib-treated patients compared with 9 (3.8%) placebo-treated patients. During OCTAVE Sustain, the incidence rates (IRs; unique patients with events per 100 patient-years) of anaemia were 2.91, 5.51, and 2.55 for PBO, tofacitinib 5 and 10 mg BID, respectively. No AEs of neutropenia were reported during OCTAVE Induction 1and2. In OCTAVE Sustain, IRs were 0.00, 0.67, and 0.64 for placebo, tofacitinib 5 and 10 mg BID, respectively. During OCTAVE Induction 1 and 2, 2 (0.2%) tofacitinib-treated patients had AEs of lymphopenia, and no AEs of lymphopenia occurred during OCTAVE Sustain. Discontinuations due to laboratory abnormalities were low.

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N-ECCO Mission

- Improve access to nurse education in IBD throughout Europe
- Guide ECCO in making decisions that affect N-ECCO
- Liaise with the national nursing organisations
- Improve quality of nursing and patient care in IBD in line with the development of N-ECCO Consensus statements

N-ECCO Activities

- Networking opportunities for sharing of best practice (N-ECCO Network Meeting, N-ECCO School & N-ECCO Research Forum)
- N-ECCO Travel Award
- N-ECCO Research Grant
- ECCO IBD Nurse Education Programme
- Improve patient understanding of IBD

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Two (0.2%) tofacitinib-treated patients discontinued in OCTAVE Induction 1 and 2 due to ALC decline (2 sequential readings <0.5 × 10^9/l) and 5 (0.6%) tofacitinib-treated patients discontinued due to Hgb decline (2 sequential values < 0.8 g/dl or >30% decrease from baseline), compared with Hgb decline in 1 (0.4%) PBO-treated patient. In OCTAVE Sustain, 1 (0.3%) pt discontinued due to Hgb decline.

Conclusions: In OCTAVE Sustain, treatment with both tofacitinib doses resulted in decreased ALC, ANC and PC, and increases in Hgb levels. There was no dose dependency in anaemia or neutropenia IRs. Similar trends were observed in rheumatoid arthritis (RA) patients treated with tofacitinib.[2] Increases in Hgb were also found in IBD and RA patients treated with TNFi.[3–5]

Table. Observed haematological parameters in OCTAVE Induction 1, and OCTAVE Induction 2 OCTAVE Sustain.

	OCTAVE Induction 1				OCTAVE Induction 2				OCTAVE Sustain				
	Baseline	Week 2	Week 4	Week 8	Baseline	Week 2	Week 4	Week 8	Baseline	Week 4	Week 8	Week 24	Week 52
Mean Hgb,* g/dL													
Tofacitinib 5 mg BID	-	-	-	-	-	-	-	-	12.88	12.95	13.02	13.48	13.85
Tofacitinib 10 mg BID	12.68	12.54	12.57	12.74	12.81	12.73	12.67	12.95	13.11	13.00	13.05	13.65	13.75
Placebo	12.82	12.72	12.78	12.91	12.92	12.76	12.68	12.92	12.96	13.10	12.96	13.37	13.70
Mean ALC, 10^9/mm^3													
Tofacitinib 5 mg BID	-	-	-	-	-	-	-	-	1.99	1.87	1.76	1.63	1.52
Tofacitinib 10 mg BID	1.87	2.04	2.04	1.87	1.86	2.05	2.05	1.86	1.92	1.92	1.82	1.62	1.46
Placebo	1.79	1.86	1.90	1.83	1.86	1.94	1.93	2.11	1.94	1.81	1.81	1.82	1.82
Mean ANC, 10^9/mm^3													
Tofacitinib 5 mg BID	-	-	-	-	-	-	-	-	5.07	4.60	4.58	4.95	4.77
Tofacitinib 10 mg BID	5.88	5.99	5.36	5.49	5.92	6.01	5.42	5.66	5.32	4.80	5.04	4.55	4.56
Placebo	5.84	5.92	5.77	5.67	6.09	5.85	6.30	5.40	5.20	5.10	5.08	4.54	4.29
Mean PC, 10^3/mm^3													
Tofacitinib 5 mg BID	-	-	-	-	-	-	-	-	306.19	297.04	295.09	293.19	283.48
Tofacitinib 10 mg BID	331.28	341.31	305.70	313.35	330.03	343.96	305.08	307.58	290.22	287.62	292.59	277.93	263.94
Placebo	337.84	335.18	332.64	328.11	335.16	336.91	337.51	330.50	293.97	304.46	309.89	283.86	273.06

During OCTAVE Induction 1 & 2, patients received either placebo or tofacitinib 10 mg BID for 8 weeks; clinical responders were re-randomised into OCTAVE Sustain for 52 weeks (received placebo, tofacitinib 5 or 10 mg BID)
*N=476, 122, 448, 119 for tofacitinib 10 mg BID and placebo at baseline and Week 8 of OCTAVE Induction 1, respectively. N=429, 112, 394, 99 for tofacitinib 10 mg BID and placebo at baseline and Week 8 of OCTAVE Induction 2, respectively. N=198, 196, 198, 108, 124, 53 for tofacitinib 5 mg BID, tofacitinib 10 mg BID and placebo at baseline and Week 52 of OCTAVE Sustain, respectively. There were the same or slightly fewer observations in the other three parameters than in Hgb
-, not applicable; ALC, absolute lymphocyte count; ANC, absolute neutrophil count; BID, twice daily; Hgb, haemoglobin; N, number of patients with non-missing data; PC, platelet count

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P480

The effect of adjuvant therapy (Sinergin®) in induction and maintaining remission in mild and moderate IBD

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Background: Recent studies regarding IBD pathogenesis have shown that in addition to genetic factors, an important role of intestinal microbiota in the perpetuation of intestinal inflammation is well established. Prebiotic OF-IN (oligofructose-inulin) has the ability to modulate not only the composition of the intestinal microbiota, but also its activity in a beneficial way, increasing the butyrate concentrations, which exhibits immunomodulatory and anti-inflammatory properties. The aim of this study was to investigate the anti-inflammatory effect of OF-IN (Sinergin®) supplementation as impact on clinical remission and biomarkers in patients with mild and moderate flare of IBD.

Methods: A prospective interventional multi-centre study was conducted between April 2015 and November 2017 in four high-volume Gastroenterology centres. Patients aged between 18 and 70 years, with histological confirmed ulcerative colitis or Crohn's disease and active flare of IBD of mild or moderate severity (Mayo 3–10, CDAI 150–220) were included. Selected patients were randomised in 2 groups: Group 1 received Sinergin (10 g/day per os) +and conventional therapy and Group 2 received conventional therapy only. Evaluation has been performed in each group at entry, 3, 7, and 11 months and consisted of: clinical evaluation, C Reactive Protein, faecal calprotectin, colonoscopy (optional) and compliance evaluation. Statistical analysis was performed with SPSS and Excel.

Results: Data were obtained from 160 eligible patients who entered prospectively in the study. 21 patients left the study in the first 3 months mainly because of bloating. Most patients were diagnosed with ulcerative colitis (64%) and had mild clinical activity (64%). The most frequent treatment was 5 ASA po. Our study showed a more rapid decrease in CRP and FCP was observed in the Sinergin® group, suggesting that adding a prebiotic (Sinergin®) accelerates induction of remission, although the values did not significantly differ between-groups at T3. Also, progressive induction of remission from 0 to> 60% in both groups, with no significant difference between groups. The proportion of moderately-severe cases decreased significantly along the study, but insignificantly between the two groups except T1 Group1 perhaps due to inflammatory burden at baseline confirmed by CPR and FCP.

Conclusions: Dynamics of biomarkers (FCP, CRP) demonstrate the progressive improvement of intestinal inflammation under conventional and combined therapy with Sinergin®. Further studies on continuous administration of Sinergin in mild-to-moderate IBD should be undertaken because data showed that it might lead to better results in maintaining remission.

P481

Efficacy of the sequential use of a second biologic agent for Crohn's disease treatment in a non-academic tertiary centre

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Background: One-third of Crohn's disease (CD) patients, treated with anti-TNF agents do not respond to the drug (primary failure), and a relevant proportion from those who respond experiences loss of response (secondary failure) or intolerance over time. The aim was to investigate the efficacy of the sequential use of a second biologic agent after failing or developing intolerance to an anti-TNF drug as well as identify predictors of treatment failure.

Methods: Retrospective cohort-study, which included all CD patients who started anti-TNF between 2003–2017. The main outcome was the efficacy of a second biologic agent, measured by 12-week clinical remission (CR), 1-year CR and 1-year endoscopic (ER). When endoscopy could not adequately evaluate inflammation (small bowel CD), resolution of inflammation as assessed by cross-sectional imaging. Secondary outcomes includes identification of predictors to second-line biologic agents failure, time to treatment failure (defined as need to dose increase, switch biologic or surgery). Deep remission (DR) was defined as CR (as described in medical records), ER (absence of ulcers and erosions in endoscopy) and in ileal Crohn's disease as absence of radiologic activity.

Results: 118 patients were included. Mean age was 39.8 years (SD 12.4) and 53.4% were females (n = 63). Anti-TNF therapy succeeded in 66.9% (n = 79), nonetheless dosing intensification was necessary in 46.8% (n = 37). Primary failure, loss of response and intolerance to anti-TNF occurred in 3.4% (n = 4), 25.4% (n = 30) and 4.2% (n = 5) respectively. A second biologic agent was started in 28.8% (n = 34). Treatment failure of a second biologic agent occurred in 67.7% (n = 23), and mean time to failure was 56.0 weeks (SD 62.3). Primary failure occurred in 20.6% (n = 7), and loss of response in 17.6% (n = 6). For a second agent 12-week CR rate was 52.9%, 1-year CR rate 71.4% and ER and/or absence of imagological activity 15.4%. Therapy was escalated to a third biologic agent in 9.3% (n = 11). There was an association between 1-year CR with anti-TNF and the need to escalate to a second biologic (p = 0.032). DP was associated with response to initial anti-TNF (p = 0.022). Failure of second biologic (primary failure or loss of response) was associated with absence oflong-term CR (p = 0.009). Failure of a second biologic agent was associated with age<40 at diagnosis (p = 0.012) and surgery for perianal disease (p = 0.004).

Conclusions: Sequential use of a second biologic agent failed in more than one third of patients, nonetheless clinical remission at 50 weeks was obtained in most patients. Younger age at diagnosis and surgery for perianal disease are potential predictors of failure of a second biologic agent.

P482

Selective prophylactic anti-tuberculosis strategy is superior for Chinese patients with inflammatory bowel disease receiving infliximab treatment: a multi-centre retrospective study

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Background: During anti-TNF therapy, inflammatory bowel disease (IBD) patients either with or without latent tuberculosis infection (LTBI) active TB can develop. It remains unclear whether IBD patients without LTBI receiving prophylactic anti-TB has any clinical value or which prophylactic anti-TB strategy (for both LTBI and non-LTBI or only for LTBI) is superior. Furthermore, the optimum treatment regimen for IBD patients with LTBI receiving infliximab (IFX) in China are both unclear. This study was to investigate the optimal prophylactic anti-TB strategies and treatment regimens in Chinese IBD subjects receiving IFX treatment.

Methods: IBD patients receiving IFX at 18 academic hospitals in China were enrolled. Incidence and risk factors for active TB during IFX treatment were studied. The incidence of active TB in IBD patients with IFX therapy receiving selective (strategy I: only anti-TB prophylaxis for LTBI) and conventional (strategy II: anti-TB prophylaxis for both LTBI and non-LTBI) prophylactic anti-TB strategies was compared. Further subgroup analysis investigated the incidence rate of active TB in LTBI and non-LTBI patients and examined effective prophylactic treatment regimens for LTBI.

Results: A total of 1968 IBD patients receiving IFX treatment were enrolled. The incidence rate of TB was 999.07 per 100 000 population per year. At baseline, 166 cases (8.43%) tested positive for LTBI and 1802 cases negative for LTBI prior to IFX treatment. Of 1433 cases receiving strategy I and 483 cases receiving strategy II, 10 and 5 cases developed active TB, respectively.

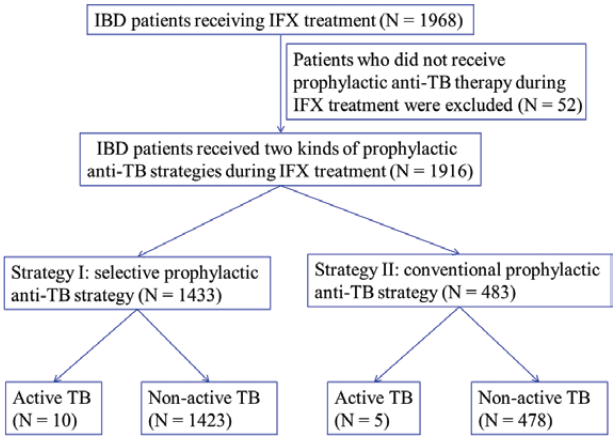

Figure 1. The incidence of activeTB in IBD patients with IFX therapy receiving different strategy.

And the incidence of active TB was not significantly reduced in IBD patients receiving strategy I compared with those receiving strategy II (0.07% vs. 1.04%, p = .67). The incidence of active TB (2.63% vs. 11.54%, p = .048) was significantly reduced but not eradicated in LTBI patients receiving prophylactic anti-TB therapy during IFX treatment, but these findings were not seen in non-LTBI patients.

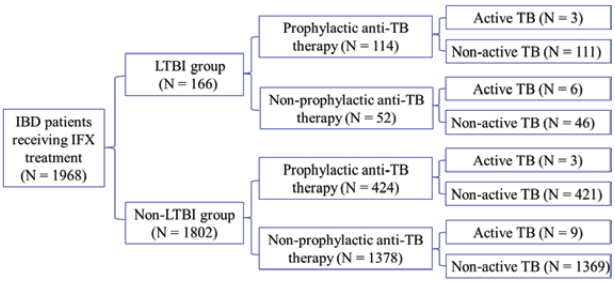

Figure 2. The incidence of activeTB in LTBI and non-LTBI patients.

Furthermore, INH treatment for 6 months significantly decreased the incidence rate of active TB (0% vs. 11.54%, $p = 0.045$) in LTBI patients.
Conclusions: Selective prophylactic anti-TB strategy may be superior for Chinese patients with IBD receiving IFX treatment and INH treatment for 6 months could be an effective treatment regimen for LTBI.

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Factors affecting the efficacy of granulomonocytapheresis in moderately-to-severely active ulcerative colitis: A multi-centre retrospective study

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Background: Adsorptive granulomonocytapheresis (GMA) with the Adacolumn has been introduced as a non-pharmacologic treatment for ulcerative colitis (UC). A subset of patients who might or might not respond to GMA has not been fully identified. In clinical practice setting, it is important to know which patients are most likely to respond to GMA to avoid futile use of medical resources or widely introduce this safe treatment and to establish its position in the management of UC. This study was conducted at centres with abundant knowledge and experience in GMA therapy with the aim of determining factors affecting the efficacy of GMA in patients with active UC.
Methods: From January 2008 to December 2017, a total of 894 active episodes (first attack or relapse) in 593 patients were treated with GMA (frequency: 1 to 5/week, session time: 60 to 120 min, the maximum number of GMA: 11). Clinical remission was defined as normal stool frequency and no rectal bleeding. Multiple clinical and laboratory parameters at entry were considered for efficacy assessment.
Results: Clinical remission was achieved during 422 (47%) of the 894 treatment cases. In univariate analysis, 6 demographic variables at entry were significantly associated with the likelihood of clinical remission. Patients with a short duration of UC (< 1 year), first UC episode, steroid naïve as well as biologic naïve patients responded well to GMA. In contrast, elderly patients (>60 years) and those with severe endoscopic activity (Mayo endoscopic subscore 3 vs. 2) did not respond well to GMA. The following factors did not affect the likelihood of clinical remission: Gender, duration of the current exacerbation before GMA, severity and the extent of UC, extra-intestinal manifestations, exposure to 5-ASA preparations, immunosuppressant drugs, and adverse events. Laboratory biomarkers at entry (leucocyte, granulocyte, lymphocyte counts, haemoglobin, platelet count, CRP, albumin) were not significantly associated with the clinical remission. In multi-variate analysis, age, duration of UC, Mayo endoscopic subscore, exposure to steroids, and exposure to biologics were independent significant factors. Clinical remission rate was 70% in patients with 4 of the 5 factors, 52% in patients with 3 factors, 46% in patients with 2 factors, 39% in patients with 1 factor, and 18% in patients with none of these factors. Overall, the clinical remission rate was significantly higher in patients with a greater number of the 5 predictors ($p < 0.0001$).
Conclusions: GMA appeared to be effective in steroid naïve and biologic naïve patients with short duration of UC. Elderly patients (>60 years) and those with severe endoscopic activity did not respond well to GMA.

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Hepatitis B vaccination in inflammatory bowel disease

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Background: Inflammatory bowel disease (IBD) patients have a lower response to hepatitis B virus (HBV) vaccination, especially those receiving anti-TNF treatment. It has been suggested that modified dosing regimens may increase response rates in these patients. Our aim was to evaluate the efficacy of HBV vaccination in an IBD cohort as well as to identify the absence of response predictive factors. We also evaluated a revaccination protocol in patients who failed seroconversion with the standard regimen.
Methods: Single-centre prospective observational study. All patients with IBD were evaluated for serological markers of HBV. The single dose HBV vaccine was administered at 0, 1 and 6 months to all seronegative patients. Subsequent determination of the anti-HBs antibody was recorded. An adequate immune response (AIR) to HBV was defined as more than 10 mIU/ml. A single booster regimen was administered to patients without AIR. A double-dose administration of the vaccine was administered at 0, 1 and 6 months to patients without AIR to the booster. We analysed AIR in patients with IBD in general and according to the therapeutic regimens (thiopurines and / or anti-TNF). The efficacy of the different vaccination regimens was also evaluated. Statistics - Chi-square and Exact tests.
Results: 118 IBD patients were evaluated [(43% males; mean age 52.5 years (20–80)], of which 55.8% with Crohn's disease. 47.5% were on immunosuppressive therapy (40% of them on biologic agents). 31.7% had already been vaccinated and 35% were immune (Anti-HBs positive) to HBV. In the subgroup of patients previously vaccinated 13% (5 patients – 2 on thiopurines and 2 on anti-TNF) were not immune and 2 did not respond to booster vaccination. With respect to vaccination-naïve patients, seroconversion with standard protocol was significantly lower in those under immunosuppressive therapy (36% vs. 71%; $p = 0.03$). A tendency for a lower response was also identified in older patients at Crohn's disease diagnosis (Montreal A3: 25% vs. Montreal A1/ A2: 52%; $p = 0.159$). A patient with AIR lost immunity under immunosuppressive therapy and regained it after a booster.
Conclusions: The response rate of IBD patients to HBV standard protocol vaccination was significantly lower in those under immunosuppressive therapy. AIR needs to be regularly assessed and booster vaccination seems effective in a subgroup of patients.

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Prediction Model Incorporating Pharmacokinetics Calculates Probability of Endoscopic Healing in Patients with ulcerative colitis Starting Infliximab Therapy

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Background: Infliximab (IFX) is effective treatment for moderate to severe ulcerative colitis (UC), however baseline parameters associated with, and probability of achieving endoscopic healing during induction and maintenance therapy are unknown.
Methods: Data from the ACT-1 and -2 trials encompassing 484 IFX-treated UC patients were analysed. A two-compartment population pharmacokinetic model was used to calculate baseline IFX clearance (CL). The Mayo endoscopic score was available at Weeks (W) 0, 8 and 30. Three logistic regression prediction models were developed using the ACT-1 dataset and externally validated using the ACT-2 dataset. The models evaluated W0 variables for prediction of endoscopic healing (MES ≤ 1) at W8 and W30, and W8 variables for prediction of endoscopic healing at W30. An online tool to calculate the probability of achieving endoscopic healing in individual patients was also created.
Results: IFX CL, stool frequency, and rectal bleeding at W0 were independently associated with endoscopic healing at W8 with an area under the curve (AUC [95% confidence interval]) of 0.73 (0.66–0.79) and 0.67 (0.60–0.74) for the derivation and validation models, respectively. IFX CL, stool frequency, white blood cell count, and weight at W0 were independently associated with achieving endoscopic healing at W30 with an AUC of 0.68 (0.62–0.75) and 0.67 (0.61–0.74) for the derivation and validation models, respectively. Rectal bleeding, stool frequency, white blood cell count, and albumin at W8 were independently associated with achieving endoscopic healing at W30 with an AUC of 0.83 (0.78–0.89) and 0.78 (0.72–0.84), for the derivation and validation models, respectively. Odds ratios for the factors predictive of endoscopic healing are shown in Table 1.

Table 1. Odds ratios for W0 and W8 factors predictive of endoscopic healing in patients receiving IFX. Variable selection was based on univariable selection ($p < 0.15$) followed by a forward stepwise multi-variable logistic regression model ($p < 0.1$).

	Odds ratio (95%CI)	P value
Baseline factors predictive of endoscopic healing at		
Week 8		
Estimated IFX clearance	0.01 (0.00-0.57)	0.02
Stool frequency	0.42 (0.27-0.65)	<0.01
Rectal bleeding	0.59 (0.43-0.82)	<0.01
Week 30		
Estimated IFX clearance	0.02 (0.00-1.03)	0.05
Stool frequency	0.57 (0.39-0.82)	<0.01
White blood cell count	0.89 (0.82-0.97)	0.01
Weight	1.02 (1.00-1.04)	0.02
Week 8 factors predictive of endoscopic healing at		
Week 30		
Rectal bleeding	0.37 (0.22-0.61)	<0.01
Stool frequency	0.66 (0.47-0.92)	0.02
White blood cell count	0.82 (0.73-0.92)	<0.01
Albumin	4.48 (1.60-12.55)	<0.01

Patient-level probabilities for endoscopic healing at W8 and/or W30 can be calculated using a free online tool available at http://premed-ibd.com. The predicted probability of endoscopic healing at W8 for a hypothetical UC patient starting IFX therapy using the online tool is shown in Figure 1.

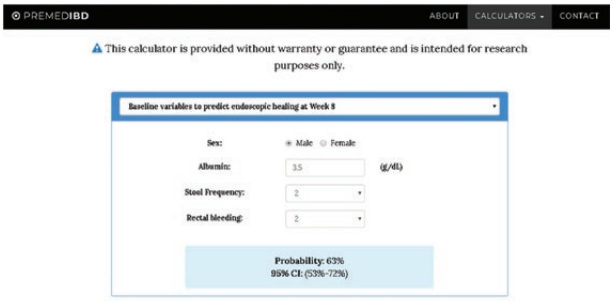

Figure 1. Probability of W8 endoscopic healing in a hypothetical UC patient. A population pharmacokinetic model uses sex and albumin to calculate W0 IFX CL, which is incorporated into the prediction model with stool frequency and rectal bleeding.

Conclusions: Three models were developed and externally validated to calculate the probability of endoscopic healing in individual patients with UC during IFX induction and/or maintenance therapy based on IFX CL, patient demographics and disease activity measures at W0 and/or W8.

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Faecal microbiota transplantation in inflammatory bowel disease: the patient's perspective

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Background: Faecal microbiota transplantation (FMT) is recognised as effective and safe for Clostridium difficile infection, leading to the study of its application in other diseases, including inflammatory bowel disease (IBD). In a recent meta-analysis clinical remission was reported in 45% of patients undergoing FMT in IBD. However, it is important to understand the patient's perspective, namely on the knowledge on FMT and its acceptability.
Methods: One hundred consecutive outpatients with IBD answered a written questionnaire consisting of 3 parts: (1) 5 questions prior to reporting on FMT; (2) FMT information leaflet on IBD; (3) 5 questions after reading the leaflet.
Results: Of the 100 patients included, 51% had Crohn's Disease and 49% ulcerative colitis. The majority of patients considered their disease to be moderate (n = 57) and 25 patients reported fear of current medication mainly due to the risk of neoplasia (n = 11) or infections ($n = 6$). The majority of the patients (89%) were unaware of FMT and without previous information 24% would accept FMT. The main reasons for the refusal were fear of infection ($n = 19$), disgusting ($n = 10$) and lack of information ($n = 7$). After reading the information leaflet, the acceptance percentage was 40% and if the treating physician stated that FMT was the best treatment, the percentage increased to 73%. When asked if they would prefer FMT or an experimental new drug, 36% preferred FMT, 36% new drug and 28% did not respond. Regarding the route of administration, the majority ($n = 59$) preferred colonoscopy.
Conclusions: TMF may be a promising therapy in IBD, but it is necessary to provide information and awareness to patients for the procedure. In our sample, we concluded that most patients were unaware of TMF, but would be willing to perform the procedure if properly informed by their physician.

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Early vedolizumab trough levels are not associated with a short-term response in patients with inflammatory bowel disease

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Background: Therapeutic drug monitoring is useful in anti-TNFa treatment of inflammatory bowel disease (IBD). However, data on vedolizumab therapy are sparse. Our aim was to assess association between early vedolizumab trough levels (VTL) and response to induction therapy in patients with IBD.
Methods: Study population comprised consecutive IBD patients from a prospective cohort of vedolizumab treated patients at our centre who had vedolizumab trough levels (VTL) and anti-vedolizumab antibodies (AVA) measured during induction phase of therapy. Included patients obtained vedolizumab 300 mg at weeks 0, 2, 6 with additional dose at Week 10 in case of inadequate response after third infusion. Clinical response evaluated by physician global assessment (PGA) was assessed 1 month after last induction dose (Week 10 or 14). Measurement of VTL and AVA was performed by ELISA assays (ImmunoGuide®, Tani Medical) with a detection limit for VTL of 1.9 μg/ml and measurement range of 0 to 600 μg/ml, and with AVA cut-off value 3 AU/ml.
Results: We included 87 patients, 31 with Crohn's disease and 56 with ulcerative colitis. At baseline, only 15% of patients were naïve to anti-TNFa therapy; 61% used systemic steroids and 26% thiopurines. Additional dose at Week 10 was needed in 39% of individuals. Clinical response to induction phase assessed by PGA was reported in 77% of IBD patients. Median VTL at Week 6 and Week 10–14 were 30.6 μg/ml (1.1–80.0) and 19.1 (0–80.0) μg/ml, respectively. Seven per cent of patients developed positive AVA until Week 10–14. Comparing patients with and without clinical response to vedolizumab no significant difference in median VTL was found, both at Week 6 (33.5 vs. 28.2 μg/ml; $p = 0.71$) and Week 10–14 (16.2 vs. 22.5 μg/ml; $p = 0.27$). Patients with previous anti-TNFa therapy had significantly lower trough levels at Week 10–14 compared with naïve ones (median 16.1 vs. 29.1 μg/ml, $p = 0.02$). Otherwise, no impact of diagnosis type or concomitant immunosuppressants on VTL was observed.
Conclusions: No association between early VTL and response to induction therapy was found in our study. Further studies have to address clinical utility of therapeutic drug monitoring in long-term vedolizumab treatment. The study was supported by the IBD-Comfort Foundation.

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Perianal Crohn's disease in the biological era

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Background: The purpose of this study was to characterise perianal disease (PD) in a cohort of patients with Crohn's disease (CD) followed prospectively for 10 years.
Methods: We performed a prospective cohort study to analyse data from 298 patients, 96 of whom with PD, over the period of 10 years (2007–2017). The characteristics of patients with PD were compared with controls with CD without PD. Perianal lesions were described in abscess, fistula, abscess and/or fistula, fissure, ulcer, fissure and/or ulcer, and stenosis. The Montreal classification was used to characterise CD.
Results: The analysis of patients with and without PD showed no difference in sex, behaviour (B1, B2, B3) and involvement of the upper gastrointestinal tract (L4). However, the group of patients with PD had a significantly lower age at onset of symptoms (median=25.5 years, IQR 20.5–34.0) vs. patients without PD (median=30.5 years, IQR 22.0–41.0) ($p = 0.018$), higher colon involvement (L2 + L3 vs. L1) (OR = 2.64, $p = 0.001$), higher rectal involvement (OR = 5.60, $p < 0.001$), higher rate of abdominal resection surgery (OR = 1.70, $p = 0.046$), and higher rate of biological therapy (OR = 2.86, $p < 0.001$). In patients with PD, 42 (43.8%) had abscess, 62 (64.6%) had fistula, 69 (71.9%) had abscess and/or fistula, 29 (30.2%) had fissure, 4 (4.2%) had ulcer, 33 (34.4%) had fissure and/or ulcer, 8 (8.3%) had anal stenosis; 37 (38.5%) had L1 involvement, 23 (24%) had L2, 36 (37.5%) had L3; 9 (9.4%) had L4 involvement; 38 (39.6%) had rectal involvement; 49 (51%) had B1 behaviour, 29 (30.2%) had B2; 18 (18.8%) had B3; 70 (72.9%) were under biological therapy; 35 (36.5%) had abdominal surgery and 60 (62.5%) had perianal surgery. In this group of patients, patients with abscesses and/or fistula had a higher rate of abdominal (OR = 3.38, $p = 0.022$) and perianal surgery (OR = 24.77, $p < 0.001$); patients with fissure and/or ulcer had a lower rate of abdominal (OR = 0.34, $p = 0.025$) and perianal surgery (OR = 0.11, $p < 0.001$); patients with anal stenosis had a higher rectal involvement (OR = 12.87; $p = 0.006$); and patients with fistula had a higher rate of biological therapy (OR = 3.66, $p = 0.005$).
Conclusions: One third of patients with CD had PD, which is more prevalent in patients with colic involvement. The severity of the perianal location can be inferred by the higher rate of abdominal surgery in this group of patients. Of the perianal lesions, abscess and/or fistula were associated with a worse overall prognosis. These data are in agreement with what is previously described in the literature. Patients with PD had higher rates of biological therapy, with a higher rate in patients with fistula compared with other lesions.

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Defective anti-microbial peptides expression in Crohn's disease mucosa can be reversed by strengthening IL-22 signalling

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Background: The intestinal epithelium can be easily disrupted during gut inflammation as seen in inflammatory bowel diseases (IBD) such as ulcerative colitis (UC) or Crohn's disease (CD). Aetiology of

IBD is still not fully understood, but recent evidences suggest that the intestinal epithelium might play a major role in the development and perpetuation of IBD. In fact, disturbances in mechanisms that control the homeostasis, protection and repair of intestinal epithelial cells can lead to increased intestinal permeability causing deregulated immune response to the commensal gut microbiota and ultimately chronic intestinal inflammation. The cytokines IL-22 and IL-17 are highly produced in the inflammatory mucosa of IBD patients. In rodent models of colitis, these two cytokines showed synergistic and protective roles during gut inflammation, by reinforcing epithelial barrier function. We have shown that IL-22 binding protein (IL-22BP), the soluble and specific inhibitor of IL-22, is also increased during IBD and could therefore hamper the protective actions of IL-22.

Methods: To further explore this hypothesis, we set up ex vivo cultures of colonic biopsies from patients with active CD and UC and analysed the expression and regulation of IL-22-dependent genes that may be controlled by IL-22BP.

Results: We first observed that, as previously described by others, the antimicrobial peptides (AMPs) BD2, BD3 and LNC2, known targets of IL-22, were induced at a lower level in the inflammatory mucosa of CD than of UC patients. We then demonstrated that this defect in AMPs expression in CD was reversed by ex vivo stimulation with IL-22 and IL-17, and identified IL-22 vs. IL-17-dependent as well as IL-22+IL-17 synergistic responses. Furthermore, we showed that the addition of IL-22BP to the culture medium blocked the induction of IL-22-dependent genes.

Conclusions: Our data strongly suggest that the defective AMPs production observed in CD might be related to lack of IL-22 and IL-17 actions on epithelial cells. We propose that the selective and transient blockade of IL-22BP could represent an interesting therapeutic strategy to unleash the protective effects of locally-produced IL-22 during flares in CD.

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A vedolizumab population pharmacokinetic model including intravenous and subcutaneous formulations for patients with ulcerative colitis

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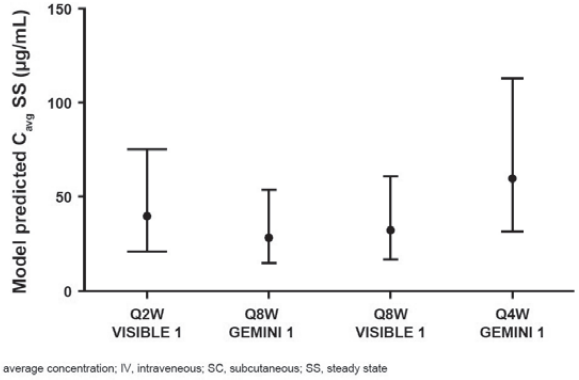
Background: Vedolizumab is a gut-selective, humanised, monoclonal α4β7 integrin antibody approved as an intravenous (IV) formulation to treat adult patients with moderately to severely active ulcerative colitis (UC). A population pharmacokinetic (PK) model was previously developed for vedolizumab IV. [1] Here we present an update of that model to include data for the investigational vedolizumab subcutaneous (SC) formulation.

Methods: The population PK analysis included data from 4 vedolizumab clinical studies: VISIBLE 1 (NCT02611830), GEMINI 1 (NCT00783718), GEMINI 2 (NCT00783692), and VISIBLE open-label extension (NCT02620046). The methods for this population PK model were reported previously.[1] In brief, the structural PK model was described by a 2-compartment model with parallel linear and nonlinear elimination.[1] The model-predicted vedolizumab concentrations were compared across different SC and IV regimens.

Results: The impact of covariates on vedolizumab clearance was similar to that described previously; the only predictors with the potential to be clinically meaningful (effect sizes greater than ± 25%) were body weight and albumin at extreme values.[1] The predicted median (90% confidence interval [CI]) average vedolizumab concentration (C_{avg}) at steady-state from VISIBLE 1 was 39.7 µg/ml (20.8–75.2) for the vedolizumab SC Q2W arm (Figure 1). The predicted C_{avg} for the IV Q8W arm [32.2 µg/ml (90% CI, 16.6–60.6)] was similar to SC Q2W and lower than IV every 4 weeks (Q4W) [59.6 µg/ml (90% CI, 31.4–113.0)] predicted from the GEMINI 1 study (Figure 1).

Conclusions: Vedolizumab SC (108 mg) administered Q2W produces average drug serum concentrations similar to those for vedolizumab IV (300 mg) Q8W and lower than those for vedolizumab IV (300 mg) Q4W.



C_{avg}, average concentration; IV, intraveneous; SC, subcutaneous; SS, steady state

Figure 1. VISIBLE 1: model-predicted average concentrations (C_{avg}) at steady state.

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INSPIRE: design and implementation aspects of a registry of complex perianal fistulas in Crohn's disease patients treated with darvadstrocel

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Background: Perianal fistulas (PAF) are a common presentation of Crohn's disease (CD), the majority being complex (CPAF).[1–4] Existing medical and surgical therapies for CPAF have low long-term success rates.[4,5] Darvadstrocel (DVS) is a mesenchymal stem cell (MSC) therapy that demonstrated efficacy and tolerability in patients with CPAF over 52 weeks,[4] and is the first MSC therapy centrally approved in Europe for the treatment of CPAF.[6] However, real-world and longer-term effectiveness data for DVS are lacking. This abstract describes the development of a DVS registry aiming to establish a framework to capture real-world clinical effectiveness and safety data. (EU PAS Register Number: EUPAS24267).

Methods: The INSPIRE registry aims to establish a data collection framework to capture real-world data on all patients treated with DVS for CPAF over 36 months. Data on patient selection, concomitant treatment, surgical technique, fistula response, remission and complications will be captured and associations between practice parameters and outcome will be assessed.
Results: An observational, multi-national, open-enrolment registry was set up to record all patients treated with DVS for CPAF. Ensuring enrolment of almost 100% of patients treated is required for sufficient longer-term evaluation of DVS and to support value-based reimbursement requests in some countries. The made to order manufacturing process and traceability lends itself to more complete data capture. The goal of this registry is to improve understanding of disease presentation, patient characteristics, treatment patterns and clinical outcomes. The primary outcomes of INSPIRE are clinical response (a reduction in ≥50% of draining PAF) and clinical remission (closure of all treated PAF on physical examination).[1,7] Health-related quality of life, patient-reported outcomes and MRI images will be collected. INSPIRE will attempt to enrol ≥1600 patients, establishing the largest CPAF database. Patient engagement will be facilitated using digital solutions where possible. Data will be reviewed by the Steering Committee who will act in an independent advisory capacity to provide scientific oversight and to evaluate the effectiveness and safety of DVS. The first patient was treated with DVS on 21 June 2018. The first site initiation visit was conducted on 31 October 2018.
Conclusions: INSPIRE will be the first registry to collect data assessing the effectiveness and safety of DVS in patients with CPAF. A comprehensive set of parameters will be collected and correlated, to better understand appropriate patient selection and surgical approach. Patient-centric features of the DVS registry are continuing to be explored.

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Influence of the interval of time between the first and the second anti-TNF in the response to treatment in patients with inflammatory bowel disease

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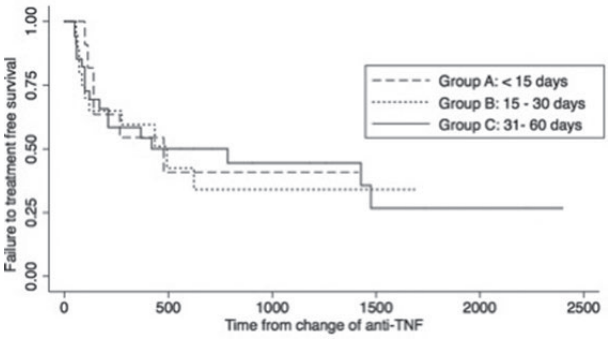
Background: There is no evidence about the time that it is reasonable to wait until starting the second anti TNF in case of loss of response. The aim of our study was to evaluate whether the time between the change from the first to the second anti TNF had an influence on the risk of treatment failure and the rate of adverse events or severe infections.
Methods: A retrospective, observational single-centre study was designed. Inclusion criteria were all adult patients who started treatment with Infliximab (IFX) or Adalimumab (ADA) for moderate-to-severe IBD and who required a change in anti-TNF (IFX or ADA) therapy due to loss of response. Exclusion criteria were patients under other types of anti-TNF treatment or those who had received treatment for different indications. We defined three groups of periods based on the interval of time before starting the second anti-TNF-treatment: Group A: very early (≤14 days), Group B: early (15–30 days) and Group C: late (30–60 days). Patients for whom the interval of time was over 60 days were excluded. Treatment failure after the second anti-TNF was defined as the need for dose intensification, surgery resection, or therapy removal for ineffectiveness. The influence of the first anti TNF agent (IFX or ADA) and the existence of adverse events or infections were also evaluated. Results are shown as percentages, median, range and Hazard Ratio (CI 95%). Fisher test and Cox Regression Analysis were also performed.
Results: 75 patients (63% CD) were consecutively included (mean age 45). Forty-seven initially under treatment with IFX and 28 with ADA. Twelve patients were included in Group A, 25 in Group B and 38 in Group C. Treatment failure was observed in 43 (57.3%) patients (30 due to intensification, 3 due to primary failure and 2 nudo to surgery). In Cox Regression, time of change of anti-TNF was not associated with increased risk of treatment failure (HR 1.02; 95% CI 0.37–2.78) with a median time until loss of response of 365.4 days in Group A, 377.2 days in group B and 491 days in Group C.



Cox regression of influence of interval of time between first and second anti-TNF and treatment failure

No differences were found in starting with IFX (HR 1.31; 95% CI 0.68–2.54) or ADA (HR 0.74; 95% CI 0.40–1.39) There were 8 adverse events that forced the stopping of treatment: 3 in Group A, 3 in Group B and 2 in Group C ($p = 0.12$). No infections that required hospitalisation were observed.

Conclusions: The interval of time between the first and the second anti-TNF had no influence on either the rates of failure to treatment, the rates of adverse events or the rates of infections.

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Inflammatory sticturing Crohn's diseases: results of medical treatment

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Background: Stricture is the most common complication of CD. Treatment of stricturing CD depends on the inflammatory or fibrotic character of the stricture. However, therapeutic management of stricturing CD remains a complex situation as it has been shown that inflammatory and fibrosis are two overlapping entities. The aim of our study was to assess the short- and long-term impacts of medical treatment in inflammation stricturing CD and to identify predictors of therapeutic failure and lead to surgery.

Methods: A retrospective study over a period of 15 years (2001–2016) including all patients with CD receiving medical treatment for symptomatic inflammatory stricture was performed. The inflammatory nature of stricture was mainly identified by cross-sectional imaging examinations showing signs of active inflammation. Therapeutic failure was defined as symptomatic recurrence leading to hospitalisation or endoscopic dilation or surgery. Short andlong-term medical therapy failure were defined by occurrence of cited above events within respectively 6 and 24 months after initiation of medical therapy.

Results: Fifty-one inflammatory strictures were collected in 43 CD patients who received medical treatment. Medical therapy was based on a full-dose of oral corticosteroids in 37 cases (73%) and anti-TNF agents in 14 cases (27%). Azathioprine was prescribed in maintenance for patients who received corticosteroids in 21 cases (63%) and in combination with anti-TNF (combotherapy) in 12 patients (85%). The short-term therapeutic failure rate was 22% ($n = 11$) and the long-term therapeutic failure rate was 45% ($n = 23$). Nineteen patients (37%) needed surgery within an average of 11 months (7–18 months). In multi-variate analysis, only the presence of fistulas was associated with short-term medical therapy failure ($p = 0.014$). Active smoking (HR 3.46, 95% CI [1.129–10.821], $p = 0.009$), age at diagnosis (A1 according to the Montreal classification) (HR 2.02, 95% CI [0.613–6.715], $p = 0.036$) and presence of enteroenteric fistulas (HR 7.188, 95% CI [1.804–28.634], $p = 0.001$) were independent predictors of long-term medical therapy failure and surgery requirement.

Conclusions: Despite the identification of inflammatory nature of intestinal stricture, medical treatment fails in half of the cases and nearly 40% of patients are operated on after 2 years. This emphasises the fact that the two entities, inflammation and fibrosis, cannot be dissociated. Identify predictors of therapeutic failure, may allow us to select from the outset patients at high risk of surgery.

P494

Regional survey on satisfaction with healthcare in inflammatory bowel disease patients

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Background: Inflammatory bowel diseases (IBD) are chronic and lifelong conditions that can have a major impact on patients' lives. Due to chronic nature of the disease, patients are in constant interaction with the healthcare system. Therefore, it is of great importance to constantly question patients' needs and satisfaction to provide better and more patient-oriented care. Aim of this study was to survey IBD patients' opinion on their overall care.

Methods: We created an anonymous questionnaire and posted it to the web-based IBD patient group that gather patients from our geographical region (Croatia, Bosnia and Hercegovina, and Serbia). Besides general information, such as gender, age and diagnosis, patients were asked about their disease activity, general satisfaction with the healthcare received, access to IBD doctor, their knowledge about the disease and changes they would take to make healthcare system better. We received 387 responses between November 2017 and November 2018, and analysed them by descriptive statistics and chi square test.

Results: A total of 193 patients with Crohn's disease and 194 patients with ulcerative colitis filled the questionnaire, of which 268 (69.3%) were female. Median age was 35 years (min. 13, max. 70 years). A majority of patients ($n = 286$, 73.9%) were satisfied with their overall care. According to their opinion, important changes that would improve patient care are: better access to IBD doctor ($n = 129$, 33.3%), more educational materials ($n = 100$, 25.8%), more interaction with other IBD patients ($n = 62$, 16.0%). Twenty-one patient (5.4%) had other suggestions, and 75 patients (19.4%) would not make any change. IBD doctor's availability was of great importance, as 91.6% of patients ($n = 219$) that could easily reach to their gastroenterologist were satisfied with healthcare received compared with only 45.3% ($n = 67$; $p < .001$) of patients whose doctor was not available. Even among patients whose disease was active, IBD doctor's availability was considered important, as 83.3% ($n = 65$) of them were satisfied with healthcare if their doctor was available compared with 25% ($n = 16$; $p < .001$) of those whose doctor was not easily reachable.

Nearly half of patients considered to be excellently or well informed ($n = 193$) about the disease, 36.7% ($n = 142$) were satisfied with their level of knowledge. Major source of information about the disease was internet, IBD doctor and patient advocacy groups.

Conclusions: Most of the patients think that better access to IBD doctor would improve patient care. Therefore, improving access to the IBD service should be of special interest to us. Our aim should also be a better education of our patients by improving educational materials and promoting patient advocacy groups.

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Spacing the administration interval of anti-TNF agents: a valid strategy for patients with inflammatory bowel disease?

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Background: Patients with psoriasis and rheumatologic diseases are eventually treated with biological agents using treatment schedules with more spaced administrations than those approved. These schedules are cheaper and they even might reduce the risk of adverse events. However, these treatment strategies are scarcely used in inflammatory bowel disease (IBD).
Methods: Aim: Two evaluate the clinical course of IBD patients treated with anti-TNF agents by means of a spacing strategy (administration interval greater than 8 weeks for infliximab or 2 weeks for adalimumab). Using the local databases from two referral centres, all the patients with IBD who were treated with infliximab or adalimumab by means of a spacing strategy, were identified. Patients with ostomy or ileoanal pouch, indication of anti-TNF therapy for perianal disease, or adverse events as the main cause for spacing strategy, were excluded. The spacing strategy success was considered if at the end of the follow-up the patient remained in clinical remission with the same spaced schedule or without biological therapy and if no return to the conventional schedule, dose-escalation, switch, swap, a course of systemic corticosteroids or surgery were required.
Results: Eighty-five patients were included (58 Crohn's disease, 27 ulcerative/IBD unclassified). Sixty were treated with infliximab (49 every 10 weeks and 11 every 12 weeks) and 25 patients with adalimumab every 3 weeks. Prior to the index course of anti-TNF, 38% of patients followed a previous course of anti-TNF, and 7% required dose-escalation. The spacing schedule was initiated after the median of 25 months of anti-TNF treatment (IQR 14–49). Thirty-seven per cent had ileocolonoscopy (3% with endoscopic activity) and 17% MRI enterography (29% with RM activity) within 6 months before spacing began. 60% of patients were on concomitant immunomodulatory treatment at the beginning of spacing. The median time on spacing schedule was 15 months (IQR 12–25). Thirty-seven per cent of patients returned to a conventional schedule and 9% required dose-escalation. In 22 patients (26%) the anti-TNF was stopped because of sustained remission (9/22), clinical relapse (3/22), adverse events (2/22) or for other reasons (3 pregnancy, 3 neoplasia, 2 other). At the end of follow-up, 50 out of 85 patients (59%) met the success criteria of the spacing strategy. No baseline characteristics were found to be associated with success.
Conclusions: Anti-TNF administration at longer intervals than the ones provided in the data sheet of the drug can be a convenient, safe, useful and cheaper alternative for IBD patients, even though, at this time, we do not have predictors of success.

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Impact of ulcerative colitis on costs, work productivity and quality of life: a prospective study in a single referral centre

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Background: Ulcerative colitis (UC) is a chronic condition with a heavy economic burden for the health system and the society. Previous reports are available, but few data have been published in Italy, especially in the south.
Methods: Our aim was to evaluate prospectively, in a 1-year period, the costs of UC in a consecutive cohort of Sicilian patients, and to assess their correlation with diseases activity (evaluated by Mayo Score), disease location, Work Productivity (WPAI-RCU) scoring and quality of life. Patients were asked to fill questionnaires on Quality of life (Eq5D), Cost of Illness (COI) and use of health resources (HRU). Data on demographic, hospitalisations, surgery, visits to the treating physician and to the emergency room, laboratory tests, radiological and endoscopic examinations, drugs.
Results: We recruited 77 consecutive patients with UC coming to our IBD clinic from May 2017 to November 2017. At baseline mean age was 46.8 ± 13.6 years, 40 were males. Disease location was pancolitis in 31 patients. Twenty-four patients were in clinical remission, 24 had mild disease and 19 moderate activity. In 1-year observation period, mean cost/patient was €2898.8 for drugs, €3076.4 if we included the cost of diagnostic tests. Cost of drugs was higher in patients with pancolitis (€4142.6) than those with a limited disease (2599.7 €) and proctosigmoiditis (€2112.9) ($p = 0.004$). A relationship was also observed between drug therapy and disease activity ($p < 0.05$). There was a statistical difference among patients on biologics (€6395.5), when compared with thiopurines (€368.7) and other conventional treatments (€554.6) ($p < 0.001$). Disease activity was significantly related with work productivity ($p = 0.05$) and quality of life ($p < 0.001$).
Conclusions: Our preliminary results confirm that in Southern Italy, UC has high direct costs mainly related to drug therapies and in particular to biological therapy. Mean cost/patient/year is €3076.4 and it is significantly associated with disease activity and extent of disease. Disease activity impacts significantly on work productivity and quality of life. These preliminary results will provide useful information to health authorities to guide resource allocation and physicians to improve disease management.

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IL-33/ST2 levels and gut microbiota characterisation can predict mucosal response to anti-TNF therapy in ulcerative colitis

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Background: IL-33/ST2 axis and gut microbiota are important factors in the pathogenesis of IBD. Anti-TNF are able to modulate the IL-33/ST2 axis as well as gut microbiota in inflammatory conditions and are effective in inducing mucosal healing in patients with moderate-to-severe ulcerative colitis (UC). The aim of our study was to explore the potential role of the IL-33/ST2 axis and gut microbiota in the mucosal healing process mediated by anti-TNF therapy in UC.

Methods: Endoscopic MAYO score was calculated before the first anti-TNF infusion (T0) and after 6 weeks (T2). Twenty-six UC patients (MAYO score at T0 ≥ 2), grouped into 14 responders (R) with mucosal healing (MAYO score ≤ 1) and 12 non-responders (NR) to anti-TNF at T2 (MAYO score ≥ 2) were enrolled. Ten healthy controls were also enrolled. At each time point, serum and faecal samples were collected. ELISA and western blot were performed. Intestinal biopsies were also taken from the rectum and IHC was done. Genomic DNA was extracted from faecal samples and V3-V4 regions of the 16S rRNA gene were sequenced by MiSeq Illumina platform for microbiota characterisation.
Results: IL-33 protein levels were significantly increased in R vs. NR, both at T0 and T2. Among R, IL-33 protein was slightly reduced at T2 vs. T0, while unchanged in NR. Interestingly, significantly higher levels of ST2 were found in R vs. NR at T0, while no differences between groups were found at T2. Among R, ST2 levels were dramatically reduced at T2 vs. T0. No significant differences were found in NR at both time points. Controls showed significantly lower levels of both IL-33 and ST2 compared with other groups. Full-length, bioactive IL33 (31 kDa), ST2L (76 kDa) and sST2 (52 kDa) were expressed in all experimental groups; the cleaved, less active form of IL33 (24 kDa) was increased in only NR vs. R and healthy controls. IHC confirmed these observations. IL-33 and ST2 staining was more intense within the inflamed and ulcerated mucosa of R compared with NR at T0. After 6 weeks, ST2 staining was even more evident in R, notably localised to the healed mucosa and in close proximity to areas of re-epithelialization. Little to no staining for both IL-33 and ST2 was present in healthy controls. Microbiota analysis showed an increased biodiversity at T0 in R vs. NR. At T0, NR showed lower levels of Verrucomicrobia (Akkermansia municiphila) and Firmicutes, with an increased abundance of Bacteroidetes vs. R.
Conclusions: Our results suggest a possible role for IL-33/ST2 and gut microbiota in predicting gut mucosal wound healing in patients with moderate-to-severe UC treated with anti-TNF. IL-33/ST2 axis and gut microbiota could thus represent a useful diagnostic tool to evaluate therapeutical options in IBD patients.

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A nationwide quality improvement program in children with Crohn's disease improves outcomes within 12 months

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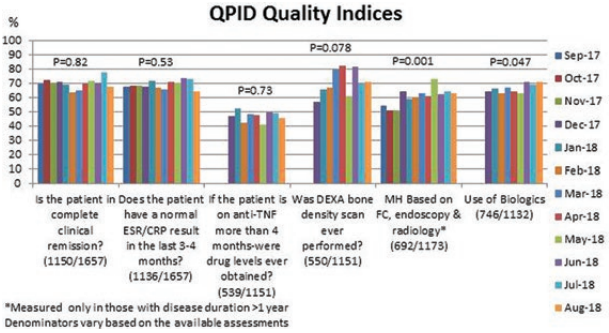
Background: Standardised management protocols of paediatric Crohn's disease (CD) are lacking in Israel, leading to a wide heterogeneity of care across paediatric centres. In this quality improvement Programme, named QPID, we aimed to construct a population-based non-research platform that records clinically important quality indicators of CD in all paediatric IBD centres in Israel, to improve treatment outcomes across the country.
Methods: Representative of all 20 paediatric IBD centres in Israel formed part of a Delphi group to select quality indicators for the QPID (including process and outcome indicators). Eligibility criteria for this program were children with CD seen in clinic, age 2–18 years, not recorded in during the previous 2 months. Children with disease duration <3 months were excluded and a cap of 20 patients per month per site avoided dominance effect of large centres. The indicators were recorded on a REDCap eCRF platform, managed at a data coordinating centre (DCC). Global assessment of longitudinal disease activity and medications were captured to account for patient-mix at each centre. Centres were coded and their allocation was concealed from all involved parties. Monthly reports were distributed, comparing the performance of the specific centre with previous months and other blinded centres.
Results: The indicators of 1657 visits were recorded from 09/2017 to 08/2018 (mean children age 14.5 ± 2.9 years; median disease duration 1.92 years (IQR 0.92–3.42)). The majority of visits reported quiescent longitudinal global assessment (55%), 30% reported mild activity, and 15% reported moderate–severe activity. On average, 66% of children were treated with biologics with increasing rates over the year (65% to 70%; $p = 0.047$) (figure)



QPID Quality Indices

https://planner.smart-abstract.com/ecco2019/submission/en/abstract/12600/image/add.html . A slight increase in measures indicating mucosal healing was note, from 53% to 64% among those with disease duration of at least 1 year ($p = 0.001$; figure). Clinical remission rate was stable at 72%. Use of steroids was <5% of all reports reflecting the wide use of nutritional therapy in Israel.
Conclusions: Quality improvement programs at a country level may be implemented with limited resources while facilitating a national standardisation of care. No causal relationship can be elucidated between the program and the observed improved endpoints. Nonetheless, providing anonymous comparisons with other centres may increase awareness and motivation to improve quality indicators.

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Efficacy and safety of 2 or 3 vedolizumab intravenous infusions as induction therapy for ulcerative colitis and Crohn's disease: results from VISIBLE 1 and 2

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Background: Vedolizumab is a gut-selective, humanised, $\alpha_4\beta_7$ integrin monoclonal antibody approved for intravenous (IV) administration to patients with moderately to severely active ulcerative colitis (UC) or Crohn's disease (CD). A subcutaneous (SC) formulation is in development as maintenance therapy. Here, we evaluate clinical response to 2 or 3 doses of vedolizumab IV induction therapy in the phase 3 VISIBLE 1 (UC; NCT02611830) and VISIBLE 2 (CD; NCT02611817) vedolizumab SC maintenance trials.
Methods: In both trials, patients received open-label vedolizumab 300 mg IV induction therapy at Weeks 0 and 2. At Week 6, clinical responders were randomised into the SC maintenance phase and non-responders were given a third IV infusion and reassessed at Week 14. Clinical response in UC was assessed at Week 6 as a ≥3-point and ≥30% decrease in complete Mayo score from Week 0 (Baseline) and at Week 14 as a ≥2-point and ≥25% decrease in partial Mayo score from Week 0, together with a rectal bleeding subscore decrease ≥1 point or absolute subscore ≤1 point at both time points. Clinical response for CD was a >70-point decrease in CD Activity Index score from Week 0. Safety of vedolizumab IV induction was assessed. The VISIBLE 1 trial has been completed, whereas VISIBLE 2 is currently ongoing (efficacy data only available as captured by an interactive voice response system).
Results: Among the 383 (UC) and 644 (CD) patients who received open-label vedolizumab induction, 56.1% (106/225) with UC and 63.7% (410/644) with CD had a clinical response at Week 6 after 2 vedolizumab IV infusions. Among patients who received a third induction infusion, clinical response rates were 79.7% (114/143) in UC and 63.2% (122/193) in CD. Overall, 86.2% (330/383) of UC patients and 82.6% (532/644) of CD patients achieved a clinical response after 2 or 3 vedolizumab IV infusions. In VISIBLE 1, treatment-emergent adverse events (TEAEs, 62.9% of patients; 17% treatment-related) and serious TEAEs (10.4% of patients; 0.5% treatment-related) were consistent with prior studies and there were no deaths. Adverse events (30.0%) and lack of efficacy (30.0%) were the main reasons for discontinuation.
Conclusions: Vedolizumab IV induced a clinical response after 2 infusions in more than half of both UC and CD patients. Patients failing to respond after 2 infusions appeared to benefit from a third infusion and responses were achieved in the vast majority of patients overall. The safety/tolerability profile of vedolizumab IV induction was consistent with previous reports.

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Post-marketing safety experience of vedolizumab in patients receiving concomitant treatment with other biologics

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Background: Vedolizumab (VDZ) is a gut-selective antibody to α4β7 integrin approved to treat moderate to severe Crohn's disease (CD) and ulcerative colitis (UC) in adults. Concomitant treatment with VDZ and other biologics is not recommended in the VDZ prescribing information and has not been evaluated in clinical trials, meaning that safety data are limited on patients receiving this combination. We compared 4 years of post-marketing safety data reported to Takeda Pharmaceutical Company Ltd. (Takeda) on patients receiving VDZ and concomitant treatment including other biologics ('with CB') with patients receiving VDZ and concomitant therapy excluding other biologics ('without CB').
Methods: The VDZ Global Safety Database contains all adverse event (AE) reports received by Takeda, including concomitant medication data if available, since VDZ approval on 20 May 2014. Reports received between approval and 19 May 2018 with concomitant medication data were identified for review using MedDRA version 21.0. VDZ exposure was estimated using the number of vials shipped globally, assuming 8 week dosing intervals.
Results: In approximately 208 050 patient-years of VDZ exposure, 80 218 AEs were reported in 32 752 patients. Of these AEs, 2847 (4%) were in 1112 (3%) patients with CB and 54 855 (68%) were in 20 201 (62%) patients without CB (other AEs were in patients with no concomitant medication reported; Table 1). There were 1003 patients with CD or UC with CB and 18 974 without CB. Infections accounted for 202 AEs (7%) in patients with CB and 4414 (8%) without CB, of which 21% and 18% were serious, respectively. There were 7 post-operative complications and 16 infusion-site reactions in patients with CB compared with 186 and 453, respectively, in those without CB (< 1% and 1% of AEs in each group). A total of 2 malignancies and 7 fatal AEs (both < 1%) occurred in patients with CB, vs. 176 malignancies and 140 fatal AEs (both < 1%) in patients without CB.

Table 1. Patient characteristics, vedolizumab continuation and adverse events in patients receiving vedolizumab with and without concomitant treatment with other biologics.

Characteristic, n (%) n = number of patients	Patients receiving vedolizumab with concomitant biologic treatment ('with CB')			Patients receiving vedolizumab without concomitant biologic treatment ('without CB')		
	Crohn's disease n = 460	Ulcerative colitis n = 543	Other indications[a] n = 199	Crohn's disease n = 8861	Ulcerative colitis n = 16 113	Other indications[a] n = 1227
Sex						
Female	279 (61)	240 (44)	69 (63)	5499 (62)	5130 (51)	723 (59)
Male	178 (39)	301 (55)	35 (32)	3341 (38)	4954 (49)	473 (39)
Not reported	3 (1)	2 (< 1)	5 (5)	21 (< 1)	29 (< 1)	31 (3)
Age, years[b]						
< 18 years	7 (2)	5 (1)	2 (2)	118 (1)	231 (2)	28 (2)
18–64 years	406 (88)	481 (89)	73 (67)	7889 (80)	8025 (79)	653 (53)
≥ 65 years	39 (8)	48 (9)	4 (4)	1484 (17)	1702 (17)	195 (16)
Not reported	8 (2)	8 (1)	28 (26)	179 (2)	155 (2)	351 (29)
Concomitant biologics[c]						
Concomitant anti-TNF alpha therapy	339 (74)	520 (96)	73 (67)			
Other concomitant biologic therapy	117 (25)	22 (4)	34 (31)	N/A	N/A	N/A
Concomitant anti-TNF alpha and other biologics	4 (1)	1 (< 1)	2 (2)			
Other concomitant immunosuppressant						
Yes	133 (29)	167 (31)	32 (29)	2110 (24)	2399 (24)	276 (22)
No	327 (71)	376 (69)	77 (71)	6751 (76)	7714 (76)	951 (78)
Concomitant corticosteroid						
Yes	180 (39)	261 (48)	49 (45)	3763 (42)	5697 (56)	432 (35)
No	280 (61)	282 (52)	60 (55)	5098 (58)	4416 (44)	795 (65)
Category of adverse event, n (%) n = number of events						
	Crohn's disease n = 1285	Ulcerative colitis n = 1363	Other indications[a] n = 199	Crohn's disease n = 25 529	Ulcerative colitis n = 26 272	Other indications[a] n = 2654
Infections[d]	98 (8)	104 (8)	40 (20)	2201 (9)	3213 (8)	438 (17)
Serious infections	22 (2)	21 (2)	18 (9)	480 (2)	324 (1)	121 (5)
Malignancies[e]	1 (< 1)	1 (< 1)	2 (1)	92 (< 1)	84 (< 1)	12 (1)
Infusion-site reactions	10 (1)	6 (< 1)	0 (0)	235 (1)	218 (1)	7 (< 1)
Fatal events[f]	4 (< 1)	3 (< 1)	1 (1)	80 (< 1)	80 (< 1)	27 (1)
Post-operative complications	4 (< 1)	3 (< 1)	2 (1)	136 (1)	51 (< 1)	23 (1)
Vedolizumab continuation following adverse event, n (%) n = number of patients						
	Crohn's disease n = 460	Ulcerative colitis n = 543	Other indications[a] n = 199	Crohn's disease n = 8861	Ulcerative colitis n = 16 113	Other indications[a] n = 1227
Treatment continued	352 (77)	446 (82)	33 (30)	7301 (82)	8566 (85)	814 (66)
Treatment discontinued	87 (19)	79 (15)	57 (52)	1143 (13)	1232 (12)	224 (18)
Not applicable	5 (1)	2 (< 1)	2 (2)	58 (1)	47 (< 1)	24 (2)
Not reported/unknown	16 (3)	16 (3)	17 (15)	359 (4)	268 (3)	165 (13)

[a]Including patients with unspecified inflammatory bowel disease, off-label use and unreported indications
[b]Vedolizumab is not approved for use in patients < 18 years of age
[c]Receipt of vedolizumab therapy concomitantly with other biologics is not recommended in the vedolizumab prescribing information
[d]The most frequently reported serious infections for patients receiving vedolizumab with CB were intestinal abscess, anal abscess and pneumonia (2 patients [9%] each) in CD and *Clostridium difficile* infection/colitis (3 patients [14%]), pneumonia and cytomegaloviral infection/colitis (2 patients each [14%]) in UC
[e]Malignancy events in both groups excluded colon adenomas, benign events and non-melanoma skin cancer, as well as malignancies in patients experiencing an event before initiation of vedolizumab therapy. Of the four malignancies in the group with CB, there was one lower GI malignancy (CD), two hematological malignancies (1 UC, 1 other indication) and one neuroendocrine malignancy (1 other indication)
[f]Of the fatal events in the group with CB, 3 reports contained the term 'death' with no further detail (all in patients with CD), 1 event was listed as adenocarcinoma (CD), 1 was leukemia (off-label use for graft-versus-host disease) and 1 patient had 3 fatal events (GC, multiple organ dysfunction syndrome and drug ineffective)
AE, adverse event; CB, concomitant biologics; CD, Crohn's disease; N/A, not applicable; UC, ulcerative colitis; TNF, tumor necrosis factor

Conclusions: This analysis provides information on VDZ safety with and without CB in the real-world setting. Limitations of post-marketing safety reports should be considered when interpreting these results, including that duration of VDZ with CB was not included in reports. Additionally, the numbers of AEs reported in patients receiving VDZ with CB were small, and the number of patients receiving VDZ with CB was much lower than those without CB. These data do not suggest an increased risk of AEs in patients receiving VDZ with CB vs. VDZ without CB.

P501

High TNF-production of CD14+ cells and short disease duration are independent predictive factors for response to Infliximab treatment

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Background: A substantial rate of primary non-response to Infliximab in patients with inflammatory bowel disease (IBD) together with the increasing availability of alternative biologics emphasise the need for predictive markers to personalize treatment. Thus, the study's aim was to identify predictive factors for response to Infliximab treatment.

Methods: 21 patients with Crohn's disease (CD) and 20 patients with ulcerative colitis (UC) without treatment with biologicals in the past 6 months were prospectively included into this observational study before their first Infliximab infusion. Harvey–Bradshaw-Index (HBI) or partial Mayo Score (pMS), C-reactive protein (CRP) and ultrasound (Limberg Score) served to quantify disease activity at baseline and Week 6, respectively. Cytokine production of LPS-stimulated PBMCs at baseline (TNF, IL-1, IL-6, IL-8, IL-10, IL-12p70) were measured by ELISA, CBA and flow cytometry. A ROC analysis for TNF-production was applied to estimate a cut-off to group patients into either low or high TNF-producers. Primary endpoint was clinical response defined as a decline in score of ≥ 2 (HBI) or ≥ 3 (pMS) at Week 6, secondary endpoints were decrease in CRP or Limberg score at Week 6. The need for urgent colectomy within the 6 weeks was defined as non-response. Mann–Whitney *U* and χ^2 test served for univariate analysis and logistic regression was used for multi-variate analysis.

Results: 41 patients (48.8% females) with a mean age of 38 (SD 12.8) were included in the analysis. Of these, 30 patients (73.2%) responded to Infliximab treatment. Responders had shorter disease duration (p = 0.018), higher Limberg score at baseline (p = 0.021) and produced significantly more TNF (p = 0.049) and IL-6 (p = 0.028) at baseline compared with non-responders. Flow-cytometry identified CD14+ cells as the main TNF-producers. For TNF-production, ROC analysis of all IBD-patients revealed a cut-off value of 500 pg/ml having a sensitivity of 82% and specificity of 78% to predict response, which was much stronger when analysing only CD patients (sensitivity of 100% and specificity of 82%). Low TNF-producers were 14.8 times more likely to have a treatment failure, compared with high TNF-producers (OR 14.8, 2.6–85.1, p = 0.003). Multi-variate analysis including all significant factors of the univariate analysis identified high TNF-production at baseline (p = 0.005) and shorter disease duration (p = 0.028) as independent predictors for response to Infliximab.

Conclusions: High TNF-production of CD14+ cells at baseline and shorter disease duration were independent factors to predict response to Infliximab in IBD patients.

P502

Correlation between soluble suppression of tumorigenicity 2 (sST2) and endoscopic activity in patients with moderate to severe ulcerative colitis under golimumab treatment: results of the EVOLUTION study

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Background: Suppressor of Tumorigenicity 2 (ST2) is an IL33 receptor detected in mucosa and serum of ulcerative colitis (UC) patients. We aimed to evaluate soluble ST2 (sST2) as a surrogate biomarker of disease activity and therapeutic response in subjects with moderately to severely active UC under golimumab and to compare with standard biomarkers such as faecal calprotectin (FC) and C-reactive protein (CRP).

Methods: Open-label single-arm multi-centre prospective study. At screening/baseline, Week 6 (W6) and Week 16 (W16), clinical and endoscopic activity (total Mayo score), histological activity (Geboes index) and biomarkers were evaluated. Biomarkers levels by UC activity were compared using Mann–Whitney test and *t*-test. Receiver-operating characteristic curves (ROC), Wilcoxon signed rank test and Spearman correlations (rs) were also used (α = 0.05).

Results: Thirty-four patients (89.5%) completed W6 and 29 (76.3%) completed W16. Mean ± sd age was 34.6 ± 12.6 years; 55.9% were female. At W16, 62.1% (18/29) achieved clinical response by total Mayo score. At W6, sST2 levels correlated with endoscopic activity (rs=0.45, p = 0.007) but not with histological activity (rs = 0.25, p = 0.151). W16 correlations were not significant. Patients with endoscopic activity at W6 had higher sST2 baseline levels: median, 24.5 vs. 18.7 ng/ml (p = 0.026) and showed no decrease of sST2 levels (median change, 0.8 vs. –2.7, p = 0.029). The best sST2 cut-off for endoscopic activity was 16.9 ng/ml (specificity=71%; sensitivity=85%). sST2 did not correlate with FC nor with CRP (Table 1).

	AUC	95%CI	p-value	SEN	SPE	PPV	NPV
ST2							
endoscopic activity *[cut-off value ≥16.9 ng/mL]*	**0.80**	**0.65-0.95**	**<0.001**	**85%**	**71%**	**81%**	**77%**
histological activity *[cut-off value ≥15.5 ng/mL]*	0.67	0.46-0.88	0.111	74%	71%	91%	42%
FC							
endoscopic activity *[cut-off value ≥353 µg/g]*	0.73	0.50-0.96	0.049	90%	67%	81%	80%
histological activity *[cut-off value ≥353 µg/g]*	**0.92**	**0.82-1.00**	**<0.001**	**84%**	**100%**	**100%**	**60%**
CRP							
endoscopic activity *[cut-off value ≥0.7 mg/L]*	0.73	0.54-0.92	0.016	95%	50%	72%	88%
histological activity *[cut-off value ≥4.4 mg/L]*	**0.82**	**0.65-0.99**	**<0.001**	**50%**	**100%**	**100%**	**35%**

AUC, area under the curve. 95%CI, 95%Confidence Interval. SEN, sensitivity. SPE, specificity. PPV, positive predictive value. NVP, negative predictive value.

Accuracy of sST2, FC and CRP measurement to predict endoscopic and histological activity at Week 6.

Conclusions: sST2 may be a surrogate biomarker of UC activity and therapeutic response. sST2, FC and CRP may be biomarkers of different components of the UC inflammatory process during early treatment with golimumab.

P503

Two year experience with vedolizumab in inflammatory bowel disease patients: results of the ICC case series, a nationwide prospective observational cohort study

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Background: Vedolizumab (VDZ) is approved for the treatment of inflammatory bowel disease (IBD). Prospective data on clinical effect, safety and usage beyond 1 year of follow-up is scarce. We aimed to study the two year real-life experience with VDZ in IBD patients.
Methods: IBD patients initiating VDZ treatment were prospectively enrolled in a nationwide, web-based registry: the ICC case series. Clinical activity scores (Harvey–Bradshaw Index (HBI) for Crohn's disease (CD), Short Clinical Colitis Activity Index (SCCAI) for ulcerative colitis (UC)), biochemical parameters (C-reactive protein (CRP) and faecal calprotectin (FCP)), VDZ dosage, concomitant medication, and adverse events were documented at week 0, 12, 24, 52, and 104, or when VDZ treatment was discontinued. Clinical remission was defined as HBI ≤4 and SCCAI ≤2. Biochemical remission was defined as a CRP concentration ≤5 mg/l and/or FCP level ≤200 µg/g. Intention-to-treat (ITT) follow-up was determined between first visit and last visit included in the ITT analysis.
Results: In total, 275 IBD (173 CD, 102 UC) patients were included (98.9% and 89.2% anti-tumour necrosis factor (TNF) exposed, respectively), with a median follow-up period of 104.0 weeks (IQR 100.7–104.0) for CD and 104.0 weeks (IQR 56.8–104.0) for UC. The proportion of patients in steroid-free clinical remission at Week 52 and 104 was 28.0% and 27.5% for CD and 33.7% and 30.9% for UC, respectively. Between Week 52 and 104, 73.7% of the CD and 73.1% of the UC patients remained in steroid-free clinical remission. clinical effect was comparable for combination of VDZ and immunosuppressive agents vs. VDZ monotherapy (Week 104: 29.5% vs. 28.4% p = 0.86). The proportion of patients in biochemical remission at Week 52 and 104 was 26.5% and 21.0% for CD and 30.6% and 22.2% for UC, respectively. An additional infusion at Week 10 was given to 83 (48.0%) CD and 17 (16.7%) UC patients, 40 (23.1%) CD and 13 (12.7%) UC patients underwent interval shortening (≤6 weeks). Ten severe infections occurred resulting in hospital admission (3.4 per 100 patients years), 8/10 used concomitant immunosuppressive agents. VDZ was discontinued in 100 (57.8%) CD and 47 (46.1%) UC patients, mainly due to primary non-response (CD: 61%, UC: 85.1%). Nine patients discontinued VDZ due to adverse events (3.1 per 100 patient-years). Twenty-six (CD: 22, UC: 4) patients discontinued after the first year.
Conclusions: We assessed clinical outcomes of VDZ in a nationwide, prospective cohort of anti-TNF experienced IBD patients with 104 weeks follow-up. Our data showed persistent effectiveness of VDZ beyond 52 weeks of treatment, as well as frequent dosage optimisation and a reassuring long-term safety profile.

P504

How acceptable is a 'treat to target' (T2T) approach to IBD patients in clinical remission?

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Background: Treatment algorithms for IBD are shifting from traditional symptom based pathways to a 'treat to target' T2T approach aiming for clinical remission and absence of mucosal inflammation. We aimed to establish whether patients with IBD in clinical remission agree to this more intense approach.
Methods: We recruited patients in steroid-free clinical remission from IBD clinics. CRP, faecal calprotectin, Hospital Anxiety and Depression Score (HADS), medication adherence and short knowledge questionnaire were recorded. Patients underwent a face to face structured interview asking them to imagine that a test had shown active inflammation and to rate how acceptable a T2T approach is to them on 10-point Likert scales. Patients rated the avoidance of complications according to level of risk and potential risk reduction. We analysed factors associated with agreement to T2T.
Results: The cohort comprised 298 patients (144 CD, 136 UC, 18 IBD-U, median age 46 years, 145 males, median disease duration 7 years). Medications included Mesalazine 44.3%, Thiopurines 30.5%, Methotrexate 3.2% and Biologics (26.1%). Abnormal HADS scores were present in 28.9% (anxiety) and 18.5% (depression). Non-adherence occurred in 15.8%. Median knowledge score was 3 out of 10. Elevated CRP was found in 24.4% and elevated calprotectin in 17.7%. Patient-reported current control of IBD correlated with calprotectin (Pearson –0.169; p = 0.004).
Patients rated a T2T approach as acceptable (Likert scale ≥8) in 66.2%. Acceptable treatment aims for patients were avoidance of a flare (risk needed to be ≥30% and relative risk reduction 25%), hospitalisation, surgery and colorectal cancer (risk ≥10%, risk reduction 50% for all).
Age, diagnosis, phenotype, surgical history, disease duration, patient knowledge, adherence, anxiety, depression, medication adherence and patient-reported control of disease were not associated with accepting a T2T approach. Patients on second-line anti-TNF were more likely to agree to a T2T approach (p = 0.012) but there were no associations with other treatments.
Conclusions: It is important to understand patient views on T2T before attempting implementation. We have demonstrated, in a cohort of patients in clinical remission where this question is most pertinent, that 66% accept a T2T approach. Patients having experienced previous loss of response to an anti-TNF were more likely to accept T2T but at the same time are the least likely to benefit. Conversely a third of patients did not agree with this approach, and the presence of occult mucosal inflammation was not associated with T2T acceptance. Patient education and counselling materials will therefore need to be developed to convince patients of the importance of T2T.

P505

Real-world short-term effectiveness of ustekinumab in Crohn's disease: Results from the ENEIDA Registry

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Background: Ustekinumab is a monoclonal antibody targeting interleukins 12 and 23. Its effectiveness in clinical practice has not yet been demonstrated. The aim of this study was to assess the real-world, short-term effectiveness of ustekinumab in medically refractory Crohn's disease (CD) (CROHNUSK study).

Methods: Multi-centre study of CD patients receiving ustekinumab after June 2017 (when it was approved in Spain) and at the recommend dose (a single iv infusion of 6 mg/kg followed by a sc injection of 90 mg at Week 8). The Harvey-Bradshaw Index (HBI) was used to evaluate clinical remission (HBI score ≤4). Values for HBI, C-reactive protein (CRP), and faecal calprotectin (FC) were recorded at baseline and at Weeks 8 and 14. Demographic and clinical data, endoscopy at baseline when available, previous treatments, adverse events (AEs), and hospitalisations were documented. Possible predictors of clinical remission were examined.

Results: A total of 305 CD patients were analysed (Table 1).

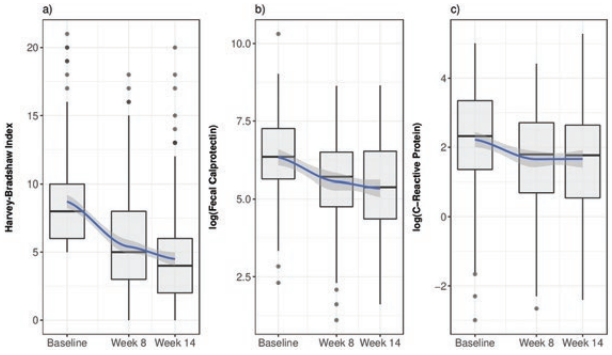
CHARACTERISTICS OF STUDY POPULATION	N=305
Male/female, n (%)	150 (49%)/155 (51%)
Age, years	44.4 (13.3); 43.7 (34.4, 53.6)
Age at diagnosis, years	31.3 (13.8); 27.5 (21.3, 38.9)
Disease duration, years	13.1 (9.1); 11.7 (5.6, 18.8)
Disease location, n (%)	
Ileal	136 (45%)
Colonic	40 (13%)
Ileocolonic	129 (42%)
Upper gastrointestinal	63 (20%)
Perianal involvement	126 (41%)
Phenotype, n (%)	
Non-stenosing/non-penetrating	173 (50%)
Stenosing	102 (30%)
Penetrating	62 (20%)
Extraintestinal manifestations, n (%)	120 (39%)
Smoking status, n (%)	84 (28%)
Previous surgery, n (%)	171 (56%)
Previous anti-TNF therapy, n (%)	
0	11 (4%)
1	98 (32%)
2	151 (49%)
≥3	45 (15%)
Previous anti-TNF experience, n (%)	294 (96%)
Primary failure	79 (27%)
Secondary failure	153 (52%)
Adverse event or intolerance	62 (21%)
Previous therapy with vedolizumab, n (%)	87 (29%)
Primary failure	29 (33%)
Secondary failure	34 (39%)
Adverse event or intolerance	24 (28%)
Severity at baseline, n (%)	200 (66%)
Mild	30 (15%)
Moderate	106 (53%)
Severe	64 (32%)
HBI score	
Baseline	7 (4.1); 6 (4, 9)
Week 8	4.4 (3.6); 4 (2, 6)
Week 14	3.7 (3.5); 3 (1, 5)
CRP (mg/L)	
Baseline	21.3 (32.5); 8.5 (2.3, 25)
Week 8	14.3 (27.7); 5.6 (2, 15)
Week 14	14.6 (27); 4.7 (1.5, 14)
FC (µg/g)	
Baseline	1165 (2556); 496 (215, 1305)
Week 8	656 (1070); 301 (109, 745)
Week 14	628 (1135); 228 (93, 689)
Immunosuppressant at baseline, n (%)	122 (40%)
Azathioprine	84 (69%)
6-mercaptopurine	7 (6%)
Methotrexate	28 (23%)
Other	3 (2%)
Corticosteroids at baseline, n (%)	109 (36%)

Data are expressed as "mean (standard deviation); median (1st, 3rd quartile)" or number (%)

TNF: tumor necrosis factor, HBI: Harvey-Bradshaw Index score, CRP: C-reactive protein, FC: fecal calprotectin.

Characteristics of study population

At baseline, 217 (72%) had an HBI score of >4 points. Of these, 101 (47%) and 126 (58%) achieved clinical remission at Weeks 8 and 14, respectively. Of the 109 patients who were on corticosteroids at baseline, 52 (48%) were in corticosteroid-free remission at Week 14. FC levels returned to normal (<250 µg/g) in 66 (22%) and 74 (24%) patients at Weeks 8 and 14, respectively. CRP returned to normal levels (<3 mg/l) in 122 (40%) and 106 (35%) patients at Week 8 and 14, respectively. HBI, FC, and CRP values over time are shown in Figure 1.



HBI, FC, and CRP values over time.

AEs were recorded in 12% of patients. A total of 40 patients (13%) were hospitalised, in 7 cases owing to AEs. Intolerance to the most recent anti-TNF agent and fewer previous anti-TNF agents were associated with clinical remission at Week 14. Endoscopic severity, but not previous vedolizumab treatment, was associated with poor response.

Conclusions: This is the first study to show the real-world safety and effectiveness of ustekinumab in a large cohort of highly refractory CD patients.

P506

Steroid treatment for longer than 2 weeks leading to admission predicts higher colectomy rates in children with acute severe ulcerative colitis

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Background: The value of second-line treatment and rescue therapy in acute severe colitis (ASC) has been established. There is lack of evidence to which factors determine adverse outcome in children with ulcerative colitis over time. Our aim was to identify risk factors for colectomy in children admitted for flare-up of ulcerative colitis.

Methods: We conducted a systematic retrospective case note review in our major tertiary GHN service and identified n = 32 patients admitted for medical treatment of active ulcerative colitis. We divided patients into 2 cohorts: Group A (n = 10); received steroids >2 weeks before admission, and Group B (n = 22); received steroids < 2 weeks before admission or did not receive steroids prior to admission. We compared both groups regarding PUCAI scores, proportion of clinical remission, flare-up, colectomy, and co-medication (azathioprine/6-mercaptopurine, infliximab) after 1 , 3, and 5 years of admission. Data were analysed using Fisher's exact test.

Results: The colectomy rate was significantly higher in Group A (received steroids >2 weeks) after 1, 3, and 5 years (Table 1). Patients in Group B were significantly higher on azathioprine treatment. Group B had a higher proportion of initial flare-up as acute severe colitis. Notably, both groups did not differ between median PUCAI score on all admissions, IV-steroid dosage (high or low-dose protocol), infliximab treatment, or antibiotics given at first flare-up.

	Entire cohort (n = 32)	Group A (n = 10); received steroids >2 weeks before ASC admission	Group B (n = 22); received steroids <2 weeks before ASC admission or did not receive steroids	Fisher's test (P-values)
Flare up rate at 5 years, n (%)	13 (40.6%)	2 (20.0%)	11 (31.8%)	0.050*
Azathioprine/6MP rates at 1 year, n (%)	27 (84.4%)	7 (70.0%)	20 (90.9%)	0.293
Azathioprine/6MP rates at 5 year, n (%)	20 (62.5%)	3 (30.0%)	17 (77.3%)	0.018*
Infliximab rates at 1 year, n (%)	2 (6.3%)	1 (10.0%)	1 (4.5%)	0.534
Colectomy at 1 year, n (%)	3 (9.4%)	3 (30.0%)	0 (0%)	0.024*
Colectomy at 3 years, n (%)	4 (12.5%)	4 (40.0%)	0 (0%)	0.006*
Colectomy at 5 years, n (%)	5 (15.6%)	5 (50.0%)	0 (0%)	0.001*
Median PUCAI score	55 (43.8-65)	42.5 (40-56.3)	50 (45-55)	0.241
Antibiotics at first flare up, n (%)	17 (53.1%)	4 (40.0%)	13 (59.1%)	0.450

Long-term outcomes of children admitted with acute severe ulcerative colitis.

Conclusions: Patients receiving steroids for longer than 2 weeks are at greater risk to requiring colectomy after 1, 3, and 5 years than patients admitted earlier. This effect was irrespective to the cumulative IV-steroid dosage, use of infliximab, or IV antibiotics, or initial flare-up as acute severe colitis. Azathioprine may provide protection against colectomy. Our study indicates the need to consider earlier escalation treatment for children not responding within 2 weeks of oral corticosteroids.

P507

Efficacy of Infliximab after failure of subcutaneous anti-TNF agents in patients with moderate-to-severe ulcerative colitis

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Background: To assess the efficacy of intravenously administered infliximab in patients with moderate to severe ulcerative colitis (UC) who have failed therapy with subcutaneously administered adalimumab or golimumab.

Methods: Retrospective analysis of prospectively collected data of all anti-TNF naive UC patients who received adalimumab or golimumab for the treatment of moderate to severe UC in the participating tertiary referral centres. Patients who showed primary non-response or secondary loss of response to the subcutaneously administered anti-TNF were scheduled to receive intravenously administered anti-TNF (infliximab). Primary non-response was defined as failure to achieve a clear improvement in symptoms and a drop in CRP, if elevated at baseline, at Week 6 through Week 14. Secondary loss of response was defined as reappearance of symptoms and re-elevation of CRP at any time period after the first 14 weeks of anti-TNF therapy. Clinical response to infliximab was subsequently assessed at Week

14 and was defined as a decrease in the total Mayo score of at least 3 points and at least 30% per cent from baseline. Finally, clinical remission, defined as Mayo score of ≤ 2 with no individual sub-score > 1, was assessed at Week 54.

Results: From September 2015 till September 2017, 58 anti-TNF naive ulcerative colitis patients (males=31, females = 27; E1=1, E2=32, E3=25, median age=40.6 years, median disease duration=38.6 months) were started on adalimumab (*n* = 38) or golimumab (*n* = 20) because of moderate–severe disease. From these patients, 21 (36.2%) were primary non responders (adalimumab = 13, golimumab = 8), while 8 more (13.7%) showed secondary loss of response (adalimumab = 7, golimumab =1). Therefore, 29 patients were started on infliximab, because of failure of subcutaneously administered anti-TNF. At Week 14, 18 patients showed clinical response (62.1%), while at Week 54, 14 patients were on clinical remission (48.3%).

Conclusions: UC patients with moderate to severe disease that are anti-TNF naive can be successfully treated with intravenously administered anti-TNF after failure of anti-TNF administered subcutaneously.

P508

Does corticosteroid therapy affect prognosis in inflammatory bowel disease patients hospitalised with *Clostridium difficile* infection?

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Background: *Clostridium difficile* infection (CDI) is a common infection among inflammatory bowel disease (IBD) patients admitted to the hospital and is associated with morbidity and mortality. While CDI therapy is mostly antimicrobial, acute IBD flares are often treated with corticosteroids (CS). Due to their immunosuppresive effect, CS therapy raises concern of worsening CDI outcomes. We aimed to assess the impact of CS therapy on outcomes of IBD patients hospitalised for flare-up and diagnosed with CDI.

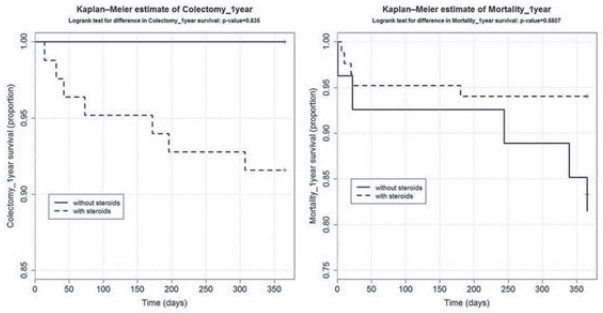
Methods: A retrospective single tertiary care centre cohort study of IBD patients admitted with first-time CDI between 2002 and 2018. Comparisons were made based on CS exposure during 48 h after admission. Patients with incomplete medical records on the index admission and non-definite diagnosis of IBD or CDI were excluded. The primary outcomes of the study were all-cause mortality or colectomy within 3 months. Other outcomes were diarrhoea improvement, length of stay, need for readmission, associated bacteraemia and 1 year colectomy and mortality rates. Cox proportional hazard model was used to assess the effects of CS use on survival by IBD subtype. Kaplan–Meier curves were used to estimate survival across time. Logistic regression was used to assess the effects of steroid use on the probability for adverse outcomes within 3 months. Univariate analysis with chi-square, Fisher or *t*-test and multi-variate analysis using different regression models were used to assess the effect of CS use on other variables.

Results: 111 patients (62 CD, 46 UC,3 IBDU) were included, 84 (75.6%)received CS. There were no significant differences in baseline IBD and CDI characteristics, demographics and medications use. At 3 months, 7 (3.6%) patients died. Four (5.4%) patients required colectomy (all exposed to CS), though CS association with colectomy was statistically insignificant (table). However, Bacteraemia and 1-year mortality rates were slightly but significantly reduced among CS exposed (figure and table). All other endpoints were not associated with CS exposure.

	CDI with in-hospital CS exposure	CDI treated without in-hospital CS exposure	P value
IBD Subtype distribution (CD/UC/IBDU) (%UC)	48/35/1 (41.7)	14/11/2 (40.7%)	NS
CD behaviour distribution (B1/B2/B3) (%B1)	22/14/10 (47.8%)	7/2/1 (70%)	NS
CD extent distribution (L1, L2,L3) (%L1)	16/16/14 (34.8%)	4/3/4 (36.4%)	NS
UC extent distribution (E1, E2, E3) (%E3)	3/9/18 (60%)	1/2/6 (66.7%)	NS
Gender (F/M) % males)	47/37 (44%)	14/13 (48.1%)	NS
Age on admission	Mean=0.107 (n=84)	Mean=0.185 (n=27)	NS
Non-CS immunosuppression (%)	37 (44%)	6 (22.2%)	0.07
Initial antibiotic Rx (none/PO metronidazole/PO vancomycin/IV metronidazole) (% oral metronidazole)	16/51/8/9 (60.7%)	1/18/2/6 (66.7%)	0.13
Mean IBD duration (years)	7.3	6.89	NS
Previous Surgery (CD only) (%)	9 (18.8%)	3 (21.4%)	NS
Mean Charlson comorbidity score	0.51	0.66	NS
Pulse over 100 bpm on admission	27 (52.1 %)	11 (40.7%)	NS
Fever >38.0 on admission	9 (10.7%)	3 (18.8%)	NS

	CDI with in-hospital CS exposure	CDI treated without in-hospital CS exposure	P value
Colectomy at 3 months (UC/CD) (%total)	4 (1/3) (4.8%)	0 (0%)	NS
Mortality at 3 months (UC/CD) (%total)	4 (2/2) (4.8%)	2(0:1) (7.4%)	NS
Readmission at 3 months UC/CD/IBDU) (%total)	13 (7/5/1) (15.4%)	6 (4/2/0) (22.2%)	NS
Bacteremia (UC/CD) (% total)	**1 (1/0) (1.1%)**	**3 (2/1) (11.1%)**	**0.01**
Mean length of stay (days)	6.56	5.6	NS
Colectomy at 1 year (UC/CD) (%total)	7 (2/5) (8.4%)	0 (0/0) (0%)	NS
Mortality at 1 year (UC/CD) (% total)	**5 (3/2) (6%)**	**5 (2/3) (18.5%)**	**0.053**
Change in diarrhea Day 2 (unchanged/improved/resolved)	28/27/5	9/12/1	NS
Change in diarrhea Day 7 (unchanged/improved/resolved)	7/49/22	3/11/11	NS

Table. Baseline characteristics and outcomes.



1-year colectomy and mortality-free survival.

Conclusions: CS exposure during the first 48 h after admission for flaring IBD patients with CDI was not associated with adverse outcomes. Albeit the largest cohort to published to date, the low rates of adverse outcomes observed still preclude deduction of definite conclusions. Larger studies are required.

P509

Long-term outcomes of adalimumab in patients with Crohn's disease: Can a doubled dose of adalimumab improve outcomes?

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Background: In anti-TNF agent therapy for inflammatory bowel disease, one agent should be thoroughly used because of immunogenicity issues. We examined the long-term outcomes of treatment with adalimumab (ADA) and effect of a doubled dose of ADA on treatment continuation.

Methods: We retrospectively studied 103 patients with Crohn's disease who received ADA from November 2010 through July 2018. The International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) assessment score (0 to 10) was used to evaluate disease activity. Remission was defined as a score of ≤1, and active phase was defined as a score of ≥2. The following variables were

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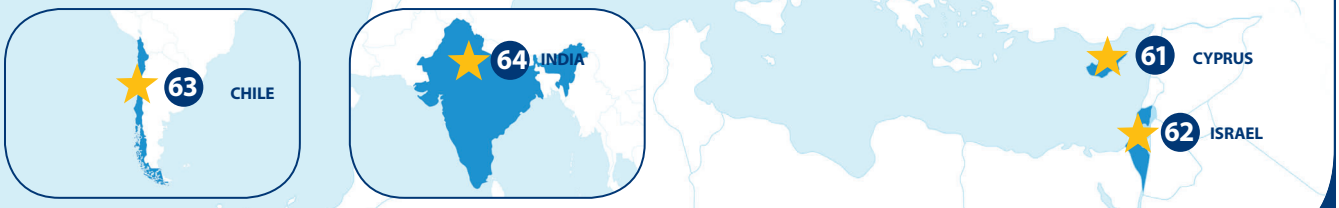

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studied: (1) the rate of continuing ADA, (2) the outcomes of patients in whom short-term ADA was discontinued, and (3) the proportion of patients in whom the dose of ADA was increased and the treatment response.
Results: (1) The rate of continuing ADA was 87% at 1 year, 73% at 2 years, and 50% at 4 years. The most common reason for discontinuing ADA was loss of response (LOR), occurring in 57% of the patients. The rate of continuing ADA was significantly higher in patients whose IOIBD score at the start of treatment was ≤1 than in patients whose IOIBD score was ≥2 (p <0.05). (2) ADA was discontinued within 1 year in 14 patients (14%). The rate of discontinuing ADA decreased from 64% to 36% after coverage of a by doubled dose by insurance. Decreased numbers of patients discontinued treatment because of primary failure, LOR or bowel complications. When demographic characteristics were compared between patients who received short-term treatment and those who received treatment for 4 years or longer (n = 25), we found that the disease duration before introducing ADA was significantly shorter in patients who received long-term treatment (p < 0.05). (3) The dose of ADA was increased in 34% of the patients. The reason for a double dose of ADA was worsening of symptoms in 52% and the presence of active residual lesions on imaging studies in 48%. At the time of dose increase, the rate of continuing treatment was 100% at 0.5 year and 73% at 1 year in patients whose IOIBD score was ≤1 as compared with 75.0% at 0.5 year and 62.5% at 1 year in patients whose IOIBD score was ≥2.
Conclusions: Low disease activity and shorter disease duration at the time of starting and increasing dose of ADA were associated with good rates of continuing treatment. Increasing the dose of ADA was associated with decreased numbers of patients who discontinued treatment because of LOR or bowel complications. Promptly increasing the dose of ADA on the detection of residual active lesions on imaging studies after the initiation of ADA can be expected to lead to the continuation of treatment and improve outcomes.

P510

Infliximab in the very young: it is all about the dosing – a multi-centre study

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Background: Infliximab (IFX) is administered intravenously using weight-based dose (5 mg/kg) in paediatric and adult inflammatory bowel disease (IBD) patients. However, previous IFX pharmacokinetic (PK) data suggest this results in lower mean serum IFX concentrations in paediatric compared with adult CD patients, especially in young patients. We hypothesise that young children need a more intensive treatment regimen than the current weight-based dose administration.
Aim: To assess IFX PK, based on existing therapeutic drug monitoring (TDM) data in a population of paediatric IBD patients below age of 10 and to compare these to paediatric IBD patients above age of 10.
Methods: TDM data were collected retrospectively in 15 European and Canadian centres. Children treated with IFX between 2004–2016 were included, if IFX was started as IBD treatment below 10 year and PK data were available. These data were compared with a control group of paediatric IBD patients above age of 10 with PK data of IFX treated paediatric IBD patients in the Erasmus MC-Sophia Children's Hospital.
Results: One-hundred and sixty paediatric IBD patients were eligible for the study (110 < 10 year; 50 >10 year). Median age IFX treatment was started was 8.3 years [IQR 6.9–8.9] in the young patients (YP), in the older patient (OP) group this was 14.3 [IQR 12.6–15.6]. In 49% of the YP trough levels were below therapeutic range (<3 μg/ml) at 14 weeks. The median interval between IFX infusions was significantly shorter (median interval days 49[39–56] vs. 56[55–56]; p < .001), while the dose (median dose 8 [5–10] mg/kg vs. 5 [5–8.5] mg/kg; p = 0.013) was significantly higher in the YP than OP at 1 year of scheduled IFX maintenance treatment. Moreover, significantly more YP developed antibodies to infliximab (ATI) during follow-up (44% in YP vs. 8.7 in OP, p = 0.004) compared with the OP group, while overall duration of response to IFX was not significantly different between both age groups (after 2 years 53%(n = 29) in YP vs. 63%(n = 26) in OP; p = 0.24).
Conclusions: To achieve therapeutic IFX trough levels in young paediatric IBD patients (<10 years) a more intensive treatment schedule is required. Sub therapeutic IFX levels may be the explanation for development of more ATI's in young patients compared with the older ones. Despite more ATI formation, duration of IFX therapy was comparable for both age groups. IFX dosing in YP is frequently suboptimal. We recommend to start with a higher dose IFX and an induction schedule with shorter intervals between infusions, beside use of early TDM to further personalise IFX treatment in young IBD patients.

P511

Radiological outcomes in perianal fistulising Crohn's disease

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Background: Perianal fistulas are a common and clinically challenging manifestation of Crohn's disease, affecting approximately a third

of Crohn's patients.[1] While the use of biologic therapy has led to improvements in patient outcomes, loss of response is common, with subsequent worsening of fistula tracts and new abscess formation.[2] Previous studies suggest that patients who achieve deeper healing, and eradication of the tract radiologically, have longer duration of response.[3] The aim of this study was to compare the clinical course of patients achieving MRI healing with those achieving clinical remission, with the hypothesis that radiological healing will lead to a longer duration of response.

Methods: A retrospective analysis of perianal fistulising Crohn's patients treated at St Vincent's Hospital, Melbourne was performed. Records were reviewed for patient demographics, disease history, clinical assessments (including PDAI scores), investigation results (including MRI pelvises), and disease flares. Clinical remission was defined as closure of all baseline fistula openings, on examination. Radiological healing was defined as the absence of any T2-hyperintense sinuses, tracts or collections. Primary endpoint was flare-free time, defined as time between achieving healing (clinical or radiological) and a patient's first signs or symptoms requiring escalation in medical and/or surgical therapy. Statistical analysis consisted of Mann–Whitney U tests, Wilcoxon Signed Rank, and Log-rank tests. Significant parameters were entered into a multi-variate Cox regression model.

Results: 93 patients were included, with a median follow-up of 4.75 years (IQR, 2.4–6 years). 85/93 (91%) received treatment with a biologic agent. PDAI and van Assche scores were significantly lower following biologic treatment. Twenty-two/44 (50)% of patients achieved clinical remission, while 15/93 (16%) achieved radiological healing. Ten/22 (45%) of patients with clinical remission had a subsequent disease flare, at a median of 7 months, compared with the 3/15 (20%) patients with MRI healing, who flared at a median of 3.6 years. Radiological healing was associated with a significantly longer flare-free period ($p = 0.01$).

Conclusions: Radiological healing is a less common, but deeper form of healing, associated with improved clinical outcomes. Further prospective trials are required to assess the benefit of earlier, and more regular imaging, with escalation of therapy based on radiological findings.

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P512

Results of interim analysis of a retrospective IGIBD study on adalimumab use in real practice in Italy: the REAL-life clinical effectiveness of ADAlimumab in ulcerative colitis

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Background: Adalimumab (ADA) is commonly use in Crohn's disease, clinical experience in ulcerative colitis (UC) is still partly limited due to later registration. Aim of this retrospective IGIBD study was to explore clinical effectiveness, safety and treatment persistence in real-world Italian patients

Methods: We report here interim analyses of 218 UC patients reported by 12 Italian IBD centres, data analysis, for sake of data completeness with at least 8 weeks of follow-up after adalimumab start were carried out on 202 cases. All basal clinical characteristics were compared with the outcomes (persistency/discontinuation and safety). Univariate and multi-variate analyses were carried out

Results: Median follow-up after adalimumab start was 11 months (±13), with a total of >2900 patients-months of observation. Fifty-two per cent of patients received ADA as first anti-TNF agent, full Mayo score (FMS) was moderate-to-severe (>6) in 83% cases, and co-treatment with steroids (32%) or azathioprine (17%) were present at start. Clinical effectiveness at Week 8 (at induction) was present in 170/202 (84%) cases, with median CRP drop among patients with basal CRP values >5 mg/l of 4.7 mg/l (95% CI 3–7) and median partial Mayo score (PMS) drop was 3 points. ADA was stopped in 107/202 (53%) cases before the end of the follow-up, in in 20/107 (19%) due to reasons other than clinical inadequacy (pregnancy, remission, patient choice). Within the end of the follow-up colectomy was carried out in 22 (11%) cases. Covariates associated to the risk of colectomy and of stopping ADA were basal FMS, basal active steroid treatment and week 8 PMS drop. Adverse events occurred in 24 (12%) cases, none being lethal, leading to stopping the treatment in 83% cases.

Conclusions: This interim analysis support the safety and effectiveness of adalimumab in UC also in Italian real-life setting. Deeper insight will be possible with the full cohort of the study fully available.

P513

Performance of a rapid test for adalimumab monitoring vs. conventional ELISA in a routine laboratory setting

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Background: Therapeutic drug monitoring of adalimumab is useful to optimise the treatment of patients with inflammatory diseases, such as inflammatory bowel disease. A recent study reported the potential benefit of rapid testing for adalimumab concentrations as early as Week 4, using the RIDA®QUICK ADM Monitoring, to help predict later anti-drug antibody development and the need for dose intensification.[1] Nevertheless, data regarding the performance of a rapid test in a routine clinical laboratory are scarce. In this study, we therefore aimed to evaluate and confirm the performance of the

RIDA®QUICK ADM Monitoring in an routine diagnostics laboratory, the Gastroenterology and Hepatology Diagnostic Laboratory (Erasmus MC, Rotterdam, the Netherlands).

Methods: A total of 56 anonymized patient samples were analysed using the RIDA®QUICK ADM Monitoring (R-Biopharm AG, Darmstadt, Germany) and results compared with a conventional ELISA, the apDia Adalimumab ELISA (apDia, Turnhout), also distributed by R-Biopharm as RIDASCREEN® ADM Monitoring. Six quality control samples, with a concentration within the assay analytical range, were used to verify the assay performance.

Results: The RIDA®QUICK ADM Monitoring was shown to correlate very well with the apDia Adalimumab ELISA (Pearson r coefficient of 0.91). The absolute bias between the two methods was 1.6 ± 2.2 µg/ml (Figure 1).

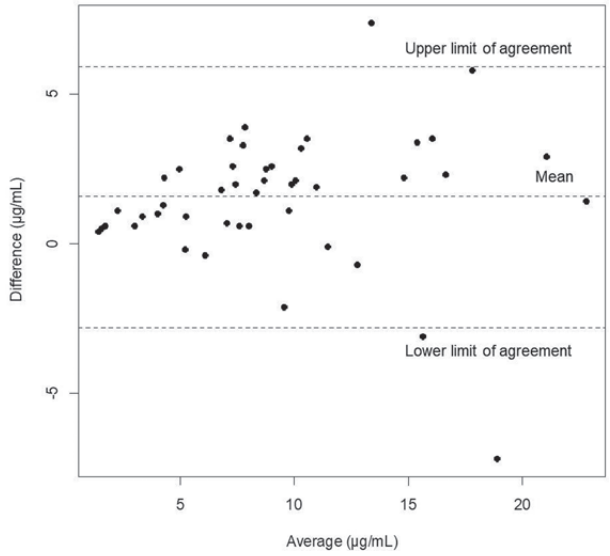

Figure 1. Bland-Altman plot showing the absolute difference between the apDia Adalimumab ELISA and the RIDA®QUICK ADM Monitoring vs. the average of the two methods. The average bias was 1.6 ± 2.2 µg/ml ($n = 56$).

Linear regression analysis showed no systemic or proportional bias between the RIDA®QUICK ADM Monitoring and apDia Adalimumab ELISA (y = 0.89 (±0.06)x – 0.48 (±0.69); y = RIDA®QUICK ADM Monitoring; x = apDia Adalimumab ELISA).

Conclusions: In this study, we confirmed the performance of the RIDA®QUICK ADM Monitoring in a routine diagnostics laboratory, revealing a very good agreement with a conventional ELISA technique. The RIDA®QUICK ADM Monitoring allows to measure one sample at a time and has a turn-around time of only 20 min.

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P514

Health Care Transition outcomes in inflammatory bowel disease: an international Delphi study

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Background: Transition programs are designed to prepare adolescent inflammatory bowel disease (IBD) patients for transfer to adult care. It is still unclear which outcome parameters define 'successful transition'. Therefore, this study aimed to identify outcomes important for success of transition in IBD.

Methods: A Delphi study in (paediatric) gastroenterologists and IBD-nurses was conducted. In Stage 1, panellists commented on an outcome list. In Stage 2, the refined list was rated from 1–9 (least-very important). In Stage 3, important outcomes (mean score 7–9 without disagreement), were ranked from 1 to 10 (least to most important). Descriptive statistics and Mann–Whitney *U* tests were used to describe the data.

Results: A total of 74 international participants participated (52.7% paediatrics). The final item list developed in Stage 1, was tested in Stage 2 where 10 items were found to be important. In Stage 3, a top-10 list was formed. The five most important items were: ability to make decisions regarding IBD (mean score 6.7), independent communication (mean score 6.3), patient satisfied transition process (mean score 5.8) medication adherence (mean score 5.6), medication knowledge (mean score 5.5). Only 'medication adherence' was given a higher mean rank by paediatric (6.28) compared with adult (4.38) providers (p = 0.033).

Conclusions: This is the first study identifying outcomes that IBD-healthcare providers deem important factors for successful transition. Self-management skills were considered more important than IBD-specific items. This is a first step to further define success of transition in IBD and subsequently evaluate the efficacy of different transition models.

P515

Costs associated with the management of refractory complex perianal fistulas in patients with Crohn's disease

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Background: Management of complex perianal fistulas (CPFs) in Crohn's Disease (CD) continues to be a controversial issue nowadays. Due to the complexity of this complication, the multiple recurrences and the absence of high-quality evidence and the limited efficacy of the available treatments there many unsolved questions and the treatment involves both medical and surgical approaches. This study aims to quantify the economic impact associated with current treatment alternatives for CPFs in CD.

Methods: An exhaustive literature review has been performed together with the analysis of the real-world clinical practice in University Hospital La Paz, Madrid, Spain. After analysing the healthcare process, an economic model has been elaborated to estimate the costs associated to the current approach of CPFs in CD. The model only contemplates a maximum of one intervention (medical or surgical) per year. The costs of recurrences, the main side effects and work productivity impact of the different therapeutic alternatives have also been calculated.

Results: The estimated direct annual cost of CPF treatment in CD in Spain, extrapolated from data from one university hospital is at least €21 253 374 (€15 241/patient) for an estimated population of 1394 patients. The estimated cost corresponding to anti-TNF drugs represents 79.80% (€16 961 154, €12 163/patient), to surgeries 6.37% (€1 354 551, €971/patient), to recurrences 8.37% (€1 779 658, €830/patient) and to secondary effects 5.45% (€1 158 011, €830/patient). The average cost of surgeries in patients who are treated surgically (40% of the total) is estimated at €2427.51/patient. With regard to indirect costs, the impact on work productivity due to absences and sick leave is at least €182 011 per year. Work absences are estimated to range between 10 and 30 days in almost 70% of patients, at an annual cost of €786 217.

Conclusions: The present study indicates that almost 80% of the total annual direct costs of the current treatment of CPFs in CD are due to anti-TNF drugs. This estimated annual cost, being a chronic

complication, would often spread over several years, so that total costs associated with the definitive remission of CPFs would be significantly higher than the one estimated here. It would be desirable to count with new treatments for the management of these patients that could contribute to decrease the need for both surgery and use of anti-TNFs, reducing the costs associated with the treatment of this type of patients.

P516

The use of first-line biologics in patients with ulcerative colitis in Norway from 2011 to 2016

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Background: Treatment of ulcerative colitis (UC) is preference based and might also be affected by drug costs. In Norway, biosimilar infliximab entered the market in 2014 at a reduced cost of 40% compared with the original product. We have previously shown an increase in the use of biologics for inflammatory bowel disease (IBD) between 2011 and 2014. In the present study, we aimed to assess whether there was a change in the proportion of patients receiving biologics between 2011 and 2016 and if the preferred first-line biologic changed after the introduction of biosimilar infliximab.

Methods: Data were collected from the Norwegian Patient Registry (NPR) and the Norwegian Prescription Database (NorPD). The study cohort was defined as all patients with at least two registered K51 (UC) within 1 year between 2011 and 2016. Patients were followed for 1 year after identification of first diagnosis code. The use of biologics is recorded with ATC codes for each patient in NPR and NorPD. The ATC codes do not distinguish between biosimilars and originators. Patients were stratified by the year of first diagnosis to examine change over time.

Results: A total of 8264 patients were included in the study. The total use of biologics stratified by year is shown in Figure 1. The proportion of patients receiving biologics within 1 year of diagnosis increased significantly from 8.2% in 2011 to 15.1% in 2016 ($p < 0.0001$). The proportion of patients receiving adalimumab as their first biologic after 1 year of diagnosis was 1.7% in 2011 compared with 0.4% in 2016. Opposed to this, the use of infliximab increased from 6.6% in 2011 to 13.6% in 2016.

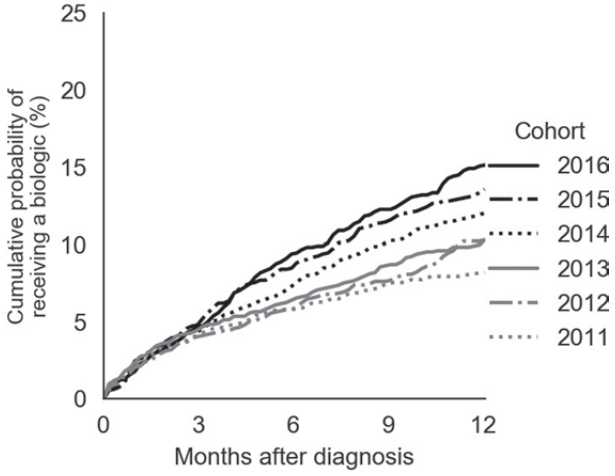

Figure 1. Cumulative probability of receiving a biologic within 1 year of diagnosis.

Conclusions: There was a significant increase in the proportion of patients who received biologics within the first year of diagnosis between 2011 and 2016. Infliximab was the preferred first-line biologic for UC both before and after 2014.

P517

Activity assessment in ulcerative colitis: correlation analysis of endoscopic and histological scores

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Background: The assessment of endoscopic and histological activity in patients with ulcerative colitis (UC) is essential in daily clinical practice, especially for therapy management. Numerous studies have correlated endoscopy and histology using different unvalidated or partially validated scores with controversial results. Recently new validated scores, as the ulcerative colitis index of severity (UCEIS) and the Nancy histological index (NHI), have been developed but their use in clinical practice is still limited. Furthermore, there is a lack of evidence about the correlation between validated endoscopic and histological indices. Aim of the study was to conduct a correlation analysis between endoscopic and histological activity using the UCEIS and NHI in a cohort of UC patients undergoing a biological treatment.

Methods: A single-centre retrospective analysis was conducted. We enrolled adults patients with moderate-to-severe UC who underwent a colonoscopy with biopsies at baseline before starting a biological treatment, and after a median of 48 weeks of treatment (control time). The assessment of disease activity was evaluated for the worst affected colonic segment, by using both the Mayo endoscopic subscore (MES) and the UCEIS for endoscopy and NHI for histology. Remission was defined as MES <2, UCEIS <2 and NHI <2. Spearman correlation analysis between the indices was performed. A p-value of less than 0.001 was considered statistically significant.

Results: Sixty-one patients were included. Twenty-eight patients were treated with Infliximab (IFX), 10 with Adalimumab (ADA), 20 with Golimumab (GOL), 3 with Vedolizumab (VDZ). At control time 42.6% (26/61), 29.5% (18/61) and 26.2% (16/61) achieved endoscopic and histological remission according to the MES, UCEIS and NHI, respectively. The analysis showed a statistically significant correlation between MES and NHI ($r = 0.70$; $p < 0.001$), higher between UCEIS and NHI ($r = 0.81$; $p < 0.001$). The correlation was high both for active and inactive disease.

Conclusions: The UCEIS correlates with NHI strongly and better than MES.

P518

Cardiovascular Risk Factors in Adolescents with inflammatory bowel disease: A Cross-sectional Population-Based Study

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Background: There is conflicting evidence regarding the association of inflammatory bowel disease (IBD) with increased risk for cardiovascular diseases (CVD). We aimed to investigate the association of IBD with cardiovascular risk factors including obesity, blood pressure (BP) and resting heart rate (RHR) at late adolescence in a large cross-sectional population-based study.
Methods: A total of 1 144 213 Jewish Israeli adolescents who underwent a general health examination from 2002 to 2016 were included. A definite diagnosis of IBD was based on accepted criteria. Covariate data included demographic measures, height, weight, BMI, blood pressure, resting heart rate, and risk factors associated with CVD.
Results: Overall, 2372 cases of IBD were identified out of 1 144 213 persons examined (0.2%). Crohn's disease (CD) accounted for 68% of IBD cases. Systolic hypertension was significantly less common among CD subjects (OR, 0.67; 95% CI 0.56–0.81, $p < 0.0001$), while no significant differences were observed for diastolic hypertension. The rates of hypertension among ulcerative colitis (UC) patients were similar to those of the control group. The proportions of overweight and obese subjects were significantly lower among CD patients, while no significant differences were observed between UC patients and the control group. Congenital hypercoagulable state (OR, 16.9; 95% CI 8–35.7, $p < 0.0001$) was significantly more common in subjects with CD, but not among subjects with UC. On the other hand, we did not detect significant differences in the risk for non-congenital venous thromboembolism. Insulin-dependent diabetes mellitus, noninsulin-dependent diabetes mellitus and hyperlipidaemia were not more common among IBD patients.
Conclusions: There appears to be an association between CD and congenital hypercoagulable state. The prevalence of traditional cardiovascular risk factors, however, including diabetes mellitus, hyperlipidaemia and hypertension, was not increased among subjects with IBD.

P519

Post-surgical recurrence predictors in the years 2000. Results of a retrospective single-centre long-term follow-up series and impact of imaging findings on outcomes

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Background: Post-operative recurrence of Crohn's disease (CD) after so-called curative ileocolonic resection is common. Early identification of features associated with recurrence and risk stratification could be essential for the postoperative management of these patients. The aim of the current study was to evaluate the impact of clinical variables and instrumental recurrence on long-term clinical and surgical recurrence.
Methods: We report data of 125 consecutive patients with CD, undergone ileocolonic resection between July 2000 and January 2010 (median follow-up after surgery 9.4 ± 4.4 years) Clinical-demographic characteristics, post-surgical therapy, endoscopy recurrence (Rutgeerts' Score ≥ 2) and ultrasound features (bowel wall thickness ≥ 4 mm, loss of wall stratification, mesenteric hypertrophy) were recorded. Kaplan–Meier survival analysis was conducted to identify variables associated with recurrence-free survival (clinical and surgical), both in all patients and in those who performed endoscopy or ultrasound within 18 months after surgery. Time-dependent Cox regression analysis was carried out for multi-variate analysis.
Results: Clinical recurrence occurred in 99 patients (80%); in 34/41 patients (83%) within 12 months and in 52/63 (83%) within 18 months. In 25 patients (31%) surgical recurrence was observed, in 3 (4%) cases within 12 months and 4 (5%) within 18 months. The only clinical variables significantly associated with outcomes were stricturing pattern for clinical recurrence and surgical indication for refractory disease for surgical recurrence. Endoscopic recurrence and selected US features were associated to clinical recurrence only. No clinical or imaging predictors were associated to clinical or surgical recurrence in multi-variate analysis.

Table 1. univariate analysis results with HR and 95% CI, multivariate analysis was non-significant for all variables

	Clinical recurrence	Clinical recurrence	Surgical recurrence	Surgical recurrence
	HR (95% CI)	*p*	HR (95% CI)	*p*
Smoking	0.85 (0.57–1.28)	0.43	1.29 (0.58–2.83)	0.52
Montreal Behaviour (B2 vs. B1/B3)	1.53 (1.01–2–31)	**0.02**	0.82 (0.37–1.82)	0.64
Surgical Indication (refractory vs. complications)	1.03 (0.64–1.65)	0.89	2.35 (0.95–5.82)	**0.02**
Post-surgical Therapy (5-ASA vs. thiop/anti-TNF)	1.43 (0.87–2.33	0.11	1.09 (0.43–2.80)	0.85
Rurtgeets ≥ i2	2.29 (1.61–5.25)	**<0.01**	3.40 (0.88–12.90)	0.21
BWT ≥ 4 mm	5.58 (2.22–13.98)	**<0.01**	1.14 (0.39–3.33)	0.82
Wall stratification loss	0.95 (0.61–1.46)	0.80	2.10 (0.83–5.32)	0.15
Mesenteric hypertrophy	1.61 (1.04–2.48)	**0.04**	0.80 (0.30–2.14)	0.65

Conclusions: Early evaluation of US and endoscopic features predicts clinical outcomes, apparently not long-term surgical outcomes, in these retrospective series. Prospective long-term follow-up studies with uniform short-term evaluation and therapeutic management are advisable to explore the yields of prognostic prediction through endoscopy or ultrasound, especially in the biologic treatments era.

P520

Endoscopic evaluation and factors affecting the endoscopic efficacy during granulomonocytapheresis in moderately-to-severely active ulcerative colitis: a multi-centre retrospective study

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Background: Adsorptive granulomonocytapheresis (GMA) with the Adacolumn is a novel non-pharmacologic strategy for treating patients with ulcerative colitis (UC). Multiple studies in Japan and Europe found that GMA was safe and therapeutically effective in patients with active UC. However, endoscopic efficacy and factors affecting the endoscopic efficacy during GMA have not been fully evaluated. This study was conducted at three IBD centres with the aim of assessing endoscopic efficacy of GMA and determining factors affecting the endoscopic efficacy during GMA.
Methods: From January 2008 to December 2017, a total of 894 active episodes (first attack or relapse) in 593 patients were treated with GMA (frequency: 1 to 5/week, session time: 60 to 120 min, the maximum number of GMA: 11). At entry, endoscopic evaluation was made in all patients. After treatment, mainly, the most affected segment at entry was observed. Endoscopic remission (= mucosal healing: MH) was defined as a Mayo endoscopic subscore of 0 or 1 after treatment.
Results: After treatment, 28 patients could not have endoscopy because 24 required emergency colectomy during GMA therapy and 4 had serious deterioration of UC at the end of the GMA therapy. These 28 patients were analysed as non-responders in the endoscopic assessment. Overall, MH was observed in 351 of the 894 treatment cases (39%). When sub-grouped, MH was achieved in 378 of 678 treatment cases (47%) with Mayo endoscopic subscore 2 at entry, which was significantly higher than 32 of 216 (15%) with Mayo endoscopic subscore 3 ($p < 0.0001$). In univariate analysis, 6 demographic variables at entry were significantly associated with the likelihood of endoscopic remission (MH). Patients with a short duration of UC (<1 year), first UC episode and proctosigmoiditis, and steroid naïve patients responded well to GMA endoscopically. In contrast, patients with severe clinical activity (Mayo score 10–12 vs. 6–9) and those with severe endoscopic activity (Mayo endoscopic subscore 3 vs. 2) did not respond well to GMA endoscopically. The following factors did not affect the likelihood of endoscopic remission (MH): Age, gender, duration of the current exacerbation before GMA, extra-intestinal manifestations, exposure to 5-ASA preparations, immunosuppressant and biologic agents, and adverse events. In multi-variate analysis, clinical severity, endoscopic severity, extent of UC, exposure to steroids and exposure to biologics were independent significant factors.
Conclusions: Approximately 40% of patients with moderately-to-severely active UC achieved MH during GMA. Clinical severity, endoscopic severity, extent of UC, exposure to steroids and exposure to biologics are independent significant factors for the endoscopic efficacy of GMA.

P521

Pre-operative enteral nutrition in adults with Crohn's disease: effect on gut microbiota and disease outcomes

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Background: Exclusive enteral nutrition (EEN) in Crohn's disease (CD) can reduce disease activity and improve nutritional status before surgical resection. The mechanism of EEN action is unclear, but is proposed to involve profound modulation of the intestinal microbiota. The aim of this study was to evaluate the effect of pre-operative EEN in adults with complicated CD and surgical indication, namely changes in gut microbiota induced by EEN.
Methods: Prospective, non-randomised study including adults CD patients with surgical indication. Patients with body mass index < 18.5 kg/m2, weight loss > 10% and/or serum albumin < 3 g/dl received EEN for at least 2 weeks. The remaining went straight to surgery. The impact of EEN on Harvey–Bradshaw Index (HBI), C-reactive protein (CRP), serum albumin, faecal calprotectin, and faecal microbiota was analysed on admission, after EEN but before surgery, and 6 months later. We used 16S rRNA gene sequencing to determine changes in the faecal microbiota. Immediate postoperative outcomes, clinical and endoscopic recurrence 6 months after surgery were compared between the two groups (pre-operative EEN vs. direct surgery).
Results: Fifteen patients were included, 9 male, with a mean age of 45.4 ± 19.1 years. Of these, 10 received EEN and 5 underwent direct surgery. The mean duration of pre-operative EEN was 46 ± 24.5 days. During EEN there was a significant reduction in mean HBI (8.7 ± 1.9 vs. 4.1 ± 2.4, $p = 0.001$) and CRP (11.7 ± 10.3 vs. 0.8 ± 0.8 mg/dl, $p = 0.008$) and increase in albumin (3.1 ± 0.6 vs. 4.0 ± 0.6 g/dl $p = 0.022$). Immediately after EEN the overall microbial composition changed (PERMANOVA, 999 permutations, $p = 0.046$) and there were a significant reduction in α-diversity (8.04 ± 2.32 vs. 5.21 ± 1.54, $p = 0.023$). EEN significantly decreased the relative abundance of 21 OTUs. At the family level, we found this was mainly due to the decrease of Enterobacteriaceae (6 OTUs). Six months after surgery α-diversity increased, albeit not statistical significant; 9 OTUs increased: 4 OTUs belonged to Lachnospiraceae family and 3 to Enterobacteriaceae family. The incidence of post-operative complications and length of hospital stay were similar in both groups, as well as clinical and endoscopic recurrence rates 6 months after surgery.
Conclusions: Pre-operative EEN improved disease activity and nutritional status in patients with CD before surgery. During EEN overall microbial composition changed and α-diversity decreased. Despite being malnourished, patients submitted to EEN did not have increased postoperative morbidity when compared with well-nourished ones. In this study, EEN did not influence postoperative clinical and endoscopic recurrence.

P522

Expression of markers of early atherosclerosis in inflammatory bowel disease: a prospective cohort of a single referral centre

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Background: Recent epidemiological studies report an association between ischaemic vascular disorders and inflammatory bowel dis-

ease (IBD). In a previous study we have shown increased expression of surrogate markers of early atherosclerosis (ATS), such as aortic stiffness and intima media thickness (IMT) in a homogeneous cohort of IBD patients, in spite of absence of traditional risk factors for ATS, suggesting a role for chronic inflammation. The aim of this study was to assess prospectively modifications of IMT and arterial stiffness in a longitudinal study on the same cohort, in relation to therapy and disease characteristics.

Methods: 39 patients with IBD (14 ulcerative colitis and 25 Crohn's disease) underwent a second clinical, bio-humoral and instrumental assessment after a mean period of 4.8 ± 0.3 years. Carotid IMT was evaluated by using high-resolution B-mode ultrasonography. Arterial stiffness was assessed by measurement of carotid-femoral Pulse Wave Velocity (cf-PWV) and Augmentation Index (AIx).

Results: We found a statistically significant increase in body mass index (22.44 kg/ m2 at baseline vs. 23.39 kg/ m2 at last follow-up visit, $p = 0.043$), white blood cell count (7339.05/mmc vs. 8291.28 mmc, $p = 0.015$) and total cholesterol (160.79 mg/dl vs. 172.08 mg/dl, $p = 0.028$); while a statistically significant reduction in glycaemia (88.69 mg/dl vs. 83.90 mg/dl, $p = 0.019$ was observed. No statistically significant variation was observed respect the AIx and carotid IMT; while an average increase in cf-PWV values was observed (8.67 m/s vs. 9.19 m/s, $p = 0.129$), but without reaching statistical significance. As far as concerns the other hemodynamic parameters, we found a trend in improvement of PAD (diastolic arterial pressure) and PAM (mean arterial pressure): respectively 75.31 mmHg vs. 71.15 mmHg, $p = 0.064$; 89.51 mmHg vs. 85.13, p = 0.062). No statistically significant difference was found for PAS (systolic blood pressure). On logistic regression analysis, the only variable that was able to influence the worsening of cf-PWV is the duration disease ($p = 0.048$).

Conclusions: in our prospective cohort of IBD patients there was no significant increase in the expression of surrogate markers of ATS, except cf-PWV which did increase over time . Disease duration was the only variable, among those evaluated, able to predict the worsening of cf-PWV. ATS in IBD is a progressive complication, however progression is slow and the timing of surveillance measures is yet to be established.

P523

Endoscopic balloon dilatation is safe and has a high success rate in patients with stricturing Crohn's disease

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Background: Stricturing Crohn's disease (CD) is associated with significant morbidity and high rates of surgery with anastomotic strictures commonly occurring after surgery. Endoscopic balloon dilatation (EBD) may avoid or delay operative management of strictures.

Methods: A retrospective audit of CD patients undergoing EBD was conducted at 11 hospitals across Australia and New Zealand. Local, prospectively maintained patient databases and procedure records were used to identify cases from June 1999 to October 2018. A stricture was defined as a narrow segment of intestine unable to be traversed with a colonoscope. Stricture length (long ≥4 cm, short <4 cm), location (ileal, ileocolonic, colonic, anorectal) and type (anastomotic vs. de novo) were collected from endoscopy reports. Dates of surgeries and follow-up were obtained from medical records. Technical success was defined as the ability to traverse the stricture following dilatation. Baseline smoking status, Montreal phenotype and medications for CD were also documented.

Results: A total of 236 patients with stricturing CD were identified (120 male, median age 48 [IQR: 10], 29% ileal, 12% colonic, 59% ileocolonic). A total of 620 dilatation procedures (303 for anastomotic strictures, 312 for de novo strictures, 5 unknown) were performed (median 2 per patient) with 428 (69%) on short strictures, 109 (18%) on long strictures, and 83 (13%) of unknown length. Balloon dilation diameter was 8 mm–20 mm (median 15 mm). Technical success was achieved in 433 (84%) of dilatations, and was significantly higher for short vs. long strictures (93% vs. 66%, $p < 0.001$). Technical success was lower in ileal strictures (72%) than colonic or ileocolonic strictures (89% and 85%, respectively, $p = 0.002$). End-to-end anastomosis had a numerically higher success rate (85% vs. 75%, $p = 0.19$). During the median follow-up time from first EBD to last review or surgery (50 months, [IQR: 30]), 55 patients (23%) required surgery for stricturing CD post-dilatation. The median time to surgery following the last dilatation was 8 months (range 0–90 months). Complications of EBD included 3 cases of perforation and two cases of aspiration. There was no major bleeding or procedure-related mortality identified.

Conclusions: In one of the largest analyses of EBD for CD strictures, EBD is found to be a safe procedure with a high technical success rate overall. The highest success was observed in strictures less than 4 cm in length and non-ileal in location. EBD may be an effective strategy for avoiding surgery in stricturing Crohn's disease and post-operative anastomotic strictures.

P524

Systematic review of calcineurin inhibitors (CNI) and vedolizumab (VDZ) combination therapy in acute severe ulcerative colitis (ASUC)

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Background: Patients with acute severe ulcerative colitis (ASUC) may be refractory to treatment with steroids and anti-tumour necrosis factor agents (anti-TNF). cyclosporine inhibitors (CNI) have been used effectively as a fast-acting bridge to slower-onset immunomodulators in thiopurine-naïve patients; concerns over toxicity limit prolonged use as maintenance. Patients who are azathioprine-exposed or anti-TNF-refractory have limited medical treatment options, often resulting in colectomy. Combination of CNI as induction and slower-acting but potentially safer vedolizumab (VDZ) has recently been used in patients with severe inflammatory bowel disease (IBD). We aim to review the utility in ASUC.

Methods: A systematic bibliographic review was conducted on PubMed using the keywords 'vedolizumab', 'calcineurin inhibitors', 'inflammatory bowel disease', 'severe ulcerative colitis'. Additional studies were identified by manual search of reference lists. 6 articles were identified within the period 2013 to October 2018. Only English language publications and abstracts on use of combination CNI+VDZ in adult ASUC patients were included. One paediatric study[1], one case report,[2] and one abstract[3] (ASUC data not reported) were excluded.

Results: There were 2 prospective observational studies[2,4] [*n* = 30] and 1 retrospective study[5] [*n* = 39]. Patients were refractory to conventional treatment with steroids [1 study, *n* = 17] and/or anti-TNF therapy [*n* = 48]. CNI (cyclosporine or tacrolimus) was used for induction of remission in majority of cases, or as rescue agent in those failing induction with vedolizumab [subgroup of 1 study, *n* = 7]. In 2 studies, IV cyclosporine 2 mg/kg titrated to goal trough level 300–400 or Tacrolimus 0.05 mg–0.1 mg/kg/day with target levels 10–14 ng/ml was started; a week later, CNI-responsive patients were given vedolizumab (IV 300 mg at week 0, 2, 6 then maintenance 8 weekly) and CNIs were stopped after 8–12 weeks per protocol. In another study, VDZ was initiated on average 30 days after CNI, with average combination CNI+VDZ of 64 days. Combination CNI+VDZ showed good short-term efficacy (1 study: 14/15 in remission). At 1 year, there was a respectable colectomy-free rate of 75% (2 studies, *n* = 39/52), comparable to other studies with infliximab/Cyclosporine combined with azathioprine.[7] In those receiving steroids at baseline, Steroid-free remission was achieved in 18/36 = 50% at Week 14. Serious adverse events (*n* = 7) were attributed to CNIs; there were no deaths.

Conclusions: Preliminary studies of combination CNI and VDZ in patients with ASUC appears promising. However, the methodology in these limited studies was heterogenous. Further prospective trials are needed for the confirmation of the utility and efficacy of this treatment strategy in the management of ASUC.

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P525

The benefits of anti-TNF drug and antidrug antibody (ADAb) level monitoring in a DGH

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Background: There are a number of time points highlighted at which to perform anti-TNF drug and ADAb levels in IBD patients on anti-TNF drugs. These include: at the time of loss of response; after induction; and yearly. Effective therapy is associated with improved quality of life, fewer symptoms and disease and surgery-free survival. Drug level and antidrug antibody (ADAb)-level testing allows a more personalised management, improves patient outcomes and can be associated with significant cost savings.[1] We retrospectively evaluated our increasing use of drug and antidrug antibody levels and reviewed how this has reflected a change in our clinical practice.

Methods: Permission to perform a retrospective audit was obtained from our trust. The IBD database was interrogated and all patients on infliximab were included. All patients had been converted to the biosimilar Remsima. Use of anti-TNF drug and ADAb levels in 2016 when compared with 2017 in the same cohort of patients. Our trust uses the ELISA assay like most areas of the UK.

Results: 74 patients received infliximab in 2016, 8 patients stopped/switched leaving 66 patients still on infliximab in 2017. 66% of the cohort had Crohn's disease in each year. 70% of patients had been on Infliximab for over 12 months in 2016 compared with 80% of patients in 2017. Levels were checked in 14% (9) of patients in 2016 and 91% (60) of patients in 2017 (see Table 1).

Drug levels	Available 2016	Unavailable 2016	Available 2017	Unavailable 2017
Number of patients	9	65	60	6
Anti-TNF stopped	1	2	15	2
Anti-TNF switched	4	1	15	
Treatment escalated		4	2	
Treatment de-escalated		1	9	
Continued	4	62	12	3
Pending decision			7	
Relocated				1

Comparison of the same group of patients treated with infliximab in 2016 and 2017.

Based on levels in 2016, 5 patients had their anti-TNF stopped (1) or switched (4). Based on levels in 2017, 41 patients had their treatment regimen changed – stopped (15), switched (15), de-escalated (9) and escalated

(2). In 2016, the majority of patients (89%) continued their anti-TNF regimen unchanged. In 2017, 15 (23%) patients have continued their treatment unchanged so far.
Conclusions: The use of anti-TNF drug and ADAb levels increased dramatically from 2016 to 2017. Profound benefits have been demonstrated with this change. There was improved decision making with the use of anti-TNF drug and ADAb levels in 2017. Treatment was de-escalated or stopped in 40% of patients in whom anti-TNF drug and ADAb levels were checked, reducing the risk of side effects and with a cost saving of £147 300 a year in total from those patients stopping Infliximab. Drug level testing in 2017 would have cost approximately £5400.

P526

Survey of adherence to treatment in inflammatory bowel disease: ENADEII STUDY

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Background: INTRODUCTION: The rate of non-adherence to medical treatment in inflammatory bowel disease (IBD) stands at around 50%, which worsens the treatment outcomes and increases morbidity and costs. Any action that increases adherence would enhance the quality of healthcare provided. The various strategies that have been tested out have been primarily targeted to patient; however, only one previous study is partially addressed to know what is being done by the doctor to improve patients' adherence.
OBJECTIVES: To determine through an on-line survey among Spanish gastroenterologists: (1) The knowledge about treatment adherence of patients with IBD. (2) The methods in routine clinical practice to improve treatment adherence.
Methods: METHODS: The Technical Secretariat of GETECCU sent an invitation e-mail to partners with a link to the survey (via the online system Survey Monkey). An anonymous questionnaire made up of 2 types of items was used to gather data: demographic ones and those specifically targeted to determine the attitude on adherence. The time for response was extended up to 2 months, and during this time interval a second and a third survey were sent.
Results: RESULTS: 760 partners were invited to participate, with an estimated participation of 646. The data were derived from 184 surveys (28.5%), women (63.2%) and 81% belonging to a university hospital. 68% of respondents had publications about IBD indexed on Medline, but only 13% dealt with adherence. Despite the fact that nearly 99% regarded treatment adherence as very important or important, 25% of doctors did not measure it during their practice; out of 77% of the doctors that did analysed treatment adherence, three-quarters did in all patients (regardless of severity). This measurement, however, was more likely among patients taking thiopurines or under treatment based on biological agents. Even though 100% of the doctors believed that improving adherence confers the best prognosis, 47% did not do a great deal to enhance it. The most widely used method for assessing and improving adherence was the yes/no question and the personal interview, used by 75% of doctors. Factors associated with measurement and treatment adherence improvement were: type of hospital in which the doctor practices; type of patient's treatment; doctor's gender; weekly time spent on IBD, having publications about IBD and about IBD adherence indexed on Medline and how relevant is adherence for the doctor.
Conclusions: CONCLUSIONS: Taking into account the impact of good adherence to treatment in patients with IBD, it is very important to apply an objective grading system to quantify and improve it.

P527

Body image dissatisfaction is increased in inflammatory bowel disease compared with healthy matched controls but not diseased controls

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Background: Body image dissatisfaction (BID) is increased in inflammatory bowel disease (IBD) and also in other chronic medical conditions. Whether the high rate of BID in IBD is a function of chronic disease in general or a particular feature of IBD is unknown. We aimed to compare BID in IBD to age- and gender-matched healthy and chronic disease control groups. We chose Type 1 diabetes as the control disease because of its demographic similarities to IBD but relative lack of known risk factors for BID.
Methods: A case–control study was conducted in Hutt Valley Hospital. Consecutive cases, aged 16 years and over, were matched 1:1:1 to normal and diabetes controls for age and gender. Cases with recent surgery, pregnancy, or other significant chronic medical diagnoses were excluded. Participant demographics were collected. Participants were asked to complete the Body Image Disturbance Questionnaire (BIDQ), the hospital anxiety and depression score (HADS), and Quality of Life measures (RAND 36).
Results: There were 45 age- and gender-matched pairs for comparison of IBD and healthy controls, and 38 for IBD and diabetic controls. 77% of the participants were female. The mean BIDQ was higher in IBD patients compared with controls (2.05 vs. 1.58, p = 0.001) but not when compared with diabetics (2.03 vs. 1.72, p = 0.77). There was no difference in mean BMI, smoking status, or relationship status between groups. IBD patients scored more highly than controls for depression (mean HDS 6.51 vs. 3.87, p = 0.002) but not for anxiety (mean HAS 5.51 vs. 4.89, p = 0.258). No difference was seen between IBD and diabetic in either HADS domain. In IBD cases, logistic regression showed increased risk of depression (OR 4.6, p = 0.025) and anxiety (OR 7.4, p = 0.015) for every 1 point increase in BIDQ, after adjusting for clinical remission, gender, age, BMI, and smoking status.
Conclusions: Our data suggest that while BID is increased in IBD patients, it may not relate directly to the effects of IBD itself, but rather is a feature of chronic disease. Increased BID is associated with the presence of depression and anxiety in IBD patients. There may be a role for diagnosing and treating BID in IBD patients.

P528

Adalimumab for patients with Crohn's disease complicated by intra-abdominal abscess: a multicentre, prospective, observational cohort study

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Background: Management of intra-abdominal abscess complicating Crohn's disease (CD) is challenging. Surgery with delayed intestinal resection is often recommended in this situation. The aim of this study was to estimate the success rate of adalimumab (ADA) in patients with CD complicated by intra-abdominal abscess, after complete resolution of sepsis and abscess, and to identify predictive factors of success.
Methods: We performed a multi-centre, prospective, observational cohort study in patients with CD complicated by intra-abdominal abscess. Patients previously treated with an anti-TNF at the time of abscess occurrence, and patients with post-operative abscesses were not eligible. Patients with complete resolution of sepsis and abscess confirmed by MR enterography (MRE) at baseline were included and received 160 mg of ADA at week 0, 80 mg at Week 2, and then 40 mg every 2 weeks. The primary endpoint was ADA success at W24 defined as no steroids use after the 12th week following inclusion, no intestinal resection, no abscess recurrence and no clinical relapse (CDAI > 220 or HBI > 4 and CRP > 10 mg/l at two consecutive visits).
Results: From April 2013 to December 2017, 190 patients from 27 GETAID centres were screened. Seventy-three patients were excluded, and 117 were analysed for the primary endpoint. Median age at inclusion was 28 years (inter-quartile range [IQR]:24–36), 58 (50%) patients were male and 39 (35%) were active smokers. Median disease duration before abscess occurrence was 2.4 (0–58.7) months. Thirty-three (28%) patients had been previously exposed to thiopurines. Small bowel CD was responsible for intra-abdominal abscess in 101 (86%) patients. The median size of abscess was 25 (18–40) mm. MRE at baseline showed a visible fistula tract in 67 (58%) patients. Eleven (9%) patients had a percutaneous drainage of the abscess and 114 (97%) patients received antibiotics for a median duration of 21.5 (IQR: 8–31) days. Median CRP and albumin level at inclusion after abscess resolution were 5 (IQR: 2–9) mg/l and 39 (IQR: 36–43) mg/l, respectively. At W24, 83/117 (71%) patients achieved ADA success. Ten (9%) patients underwent an intestinal resection. At least one serious adverse event was reported in 40 patients, with relapse of intra-abdominal abscess in 10 patients, other infections in 7 patients, and gastrointestinal disorders including CD worsening in 27 patients. No death was reported.
Conclusions: In this prospective cohort of CD patients complicated by intra-abdominal abscess, ADA success was observed in 71% of cases at W24. During this period, 9% of cases had an abscess recurrence and 9% needed an intestinal resection. No death was reported. Investigation into the predictive factors of ADA success is ongoing.

P529

Exposure–response relationship of vedolizumab subcutaneous treatment in patients with ulcerative colitis: VISIBLE 1

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Background: Vedolizumab is a gut-selective, humanised, monoclonal α4β7 integrin antibody approved for intravenous (IV) administration to treat adult patients with moderate–severe ulcerative colitis (UC). The VISIBLE 1 study assessed the efficacy and safety of a novel vedolizumab formulation for subcutaneous (SC) administration in adult patients with moderate–severe UC. We report the exposure–response and immunogenicity results for vedolizumab SC vs. vedolizumab IV. Pharmacokinetic (PK) and exposure–response data for vedolizumab IV are published.[1,2]
Methods: VISIBLE 1 (NCT02611830) was a Phase 3, double-blind, double-dummy, randomised, placebo-controlled trial. After open-label vedolizumab IV induction treatment (300 mg IV at Weeks [Weeks] 0 and 2), patients with a clinical response at WK6 were randomised to maintenance treatment with placebo, vedolizumab 108 mg every 2 weeks SC, or vedolizumab 300 mg every 8 weeks IV. PK serum samples were taken at prespecified time points. Descriptive statistics were used to summarise vedolizumab PK and immunogenicity using a drug-tolerant electrochemiluminescence assay. Vedolizumab trough concentrations (C_{trough}) at WK46 (the final comparable trough sample) were grouped by quartiles and clinical outcome rates were calculated.
Results: A total of 216 patients were randomised to placebo (n = 56), vedolizumab SC (n = 106), and vedolizumab IV (n = 54). Both higher vedolizumab SC C_{trough} and vedolizumab IV C_{trough} concentrations were associated with greater efficacy at WK52, with improved response for low-exposure patients in the SC arm. An increase in WK52 clinical remission was observed in both arms, from 50% to 83% of patients in SC and from 18% to 90% in IV. An increase in WK52 mucosal healing was observed in 50% to 89% of patients in SC and 27% to 100% of patients in IV. A similar trend was observed for both predicted steady-state average concentration and troughs. WK52 exposure–response results for vedolizumab IV were generally comparable with GEMINI 1 results. [1] Immunogenicity was similar for vedolizumab SC and IV and was not associated with injection-site or hypersensitivity reactions.
Conclusions: Exposure–response relationships in VISIBLE 1 were similar to those seen previously in GEMINI 1.[1,2] Higher serum concentrations of vedolizumab with SC and IV administration during maintenance therapy are associated with greater proportions of patients achieving clinical remission and mucosal healing.

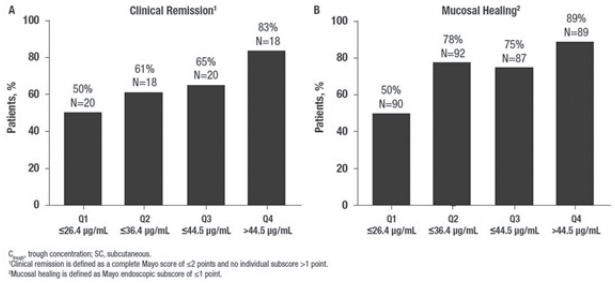

Figure 1. Week 52 vedolizumab SC efficacy according to C_{trough} quartiles.

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P530

Ultra-proactive therapeutic drug monitoring incorporating infliximab point-of-care testing with ad hoc dose adjustment reduces C-reactive protein levels in patients with IBD during infliximab maintenance treatment

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Background: Therapeutic drug monitoring (TDM) of infliximab (IFX) improves patient outcomes and is cost-effective. The short turnaround time of point-of-care testing (POCT) allows ad hoc dose adjustment. We aimed to determine the feasibility and pilot effectiveness of an ultra-proactive TDM algorithm including POCT of IFX in patients with inflammatory bowel disease (IBD).
Methods: All IBD patients with maintenance IFX treatment at our referral IBD clinic were prospectively included between June and August 2018. An ultra-proactive IFX TDM algorithm was applied as follows. All patients had an ELISA trough level (TL) measurement at baseline, of which the result determined the follow-up pathway: (A) TL between 3–7 µg/ml: continuation at same dose and interval; (B) TL >7 µg/ml: interval prolongation allowed; (C) TL <3 µg/ml: interval shortening with minimum 2 weeks, with the next IFX TL measured using a POCT. (i) If the POCT showed an IFX TL <3 µg/ml, dose was optimised ad hoc using a linear dosing formula ($Dose^n = (TL^{target} * Dose^{n-1}) / TL^{measured}$), followed by a new POCT test at next visit with the same interval. (ii) If the POCT showed an IFX TL ≥3 µg/ml, no additional dose was given and routine TL testing with ELISA was retaken at next visit. Physician's global assessment, C-reactive protein (CRP), haemoglobin and albumin levels were sequentially evaluated according to standard of care.
Results: In total, 115 patients were included (Crohn's disease/ulcerative colitis/IBDU *n* = 80/34/1; median CRP 1.2 mg/l (IQR 0.6–3.8); median TL 4.6 µg/ml (IQR 2.6–7.4)). A median of 3 infusions (IQR 3–4) during follow-up led to a total number of 371 TL measurements. There was a significant drop of low TL (<3 µg/ml) over time (38/115 at baseline vs. 22/256 during follow-up; $p = 0.0001$). The need for POCT reduced from an initial 28% to 8.7% ($p = 0.0001$). Additional dosing based on POCT measurement was needed in 7/43 (16.3%) cases. Patients needing ad hoc dose adjustment after interval shortening had significant lower TL at the previous measurement than those who did not (median (IQR) TL 0.9 µg/ml (0.7–1.8) vs. 2.3 µg/ml (1.5–2.6); $p = 0.036$). An IFX TL cut-off of 1 µg/ml predicted an ad hoc extra dose after interval shortening with an NPV of 96% (90% sens, 75% spec). In patients with elevated CRP at baseline ($n = 26$), ultra-proactive TDM resulted in a significant reduction of CRP over time, with a median (IQR) of 7.8 (6.5–18.3) mg/l at baseline compared with 6.3 (4–9.9) mg/l during follow-up ($p = 0.025$).
Conclusions: Ultra-proactive TDM based on a strict algorithm including POCT and ad hoc dose adjustment is feasible and significantly lowers CRP levels in IBD patients treated with maintenance IFX. Less than 10% of patients need POCT over time.

P531

Efficacy of tofacitinib maintenance therapy for ulcerative colitis in remitting patients vs. patients with clinical response after 8 weeks of induction treatment

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Background: Tofacitinib is an oral, small-molecule JAK inhibitor approved in several countries for the treatment of ulcerative colitis (UC). Here, we present data from the Phase 3 OCTAVE Sustain (NCT01458574) study,[1] comparing the 52-week maintenance efficacy of tofacitinib in patients with UC who achieved baseline remission (ie, remitters), to that of those who achieved clinical response but not remission (ie, non-remitters) after 8 weeks of induction therapy.
Methods: Patients who had achieved clinical response (≥3-point and ≥30% decrease from induction study baseline total Mayo score, plus a ≥1-point decrease in rectal bleeding subscore or an absolute rectal bleeding subscore ≤1) after 8 weeks of therapy in OCTAVE Induction 1 or 2 (NCT01465763; NCT01458951) were re-randomised at baseline to receive placebo, tofacitinib 5 or 10 mg twice daily (BID) in the double-blind, parallel-group, multi-centre OCTAVE Sustain study. The proportion of patients in remission (total Mayo score ≤2 with no individual subscore >1, and a rectal bleeding subscore of 0), and the proportion of patients with mucosal healing (Mayo endoscopic subscore ≤1) at Week 52, were analysed in baseline remitters ($n = 165$) vs. non-remitters ($n = 358$), excluding patients treated with placebo who achieved clinical response at baseline. This analysis was also performed for prior tumour necrosis factor inhibitor (TNFi) failures ($n = 234$) and non-failures ($n = 283$), although the six patients who did not meet clinical response criteria at baseline of OCTAVE Sustain were also excluded.
Results: A numerically higher proportion of tofacitinib-treated patients who were baseline remitters achieved remission at Week 52

vs. non-remitters, regardless of tofacitinib dose received or TNFi failure status. Similar findings were also observed for mucosal healing at Week 52. The relative increase in the observed treatment effect of tofacitinib 10 over 5 mg BID was generally similar between baseline remitters and non-remitters. Furthermore, the greater dose-related relative increase in efficacy in the TNFi failure vs. the TNFi non-failure subpopulation was evident regardless of the maintenance baseline remission status (table).

Conclusions: A numerically higher proportion of baseline remitters vs. non-remitters treated with tofacitinib achieved remission or mucosal healing at Week 52 in OCTAVE Sustain, although a large proportion of non-remitters and prior TNFi failures still achieved remission or mucosal healing at Week 52.

Table. Week 52 efficacy of tofacitinib in baseline remitting responders and responders in OCTAVE Sustain (mFAS NRI)*.

	Placebo	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID
Remission at Week 52, n/N (%)			
Remitter at baseline	5/52 (9.6)	28/60 (46.7)	30/53 (56.6)
Non-remitter at baseline	13/122 (10.7)	29/116 (25.0)	41/120 (34.2)
Mucosal healing at Week 52, n/N (%)			
Remitter at baseline	5/52 (9.6)	30/60 (50.0)	31/53 (58.5)
Non-remitter at baseline	17/122 (13.9)	33/116 (28.4)	49/120 (40.8)
Remission at Week 52 – remitter at baseline,[b] n/N (%)			
Prior TNFi failure	1/20 (5.0)	5/18 (27.8)	9/18 (50.0)
Prior TNFi non-failure	4/32 (12.5)	23/42 (54.8)	21/35 (60.0)
Remission at Week 52 – non-remitter at baseline,[b] n/N (%)			
Prior TNFi failure	8/60 (13.3)	11/58 (19.0)	19/60 (31.7)
Prior TNFi non-failure	5/60 (8.3)	18/55 (32.7)	22/59 (37.3)
Mucosal healing at Week 52 – remitter at baseline,[b] n/N (%)			
Prior TNFi failure	1/20 (5.0)	7/18 (38.9)	9/18 (50.0)
Prior TNFi non-failure	4/32 (12.5)	23/42 (54.8)	22/35 (62.9)
Mucosal healing at Week 52 – non-remitter at baseline,[b] n/N (%)			
Prior TNFi failure	9/60 (15.0)	14/58 (24.1)	21/60 (35.0)
Prior TNFi non-failure	8/60 (13.3)	19/55 (34.5)	28/59 (47.5)

[a]Central read endoscopy; all patients were randomised, excluding patients treated with placebo who achieved clinical response at baseline
[b]Excludes the six patients who did not meet clinical response criteria at baseline of OCTAVE Sustain
Baseline non-remitters includes patients who were responders at baseline, but were not in remission. Remission was defined as a total Mayo score of ≤2 with no individual subscore >1, and a rectal bleeding subscore of 0. Mucosal healing was defined as a Mayo endoscopic subscore ≤1
BID, twice daily; mFAS, modified full analysis set; N, number of patients in each group at Week 52, and used as denominator in percentage calculation; n, number of patients in remission or with mucosal healing at Week 52; NRI, non-responder imputation; TNFi, tumour necrosis factor inhibitor

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P532

Safety and efficacy of endoscopic dilation of small bowel Crohn's disease strictures by balloon-assisted enteroscopy: pooled analysis of individual data from 210 patients

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Background: Strictures are a common complication of Crohn's disease (CD). While colonoscopy has been proven suitable and effective for dilation therapy of CD-associated strictures of the ileocaecum, the published evidence on safety and efficacy of balloon-assisted enteroscopy (BAE) for balloon dilation therapy of CD strictures of the small intestine is scarce. We therefore performed a pooled safety and efficacy based on individual patient data.

Methods: A systematic literature review was performed to assess all relevant citations found in Embase, Medline and the Cochrane library regarding BAE used for EBD of small intestinal CD strictures. In addition, conference proceedings including DDW, ECCO, UEGW, A-IBD, AGA and German Gastroenterology Congress were screened for additional data. Study authors were contacted to provide individual patient data. Descriptive statistics were used to summarise patients' characteristics. Univariate cox proportional hazards regression model was applied to find out possible risk factors for need for re-dilation and surgery. Backward model selection procedure was used and multi-variate cox model were built.

Results: 19 publications with a total of 468 CD patients and 1194 performed dilation procedures were included. 25.1% of strictures were anastomotic strictures (74.9% de novo,, respectively). Technical success rate was 88.1%, resulting in clinical efficacy in 78% of patients. Major complications defined as perforation, bleeding or dilation-related surgery occurred in 3.7% of all procedures. During a mean follow-up period of 16 months, 45.7 of patients reported symptomatic recurrence, while 38.1% of patients needed to undergo re-dilation and 27.5% required surgical intervention.

Multi-variate analysis of 210 individual patients identified a 56% higher hazard of re-dilation in CD patients with symptomatic recurrence compared with asymptomatic patients and a 60% higher hazard in patients with prestenotic dilation compared with patients with no prestenotic dilation. Additionally, increased CRP values at dilation (elevation of CRP per 0.1 increased the hazard for surgery by 9.3%) and inflamed mucosa at dilation (4 times increased hazard when compared with non-inflamed mucosa) were identified as risk factors for the need for surgery.

Conclusions: *Balloon-assisted enteroscopy* for dilatation therapy of CD-associated strictures of the small intestine possesses a high rate of short-term technical and clinical success with acceptable complication rates. Main predictors for intermediate therapeutic failure are prestenostic dilation, increased CRP values and mucosal inflammation at the time of dilation. Endoscopic dilation by BAE is a valuable alternative to surgery in selected patients with small bowel CD associated strictures.

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Ustekinumab therapeutic drug monitoring in Crohn's disease patients with loss of response

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Background: Crohn's disease (CD) patients on ustekinumab (UST) may experience a partial or secondary loss of response (LOR). The

aim of the study was to assess the role of UST therapeutic drug monitoring (TDM) in patients with a LOR.

Methods: In this prospective study, trough UST TDM was performed in CD patients experiencing either a partial response or a secondary LOR to UST based on clinical (HBI ≥5) and/or objective inflammation (CRP ≥5 or FCP ≥250 or SES-CD >2). Patients were treated at the discretion of the physician prior to the UST TDM results becoming available. Patients were reassessed for complete remission (HBI <5, CRP <5 and FCP < 250) or for response (HBI decrease by >3 points and a 50% decrease in CRP, FCP). UST drug and antibody concentrations were assessed using a liquid phase assay (Prometheus Laboratories Inc.).

Results: 38 instances of clinical LOR were identified in 35 patients. The median age at LOR was 39 years (range 18–72), 57% were male and 91% were biologic experienced. The median follow-up visit occurred at 3.8 months (IQR 3.1–4.4 months). Treatment interventions and outcomes are listed in Table 1. When UST was dose escalated with q 4 week dosing or re-induction, patients with active inflammation achieved complete remission and response in 38% and 31%, respectively. When baseline TDM was available (n = 35), the mean UST concentration was significantly lower in patients with active biochemical or endoscopic inflammation (n = 31) compared with patients with no objective inflammation (n = 4): 5.21 vs. 18.74 μg/ml, p < 0.0001. In the 27 patients with active inflammation in whom UST treatment was continued (29 instances), the mean baseline UST concentration was higher in patients who achieved complete remission (n = 10), compared with those who did not (n = 19): 7.61 vs. 4.01 μg/ml, p = 0.01. The mean baseline FCP was significantly lower in patients who achieved complete remission, compared with patients who did not (414 vs. 993 μg/g, p = 0.03). The mean post treatment UST drug concentration was significantly higher in patients who achieved complete remission (n = 8), compared with those who did not achieve complete remission (n = 14): 13.04 vs. 8.57 μg/g, p = 0.03.

Treatment: *n* (%)	Complete remission *n* (%)	Response *n* (%)	No response *n* (%)
No change: 4 (11)	3 (75)	1 (25)	0 (0)
Q8 to Q4 weeks: 22 (58)	10 (45)	7 (31)	5 (23)
IV/SQ re-induction: 7 (18)	1 (14)	2 (29)	4 (57)
Immunosuppression added: 3 (8)	0 (0)	1 (33)	2 (67)
Changed out of class: 2 (5)	0 (0)	1 (50)	1 (50)

Treatment intervention and outcomes.

Conclusions: Overall, ustekinumab dose escalation or reinduction in CD patients with a LOR resulted in complete remission or response in 69% of patients. Baseline higher drug concentrations and low FCP were associated with significantly increased rates of complete remission. Higher post-treatment drug concentrations were significantly associated with increased rates of complete remission.

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IBD-related malignancies observed in 2015–2018: 4 years' results from the prospective nationwide Hungarian registry

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Background: Inflammatory bowel diseases (IBD – Crohn's disease (CD); ulcerative colitis (UC)) are associated with an increased risk of colorectal cancer (CRC). Other extraintestinal malignancies have shown variable incidence rates.

Methods: The aim of our nationwide registry was to prospectively collect IBD-related malignancies diagnosed in the Hungarian IBD population. Data on all malignancies developed between January 2015 and November 2018 in IBD patients were recorded. Each members of the Hungarian Society of Gastroenterology were prospectively interviewed three monthly by personal emails to report malignancies observed in their patient population. Demographic and clinical data including adherence, tumour stage, previous immunosuppressive and biological therapy were also collected.

Results: 106 newly diagnosed malignancies were reported. Half of the cancers were colorectal cancers. Mean disease duration at the time of the diagnosis of CRC was 18.7 (1–43) years, mean age was 52.4 (33–87) years. 69.8% of the CRC cases were associated with UC, 51% with pancolitis, 24% with left-sided colitis. From the CD's patients the ileocolonic and colonic localisation were observed in 41.6% and 50% of the patients, respectively. According to our results CRC was more common in male patients (66%). The most common CRC localisation was the rectosigmoidal part of the colon (58.5%). Only 1/3 of the CRC's cases were diagnosed in early stage. 20.1% of the patients died during the observation period. Other frequent malignancies were haematological malignancies (7.5%), lung cancer (6.6%), non-melanotic skin cancer (5.6%). The most common extraintestinal malignancies were non-melanotic skin cancer (14%), 80% of them were treated with biological therapy (immunosuppressive therapy: 20%, biological therapy and immunosuppressive therapy combination: 80%).

Conclusions: The most frequently observed IBD-related malignancy was colorectal cancer in our cohort, which mainly involved the distal part of the colon. CRC presented typically in male UC patients with pancolitis or left-sided colitis. The most common extraintestinal malignancies were non-melanotic skin cancer.

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Azathioprine vs. mesalamine for prevention of post-operative clinical relapse in Crohn's disease patients with severe endoscopic recurrence: data on efficacy and safety from an IG-IBD multi-centre randomised double-blind double-dummy trial

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Background: More than 70% of patients with Crohn's disease (CD) require surgery at least once during the course of their disease. Unfortunately endoscopic recurrence (ER) is up to 100% at 5 years with a risk of six-month severe ER (≥ i2) around 50% as showed in a previous Italian study. As well know symptomatic recurrence is strongly related to the severity of ER and ECCO guideline recommended prophylactic treatment after ileocolonic resection despite effectiveness of immunosuppressants remain debated.

Methods: We performed a multi-centre randomised double-blind double-dummy trial to assess the role of azathioprine (AZA) vs. high dose of mesalamine (5-ASA) as treatment of early severe POR (Rutgeerts' score ≥ i2) and as prophylaxis for clinical relapse (eligible patients and treatment allocation are showed in Table 1).

Characteristics of eligible patients and treatment allocation	Patients were enrolled from 11 Italian referral centers for inflammatory bowel disease from April 2005 to June 2010. All consecutive Crohn's disease patients who had been treated by a first or second curative resection of the terminal ileum and part of the right colon were included in the study. All the patients started 2.4 g daily of 5-ASA until endoscopy that was performed 6 month after surgery. Patients with severe post-operative recurrence were randomized to azathioprine (2-2.5 mg/kg) + mesalamine placebo or high dose of mesalamine (4 gr/die) + azathioprine placebo (1:1).
Screened patients	252 consecutive patients were operated-on and 211 of them underwent curative resection of the terminal ileum and part of the right colon: 24 patients were lost at the follow-up, 82 did not undergo colonoscopy at 6 month and were excluded, 105 underwent colonoscopy 6 months after surgery.

Table 1

Primary outcomes: endoscopic improvement and clinical relapse after 12 months from randomisation. Post-trial analysis: data on clinical and endoscopic outcomes up to 10 years from T0.

Results: According to inclusion/exclusion criteria 46 patients were randomised (characteristics of screened patients are showed in Table 1): 65% males, overall median age at diagnosis and at surgery of 29.5 and 36.5 years, respectively. At the final analysis 17% of patients experienced a clinical relapse within 12 months from randomisation without differences between AZA and 5-ASA groups. Considering POR after 12 months of treatment no significant improvement were observed from T0 in both groups (p = ns). At the post-trial analysis, 53% of patients experienced a clinical relapse without differences between those previously treated with AZA or 5-ASA (p = ns). Smoking and previous surgery at T0 were risk factors for clinical relapse (p = 0.031 and 0.003). No significant AE were recorded.

Conclusions: This multi-centre RCT does not show efficacy of AZA or 5-ASA in the treatment of severe POR or as prophylaxis for clinical relapse. In the post-trial analysis, in those with POR at 6-month from surgery, risk factors for severe CD (smoking and multiple surgery) could help to identify patients with worse prognosis to start biological therapy.

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Thiopurine metabolite levels in pregnant IBD patients and infants following intrauterine thiopurine exposure

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Background: Data regarding the pharmacokinetic effects of pregnancy on thiopurine metabolism and infant exposure to thiopurine metabolites is very limited. Data on 30 women suggested that maternal 6-thioguanine nucleotide (6-TGN) levels decreased in pregnancy, while infant 6-TGN correlated with maternal 6-TGN[1]. 6-methylmercaptopurine (6-MMP) was undetected in infants (lower limit of detection 100 pmol/8 × 10^8 RBCs).[1] We aimed to measure thiopurine metabolites in each trimester and in infants at delivery.

Methods: Female patients with IBD on a thiopurine and pregnant or planning pregnancy were enrolled. Thiopurine metabolites were measured pre-conception when possible, in each trimester of pregnancy, at delivery and post-partum. Participants were offered thiopurine metabolite testing in the umbilical cord at delivery. The Wilcoxon signed-rank test was used to compare medians.

Results: 22 patients were included with at least two measurements on stable dosing. Patient characteristics and metabolite levels are shown in Table 1. Median 6-TGN levels were lower during pregnancy than pre-conception and post-partum (Figure 1). Two patients required dose increases during pregnancy (levels post dose change not included). No significant difference was found between median 6-MMP levels. All patients to date (16/22) delivered babies at term with normal birth weight and no congenital anomalies. Thiopurine metabolite levels are available in five infants. In two infants, whose mothers were on low-dose thiopurine as co-therapy with anti-TNF, 6-TGNs were undetectable. One had undetectable 6-MMP, and one had 6-MMP of 27 pmol/8 × 10^8 RBCs. In the other three infants, both 6-MMP and 6-TGN were detected but were lower than maternal levels. One of these infants had a mild thrombocytopenia 102 × 10^9/l, which resolved (6-TGN 70 pmol/8 × 10^8 RBCs).

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	Median (IQR) or n (%)
Age at beginning of pregnancy (y)	33.5 (29.9-36.5)
Weight (kg)	65.2 (57.8-74.2)
Disease:	
-CD	13 (59%)
-UC	6 (27%)
-IBDU	3 (14%)
Duration of IBD (y)	6.5 (2.2-10.5)
Type of thiopurine:	
-AZA	11 (50%)
-6MP	11 (50%)
Concomitant medications:	
-5-ASA or SSZ	8 (36%)
-Anti-TNF	13 (59%)
-Allopurinol	1 (5%)
Dose of AZA (mg/kg)	1.21 (0.96-1.88)
Dose of 6MP (mg/kg)	0.89 (0.60-1.33)*
Median 6-TGN levels:	
-Pre-conception	271 (167-357)
-Trimester 1	231 (174-314)
-Trimester 2	148 (111-270)
-Trimester 3	215 (134-318)
-Post-partum	279 (170-498)
Median 6-MMP levels:	
-Pre-conception	385 (311-1391)
-Trimester 1	456 (450-1125)
-Trimester 2	391 (250-1103)
-Trimester 3	350 (178-1041)
-Post-partum	236 (147-357)

**Dose excluded for patient on allopurinol supplementation*

Table 1. Patient characteristics (mothers) ($n = 22$).

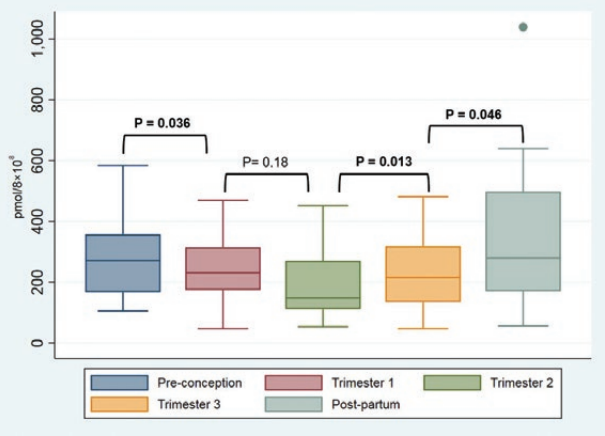

Figure 1. Maternal 6-TGN levels during pregnancy.

Conclusions: Thiopurine pharmacokinetics appear to be altered in pregnancy. Our preliminary results confirm 6-TGN levels may decrease in pregnancy. Infants can be exposed to both 6-TGN and 6-MMP, although at low levels. Improved knowledge of the metabolism of these drugs in pregnancy is imperative to inform dosing.

Reference

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The impact of early disease control with vedolizumab on surgery rates among patients with Crohn's disease: a post-hoc analysis of the GEMINI trials

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Background: In Crohn's disease (CD), short disease duration is associated with greater response to anti-tumour necrosis factor α therapy. The impact of disease duration on surgery rates in vedolizumab-treated patients with CD has not been established. A clinical decision support tool (CDST) was developed using data from the GEMINI 2 trial and validated with data from the VICTORY consortium to predict clinical and endoscopic remission with vedolizumab in CD.[1] Whether earlier treatment with vedolizumab reduced the risk of CD-related surgery in patients with low, intermediate, or high probability of response to vedolizumab was assessed.

Methods: Individual patient data from GEMINI 2 and the open-label GEMINI long-term safety studies were evaluated. Early and late disease were defined as ≤2 vs. >2, ≤3 vs. >3, and ≤5 vs. >5 years of disease duration. CD-related surgery was defined as bowel resection and colectomy. Patients were stratified according to the CDST into low, intermediate, or high probability of response to vedolizumab, and logistic regression and Cox-proportional hazard analyses were used to assess the impact of early disease intervention with vedolizumab in these subgroups. Odds ratios (ORs) with 95% confidence intervals (CIs) are reported.

Results: A combined total of 1253 patients with CD from the GEMINI studies were included (mean [SD] age, 36.4 [12.4] years; 55.1% female), with 113 (9.0%) requiring CD-related surgery during the 7-year follow-up period. Surgical rates were 12.9%, 8.1%, and 6.0% for the low, intermediate, and high probability of vedolizumab response groups based on the CDST. Patients with low probability of response had a 2-fold (hazard ratio, 2.32; 95% CI, 1.29–4.30) increased risk of surgery while receiving vedolizumab relative to the high probability of response group. Overall, there was a trend of lower rates of CD-related surgery among patients treated earlier in their disease course (table). For the low probability of vedolizumab response group, patients with CD with a disease duration of ≤5 years had 39% lower odds of requiring CD-related surgery compared with patients with disease duration >5 years (OR, 0.61; 95% CI, 0.36–0.99).

Conclusions: This post hoc analysis suggests that treatment of patients with CD with vedolizumab earlier in their disease course is associated with lower rates of surgery up to a 7-year time horizon, regardless of baseline probability of response to vedolizumab.

Table. CD-Related Surgery Stratified by Probability of Response to Vedolizumab and Disease Duration[a]

Probability of Response to Vedolizumab	Disease Duration (Time Since Diagnosis)									
	≤2 y	>2 y	Odds Ratio (95% CI)	≤3 y	>3 y	Odds Ratio (95% CI)	≤5 y	>5 y	Odds ratio (95% CI)	Total
Low/intermediate probability, n (%)	9 (8.0)	88 (10.1)	0.77 (0.36-1.53)	14 (7.7)	83 (10.3)	0.73 (0.39-1.29)	21 (7.0)	76 (11.0)	0.61 (0.36-0.99)	97 (9.8)
High probability, n (%)	6 (7.7)	10 (5.3)	1.44 (0.47-4.13)	6 (5.6)	10 (6.5)	0.86 (0.28-2.44)	8 (5.3)	8 (7.3)	0.71 (0.25-2.03)	16 (6.1)
Odds ratio (95% CI)	1.04 (0.35-3.26)	1.93 (1.02-4.00)		1.41 (0.53-4.10)	1.65 (0.86-3.43)		1.35 (0.59-3.30)	1.58 (0.77-3.81)		1.67 (0.98-2.97)

[a]The model used response probability as described in Dulai et al. 2018[1] and included the following variables: prior bowel surgery, prior anti-tumour necrosis factor alpha use, prior fistulizing disease, baseline albumin, and baseline C-reactive protein.
CI, confidence interval; n, number of surgeries within specified probability of response cohort and disease duration subgroup.

Reference

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Vedolizumab is effective in real life paediatric inflammatory bowel disease: report from the prospective, multi-centre VEDOKIDS cohort study

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Background: Vedolizumab (VDZ) has proven to be effective in adults, both in Crohn's disease (CD) and ulcerative colitis (UC). Limited data are available in children and none are prospective. We evaluated the short- and mid-term effectiveness and safety of the drug in an interim analysis of the prospective, multi-centre VEDOKIDS cohort study of children with IBD who commenced VDZ.
Methods: Although children were managed according to the discretion of the local physician, the study protocol recommended standardised management including VDZ dose of 177 mg/BSA up to 300 mg. Explicit demographic, clinical and safety data were recorded via a REDcap electronic eCRF at weeks 0, 14 and 30. Clinical remission was defined as steroid and EEN-free remission (ie, wPCDAI < 12.5 or PUCAI < 10) without the need for new medications or surgical interventions. Complete remission was defined as clinical remission with CRP < 0.5 mg/dl and ESR < 20 mm/h.
Results: Forty-three children were enrolled, 23 (53%) with CD, and 20 (47%) with UC/IBDU (14 (33%) males, 35 (81%) failed previous anti-TNF, median disease duration 2.3 years (IQR 1.2–5.0)). Four children (9%) discontinued the drug due to primary or secondary non-response and their data were imputed for ITT analysis using the blended non-response imputation and LOCF approach for continuous data. Clinical remission rates at Weeks 14 and 30 were 35% and 30% for CD, and 45% and 45% for UC, respectively. The sustained clinical remission rates (at both Weeks 14 and 30) were 22% in CD and 40% in UC ($p = 0.19$). Complete remission at Week 30 was noted in 3 children (13%) in the CD group and 4 (20%) in the UC/IBD-U group ($p = 0.42$). In the CD Group 19 children (83%) had elevated CRP and/or ESR at week 0, of whom 11% and 5% normalised both markers at Weeks 14 and 30, respectively. In the UC/IBD-U group, 10 (50%) had elevated CRP and/or ESR at baseline, of whom, 40% and 30% normalised the markers at Week 14 and 30, respectively. In the CD group, the mean height z-score improved slightly from –1.17 at baseline to –0.95 at Week 30, but this was not significant ($p = 0.297$). Eighteen adverse events (AE) were recorded in 14 children. The 5 AEs graded as possibly related to VDZ were mild–moderate and included back pain, parotitis, myalgia and upper respiratory infection and leukocytoclastic vasculitis; only the latter led to discontinuation of VDZ. There were 5 serious AEs, none likely related to VDZ.
Conclusions: In this prospective cohort study, VDZ was safe and effective in a refractory cohort of paediatric IBD. VDZ was numerically more effective in UC/IBD-U than in CD in children, both at Week 14 and Week 30, across all outcomes.
This study is supported by grants from ECCO and ESPGHAN.

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Impact of a multi-disciplinary team meeting for managing inflammatory bowel disease patients: professional practice analysis based on 869 cases

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Background: Multi-disciplinary team (MDT) meetings have been implemented in several inflammatory bowel disease (IBD) referral centres within the last years. In our regional IBD centre, a monthly MDT meeting exists since 2001. Our objective was to realise a critical analyse of a tertiary referral centre IBD-MDT meeting through a professional practice evaluation (PPE).
Methods: Three steps were defined for the PPE of the IBD-MDT meeting. Firstly, all cases discussed from January 2014 to December 2017 were retrospectively retrieved for a practice enquiry with indicator. The chosen indicator was whether the MDT meeting decision had been applied or not. Secondly, an audit was realised through 2 video-recorded MDT meeting, critically analysed to draw area for improvement. Finally, a satisfaction questionnaire was distributed to gastroenterologists during a regional post-graduate meeting.
Results: For the practice enquiry, among the 1163 cases discussed during the 4-year period, 335 were excluded by lack of information about patients' outcome and 4 due to missing referent gastroenterologist's name; 863 IBD cases could be analysed (median age 38 years, 50% female). The MDT meeting decision was applied in 72% of cases, not applied in 16% of cases, no clear information found in medical report in 11% of cases. In multi-variate analysis, for patients with Crohn's disease, the workplace of the referring physician was associated with a poorer follow-up of the decision (p = 0.02 for global factor, private centres vs. university hospital; OR: 3.3 (95% CI) 0.9–11.3)). In patients with ulcerative colitis, patient's female gender was related to a poorer follow-up of the decision (OR: 5.7 (95% CI, 1.8–19.5); $p < 0.01$). Between March and May 2018, 45 case discussions have been video -recorded. Median (interquartile range) duration of case discussion was 5.0 (3.0–5.6) min; the referent gastroenterologist was absent in 58% of cases; a reinterpretation of medical imaging was needed in 53% of cases. The more frequent incident was telephone ringing during the MDT meeting (22% of discussions impacted). Finally, 23 gastroenterologists answered the satisfaction questionnaire. For all of them, the IBD-MDT meeting

was considered helpful for patients' management. Practical modalities of the MDT were known by 91% of participants but several modifications were suggested regarding the timing of the meeting or the availability of a videoconference system.

Conclusions: Rate of IBD-MDT meeting decision followed is high but could be improved. This PPE led to several proposals of improvement. IBD-MDT will soon be essential regarding the growing number of therapeutic options and drug costs. National and international organisations guidelines could help to structure these meetings.

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Therapeutic drug monitoring in ustekinumab: which factors affect trough levels?

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Background: Ustekinimab (UST) is a fully human monoclonal antibody against the p40 subunit of interleukin-12 (IL-12 and interleukin-23 (IL23). Efficacy of biological drugs can be optimised by ensuring adequate exposure to these drugs, by using trough level-based therapeutic drug monitoring. The aim of our research was to identify (bio)markers that influence UST trough levels. Furthermore, we aimed to assess the relationship between exposure and response to UST.

Methods: An observational study was carried out. All adult patients with Crohn's disease that received UST treatment between December 2016 and November 2018 were included. Patient were treated with an initial intravenous induction therapy, followed by subcutaneous maintenance therapy . Patients demographics were collected (concomitant medication use, biological uses in the past, disease localisation, body weight, body-mass index), as were disease activity measures (Harvey–Bradshaw Index (HBI); faecal calprotectine (FCP); C-reactive protein (CRP) and Albumin. UST dosage and interval, trough levels and antibodies were collected as treatment specific data. Nonlinear mixed-effect modelling was used to estimate pharmacokinetic parameters based on the collected UST trough concentrations as implemented in the NONMEM software package (version 7.3.0) using PsN toolkit 4.7.0 and Piraña version 2.9.7 as modelling environment. Plotting of the results was performed using statistical software package R (v3.4.4) and R studio Version. Parameters calculated were Distribution Volume (V; litres) and clearance (CL/L/Day).

Results: 50 patients (34.6% male, mean age 43 years, mean disease duration 17 years) with Crohn's disease were included. A total of 365 doses UST were administered, and a total of 196 trough levels were measured. A one compartment model with first-order elimination was identified. The typical value of CL 0.28 L/day, V was 6.94 L. The inter-individual variability was estimated 35.1% for CL and 35.2% for V. Among the evaluated covariates, body weight significantly affected CL. In addition, baseline albumin and a CRP level >10 were found to be significantly affect V. In the exposure response analysis a relationship between HBI , CRP ad FCP and ustekinumab levels was identified. Patient with higher Ustekinumab levels had a lower HBI score and lower CRP and FCP levels.

Conclusions: A population pharmacokinetic model for ustekinumab was developed. Bodyweight, baseline albumin and CRP had a significant influence on ustekinumab pharmacokinetics. Patient with higher ustekinumab levels had a lower HBI score, lower FCP and lower CRP. These results show a possible rationale for TDM of ustekinumab however further research is required to establish a clear therapeutic window.

P541

Real-life effectiveness of ustekinumab in inflammatory bowel disease patients with concomitant psoriasis or psoriatic arthritis: an IG-IBD study

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Background: Ustekinumab has been licensed for treating psoriasis, psoriatic arthritis and Crohn's disease. Few data exist regarding the effectiveness of ustekinumab in inflammatory bowel disease (IBD) patients treated for concomitant dermatological or rheumatological conditions. This study aimed to describe the outcomes of IBD patients who received subcutaneous ustekinumab through a dermatological or rheumatological prescription.

Methods: This multi-centre, retrospective study included all IBD patients who were started on subcutaneous ustekinumab for concomitant active psoriasis or psoriatic arthritis, irrespective of IBD activity. The primary endpoint was overall ustekinumab persistence, defined as the maintenance of therapy because of sustained clinical benefit for IBD.

Results: Seventy IBD patients (64 Crohn's disease / 6 ulcerative colitis) were enrolled. Most patients (95.7%) had been previously exposed to anti-TNFα drugs. The median follow-up on ustekinumab therapy was 10.7 months (range, 1.4–67.3). Twelve patients (17.1%) withdrew the treatment after a median of 7.4 months (range, 0.9–23.8). The cumulative probability of maintaining ustekinumab treatment was 97.1% at 6 months and 77.1% at 12 months. Among the 56 patients with active IBD at baseline, 34 (60.7%) were in clinical remission at the last follow-up visit, and their cumulative probability of achieving IBD clinical remission was 84.7% and 63.9% at 6 and 12 months, respectively. Ustekinumab induced clinical remission of psoriasis or psoriatic arthritis in 37/45 (82.2%) and in 15/25 (60%) patients, respectively. Nine patients experienced an adverse event, but only two stopped ustekinumab.
Conclusions: Subcutaneous ustekinumab had a good effectiveness profile for IBD patients treated for concomitant dermatological or rheumatological conditions.

P542

Efficacy and safety of biological therapies in chronic antibiotic-refractory pouchitis: a retrospective single-centre experience

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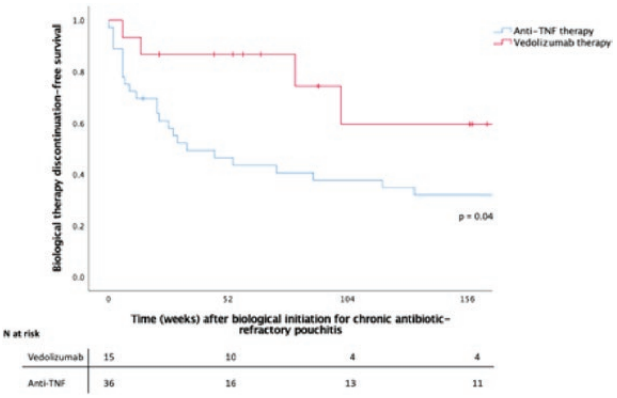
Background: Chronic antibiotic-refractory pouchitis affects up to 15% of patients with ulcerative colitis (UC) following colectomy with ileal pouch-anal anastomosis (IPAA). In retrospective series, infliximab (IFX), adalimumab (ADM) and vedolizumab (VDZ) have demonstrated efficacy, but data are limited. We here report single-centre data of biological therapy in refractory pouchitis.
Methods: We retrospectively assessed all records from UC patients who underwent IPAA and were exposed to IFX, ADM or VDZ thereafter at our centre. Patients with a baseline modified pouchitis disease activity index (mPDAI)< 5 or with Crohn's disease-related complications of the pouch were excluded. Clinically relevant remission, defined as a mPDAI <5 and a reduction of mPDAI 2 points from baseline, was assessed at Week 14. Non-responder imputation was applied in case of discontinuation prior to Week 14.
Results: Thirty-three unique patients were included (69.7% male, median [IQR] age 39.6 [33.7–52.8]). Three (9.1%) underwent colectomy because of high-grade dysplasia, whereas 90.9% had surgery due to refractory UC. Prior to surgery, patients had been exposed to cyclosporine (n = 14), IFX (n = 12), ADM (n = 3), and/or VDZ (n = 3). J-pouches were constructed mainly in (modified) 2-stage (n = 25) procedures. All developed chronic antibiotic-refractory pouchitis after a median of 3.1 years, for which they received IFX (n = 23), ADM (n = 13) or VDZ (n = 15). Clinically relevant remission at Week 14 was observed in 43.5% of IFX group, and 38.5% and 60.0% in the ADM and VDZ group. With a median follow-up of 1.0 (0.3–3.1) years, significantly more patients continued VDZ compared with anti-TNF therapy (HR 2.9 [95% CI 1.1–8.5], p = 0.04) (figure).



Kaplan–Meier curve representing the biological therapy discontinuation-free survival in chronic antibiotic-refractory pouchitis

Compared with baseline, VDZ resulted in a significant drop in endoscopic PDAI score at final follow-up (p = 0.004), whereas IFX and ADM led to a more modest drop (p = 0.03, p = 0.1, respectively). Adverse events (mainly infusion reactions) and undetectable serum levels explained 48.1% of the patients discontinuing anti-TNF therapy, whereas discontinuation of VDZ was only related to insufficient efficacy. Overall, 4 patients (12.1%) ended up with a permanent ileostomy.
Conclusions: In this case series, the use of anti-TNF agents for the treatment of chronic antibiotic-refractory pouchitis was hampered by the high rate of adverse events partly related by pre-colectomy exposure to the same drug. Therefore, VDZ might be an efficacious and safe alternative, which is currently being studied in a phase IV randomised trial.

P543

Seven-year efficacy and safety of azathioprine treatment in the maintenance of steroid-free remission in inflammatory bowel disease patients

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Background: Azathioprine (AZA) and thiopurine are widely used for induction and maintenance of remission in dependent steroid patients with inflammatory bowel disease (IBD). The treatment must be withdrawn in 5–30% of patients due to the occurrence of adverse events. Aim of this study has been to investigate its efficacy and safety in maintaining steroid-free remission in steroid dependent IBD patients seven year after the institution of treatment.
Methods: Data from consecutive IBD outpatients referred in our Institution, between 1985–2016, were reviewed and all patients treated with AZA were included in this retrospective study. AZA was administered at the recommended dose of 2–2.5 mg/kg. Blood chemistry was analysed before administration of the drug, every 10–15 days for the first 3 months and then every 1–2 months following the institution of treatment.

Results: Out of 2802 consecutive IBD outpatients visited in the index period, AZA was prescribed to 433 patients, 236 (54.5%) were affected by Crohn's disease (CD) and 197 (45.5%) by ulcerative colitis (UC). One hundred and seventy-nine patients with a follow-up < 84 months were excluded from the study. Two hundred and fifty-four patients were evaluated, 141 (55.5%) with CD and 113 (44.5%) with UC. One hundred and thirty-nine (54.7%) were male and 115 (45.3%) female (average age of 35.62 ± 14.20 SD years, range 14–74 y.). Seven year after the institution of treatment, 127 (50%) patients still were in steroid-free remission (83 CD vs. 44 UC, 58.8% and 38.9%, respectively, $p = 0.0024$), 71 (27.9%) had a relapse requiring retreatment with steroids (29 CD vs. 42 UC, 20.6% and 37.2%, respectively, $p = 0.0047$), 56 (22.1%) discontinued the treatment due to side effects (29 CD vs. 27 UC, 20.6% and 23.9%, respectively). Loss of response from first to seventh year of follow-up was low, about 20%.

Conclusions: Seven year after the onset of treatment 50% of patients did not require further steroid courses. After the first year loss of response was low in six subsequent years. In the present series the maintenance of steroid-free remission was significantly higher in CD than in UC patients. The occurrence of side effects leading to the withdrawal of AZA treatment has been low.

P544

Impact of patient education on switch acceptance in IBD patients in remission, with infliximab originator switched for an infliximab biosimilar: a prospective study

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Background: CT-P13, the first biosimilar to infliximab (IFX), has an efficacy and tolerance profile comparable to IFX originator, at a lower cost. Physicians are thus strongly encouraged to propose a biosimilar. However, for patients, the switch from IFX originator to a biosimilar is not always accepted. The aim of this study was to evaluate the impact of patient education (PE) on the acceptance of a switch from IFX originator to biosimilar in IBD patients treated with IFX originator.

Methods: In a monocentric prospective study, all IBD adult patients treated with IFX originator between June 2017 and June 2018, in clinical remission for at least 6 months, were asked to complete a questionnaire specifically designed for this study, to assess their knowledge on biosimilars and their acceptance of a switching strategy. Patients had the choice whether or not to accept the switch, with or without PE. The primary endpoint was the percentage of patients who accepted the switch, after receiving a PE session due to an initial refusal. Secondary endpoints were the evaluation of patient knowledge and feeling regarding biosimilar treatment; clinical remission, based on the Harvey–Bradshaw Index (score < 4) for CD and the partial Mayo score (< 2) for UC; biological remission: C reactive protein (N<5 mg/l) and faecal calprotectin (N<150 µg/g stool) and immunogenicity after the switch, trough levels of IFX (TLI) and anti-IFX antibodies (ATI).

Results: 86 patients (median age: 44 years [19–79]) were included (36% UC and 64% CD). The switch was initially refused by 47% of patients. In this subgroup, 78% agreed to participate in an educational interview with the PE nurse; 68% finally accepted the switch. At Week 16, the persistence on biosimilar was 91%. At weeks 0, 8 and 16, respectively, Mayo score was 0.68 ± 0.69, 0.81 ± 0.95 and 0.57 ± 0.76 ($p = 0.733$) and Harvey–Bradshaw score was 0.88 ± 1.70, 1.95 ± 2.27 and 2.14 ± 2.36 ($p = 0.134$); CRP was 2.92 ± 4.52, 3.48 ± 5.99 and 4.33 ± 10.82 ($p = 0.724$); faecal calprotectin was 291 ± 402, 418 ± 596 and 427 ± 459 ($p = 0.745$); TLI was 5.00 ± 3.98, 4.81 ± 3.97 and 4.44 ± 3.34 ($p = 0.642$); no patients had immunisation after the switch; IBDQ was 182.61 ± 28 at W0 and 175 ± 34 for at W16 ($p = 0.494$). The evaluation on the knowledge of biosimilars at W0 showed that 77% of patients had never heard about it, 85% were in favour of the switch and 61% expressed fears about their use. At Week 16, the same evaluation showed that 84% of patients said they knew about biosimilars, 93% were in favour of the switch and 39% were still concerned about their use.

Conclusions: This study confirms the safety of switching infliximab by CT-P13 and demonstrates for the first time that PE plays a key role in switch acceptance by patients.

P545

Elderly patients with inflammatory bowel disease (IBD) are less likely to persist on anti-TNF therapy compared with younger patients: data from the Sicilian Network for Inflammatory Bowel Diseases (SN-IBD)

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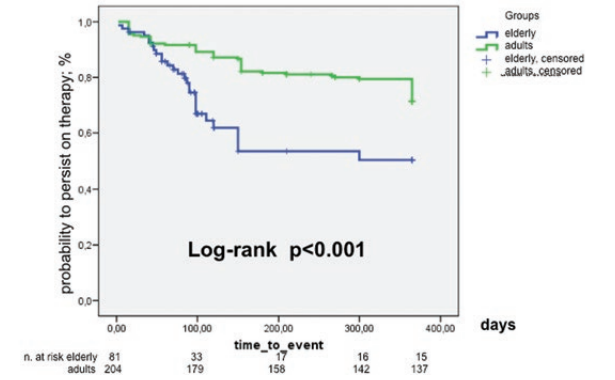
Background: Elderly patients with IBD are frequently difficult to treat because they are at increased risk for severe adverse events when treated with immunomodulators or anti-TNF therapies. Moreover, little is known about their response to biological treatments. The aim of this study was to compare persistence on therapy during the first course on anti-TNF treatments in IBD patients over 60 years of age with that of younger IBD patients.

Methods: Data of consecutive IBD patients > 60 years of age at their first course of anti-TNF treatment from January 2013 to June 2018 were extracted from the cohort of the SN-IBD and compared with patients ≤ 60 years of age. Information on gender, type, duration and extension of disease, and familiarity were analysed.

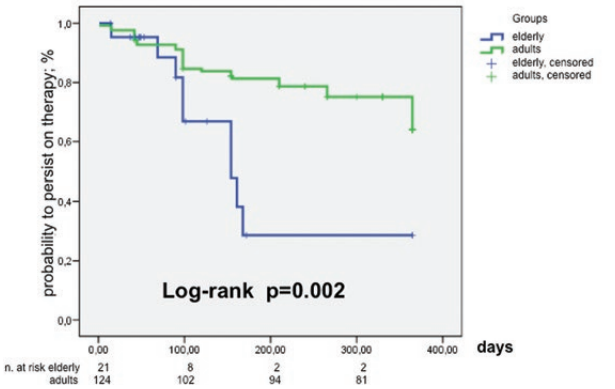
Results: Eighty-one patients with Crohn's disease (CD; M = 43) (median age 64 (range 61–80) years) and 43 patients with ulcerative colitis (UC; M = 29) (median age 65 (61–77) years) were included and compared with 204 patients (M = 119) with CD (median age 39 (18–59) years) and 143 with UC (M = 77) (median age 40 (18–59) years). Persistence on therapy was significantly higher (log-rank $p <$ 0.0001) in younger CD patients for every kind of anti-TNF therapy (Figure 1)

Persistence in therapy with anti-TNF (i.v. + s.c.) in Crohn's disease



persistence on therapy with anti-TNF (i.v.+s.c.) in Crohn's disease. as well as in younger UC patients on i.v. anti-TNF therapy (p = 0.002) (Figure 2).

Persistence in therapy with i.v. anti-TNF in ulcerative colitis



Persistence on therapy with i.v. anti-TNF in ulcerative colitis.

On univariate regression analysis, persistence was significantly associated with younger age ($p <$ 0.0001) in CD and with younger age (p = 0.004) and with i.v. vs. s.c. administration (p = 0.02) in UC. Duration of disease, gender, or type of disease were not associated with persistence. While primary failure to therapy was not statistically significant (3.7 vs. 6.2%), loss of response ($p <$ 0.001) and adverse events (p = 0.005) were more frequent in the elderly (LOR 21% vs. 7%, AE 27 vs. 14%; elderly vs. adults,, respectively)

Conclusions: in this large cohort of anti-TNF naïve elderly patients we showed for the first time that elderly patients with CD or UC were significantly less likely to persist on therapy within the first 12 months of treatment. The only predictor for treatment persistence was a younger age for CD and a younger age and the use of i.v. anti-TNF agents in UC.

P546

Therapeutic drug monitoring of vedolizumab in inflammatory bowel disease

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Background: Clinical utility of infliximab and adalimumab therapeutic drug monitoring (TDM) is unquestionable. However, little is known on the clinical utility of TDM-guided patient management for vedolizumab (VDZ) in inflammatory bowel disease (IBD), and more studies are needed to understand the correlation between VDZ trough levels (VTL) and clinical response, and to establish solid cut-off therapeutic levels of VDZ.

Methods: A prospective cross-sectional observational study is ongoing at La Paz University Hospital (Madrid, Spain) to explore the correlation between VTL and loss of clinical response in IBD patients treated with VDZ. Trough serum samples were collected from 21 IBD patients at baseline and during the course of treatment from 4 months to 2 years. VTL and anti-VDZ antibodies were measured with Promonitor®-VDZ and Promonitor® Anti-VDZ tests (Progenika, a Grifols company, Spain), based on ELISA technology, respectively. All statistical analysis performed used a non-parametric approach (JMP software 14.0).

Results: Here we report preliminary results for 21 patients (66.7% CD and 33.3% UC) recruited so far. VDZ was administered every 4 weeks (n = 3) and 8 weeks (n = 18). VTL measurement was performed at baseline (3.8%), induction therapy (28.2%) and maintenance therapy (67.9%) in 101 samples. None of the patients developed antibodies against VDZ. Median VTL was 9.1 µg/ml (range, 0–72.3). The median VTL during induction was significantly higher 32.4 µg/ml (IQR: 13.8, 43.1) vs. 8.2 µg/ml (IQR: 6.3, 16.2) during maintenance ($p <$ 0.0001), therefore, all analyses accounted for this effect. Median VTL was higher in patients who received VDZ every 4 vs. 8 weeks (11.9 µg/ml vs. 8.0 µg/ml, respectively; p = 0.182). Significant inverse correlations between CRP and VTLs, and between VTL and platelets were observed during maintenance (Spearman Rho –0.27, p = 0.03; Spearman Rho –0.40, $p <$ 0.001, respectively). A high statistically significant inverse correlation between VTLs and GOT/GPT was noted in the UC group (Spearman Rho –0.79; $p <$ 0.0001). There were no significant differences between median VTLs and the rest of analytical variables tested (haemoglobin, leucocytes, albumin, ESR and creatinine).

Conclusions: VTL are in line with those reported in other studies. Low CRP and platelets which are related with less disease are significantly associated with higher VTL.

P547

Distribution of mesenteric macrophage polarisation: a guide for surgical resections in Crohn's disease?

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Background: Mesenteric involvement in Crohn's disease (CD) has been suggested as a potential factor in post-surgical disease recurrence. Although surgical guidelines recommend a limited ileocaecal resection for CD, preliminary data suggest a benefit of resecting more mesentery. Aberrancies in macrophage polarisation in the mesorectum are found to be related to post-operative complications after proctectomy for Crohn's colitis, with improved outcomes after mesorectal excision. Trials are currently evaluating wide mesenteric excision vs. sparing of the mesentery for ileocaecal resections. The aim of this study was to assess the distribution of mesenteric macrophages in Crohn's disease as a potential guide for mesenteric excision in rectal and ileocaecal resections.
Methods: In 39 CD patients and 5 non-IBD controls undergoing ileocaecal resection, three mesenteric tissue samples were obtained: adjacent to the inflamed terminal ileum (creeping fat), adjacent to the non-inflamed ileal resection margin, and centrally along the ileocolic artery (where a wide mesenteric resection would end). In 10 CD patients undergoing proctectomy for therapy-refractory perianal fistulas and in 5 controls with ulcerative colitis, mesenteric tissue specimens were also sampled at three locations: distal (rectum), mid, and proximal (sigmoid) (Figure 1). Tissue specimens were cultured for 48 h and analysed by flow cytometry. The primary outcome was the ratio between regulatory (CD206+) and pro-inflammatory macrophages (CD206-).
Results: In the mesorectum an unfavourable ratio of CD206 expression (predominantly pro-inflammatory macrophages) was observed at the distal site, with an increased presence of regulatory macrophages towards the proximal sigmoid. No such gradient was found in the control group. In contrast, in the ileo-colic mesentery close to the affected small bowel, a favourable ratio of CD206 comparable to that of the control group was found. This gradient became more unfavourable towards the central mesentery. In a subset of patients with L3 (ileo-colic) disease, predominance of pro-inflammatory macrophages was found throughout the ileo-colic mesentery.

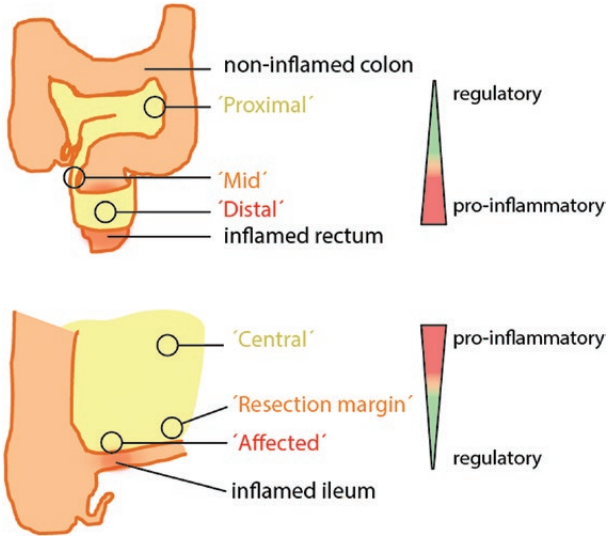

Figure 1. Diagram of sample locations. Gradients on the right represent macrophage polarisation in relation to anatomic location (red, pro-inflammatory; green, regulatory).

Conclusions: These data indicate that not all parts of the mesentery are affected equally in CD patients. The gradually increasing presence of pro-inflammatory macrophages towards the central ileo-colic mesentery does not support the rationale to perform an extensive mesenteric excision in ileocaecal resections in Crohn's disease patients.

P548

Vedolizumab clinical decision support tool predicts hospitalisation, surgery, and healthcare resource utilisation

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Background: A clinical decision support tool (CDST) has been developed and validated to predict clinical and endoscopic remission with vedolizumab (VDZ) in Crohn's disease (CD).[1] We assessed whether this CDST could be applied in real-world settings using retrospective claims database to predict differences in CD-related hospitalisation, surgery, and other healthcare resource utilisation.
Methods: The Truven MarketScan Database was used to identify CD patients treated with VDZ after 1 May 2014. Patients were stratified into low or high probability of VDZ response based on the previously validated CDST. Rates of CD-related hospitalisation and surgery, rates of other healthcare resource utilisation, and related costs (hospitalisation, surgery, emergency department (ED) visit, office visit, endoscopy, imaging, and laboratory tests) were compared between the low and high probability of VDZ response groups for the 12 months after VDZ initiation.
Results: A total of 1445 CD patients (n = 935 high probability, n = 510 low probability) were included (mean age, 43.4 years; 57.2% female). A significantly lower proportion of the high-probability group experienced a CD-related hospitalisation (14.4% vs. 19.6%, $p = 0.011$) or CD-related surgery (13.5% vs. 23.3%, $p < 0.001$) during the 12 months after VDZ initiation. The high-probability group had significantly lower non-drug-related healthcare expenditure costs during the 12 months after VDZ initiation (mean $8842 vs. $14 591, $p < 0.001$), which was driven by the lower costs incurred for CD-related hospitalisation and surgery. No significant difference was observed between the low- and high-probability groups for rate of ED visits, endoscopy, imaging, or laboratory tests.
Conclusions: The VDZ CD CDST can stratify probability of CD-related hospitalisation and surgery, and we observed a significant difference in non-drug–related healthcare cost between the high and low probability of VDZ response groups. Further studies are needed to assess whether up-front stratification of CD patients with this tool could optimise the cost-effectiveness of VDZ utilisation.

Reference

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P549

Vitamin D deficiency as a part of extraintestinal manifestations in IBD Patients: a single-centre experience

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Background: Vitamin D deficiency is more common in inflammatory bowel disease (IBD) patients than it is in the general population. The aim of this study was to evaluate the vitamin D serum levels in IBD patients as a part of the extraintestinal manifestations (EIMs) and to correlate the prevalence of hypovitaminosis D with existence of other EIMs.
Methods: The Vitamin D (25 OH D) status was measured in 94 IBD patients, 54 with CD and 40 with UC. 25(OH) D serum concentrations were measured by a commercial paramagnetic particle chemiluminescent immunoassay for the quantitative determination of total 25-hydroxyvitamin D [25(OH) vitamin D] levels. Vitamin D deficiency is defined as a serum level of 25OHD <50 nmol/l, and a serum level >50 nmol/l <75 nmol/l is classified as vitamin D insufficiency. The clinical course and the occurrence of EIMs were monitored. All Patients were classified according to the Montreal classification. CD activity was assessed using the BEST index (CDAI - Crohn Disease Activity Index) and the partial Mayo score was used to determine UC activity.
Results: Across all patients the mean serum 25(OH) D level was 44.47 ± 18.14 (nmol/l). Almost 95% of IBD patients have Vitamin D insufficiency and deficiency, respectively CD- 96.29% (*n* = 52), UC 92.50% (*n* = 37), as Vitamin D serum levels < 50 nmol/l were detected in 61 (64.89%) of IBD patients - 66.66%(*n* = 36) for CD and 62.50% (*n* = 25) for UC. There was no significant difference between mean 25(OH) D levels in both diseases (*p* = 0.604). In 89% (*n* = 84) of IBD patients there was a presence of EIMs, in 96.42% (*n* = 81) of these patients there were low Vitamin D serum concentrations, respectively, CD 59.25% (*n* = 48) and UC 40.74% (*n* = 33). In IBD patients with EIMs the mean 25(OH) D levels were significantly lower (42.67 ± 17.29 vs. 59.58 ± 18.94) (⊠ = 0.005). We found a significant difference between measured mean 25(OH) D concentrations in UC patients and EIMs presence (43.02 ± 17.38 vs. 63.70 ± 18.48) (p= 0.018), while in CD patients there is not a significant difference (p=0.122). The most common EIMs among our IBD patients are: iron deficiency without anaemia - 39.40% (*n* = 37), liver steatosis – 38.30% (*n* = 36), IBD associated arthropathy (IBDAA) - 33% (*n* = 31), followed by: Vitamin B 12 deficiency without anaemia, latent iron deficiency, ocular manifestations and primary sclerosing cholangitis (PSC). All IBD Patients with Iron and Vitamin B12 deficiency anaemia, latent Vitamin B12 deficiency and malabsorption syndrome have low 25(OH) D serum levels.
Conclusions: Over 96% of patients with the EIMs also have a low Vitamin D serum levels. This correlation leads to the need for systematic monitoring of 25-hydroxyvitamin D levels during the course, follow-up and treatment of IBD

P550

Anti-mycobacterium paratuberculous therapy in Crohn's disease: outcomes from tertiary IBD referral centres

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Background: Mycobacterium avium paratuberculosis (MAP), an obligate intracellular pathogen, has long been proposed as an aetiological factor in Crohn's disease. Prolonged, combination antibiotic therapy has shown beneficial effect in the induction and maintenance of remission in a small number of studies but was not replicated in an RCT.[1] However, the evidence remains conflicting, particularly with criticisms on experimental design and subtherapeutic antibiotic dosing in the latter. We report the outcomes of this therapeutic option in a selected cohort of patients at our institutions.
Methods: A retrospective study was conducted by examining the records of adult patients commenced on anti-MAP therapy (AMT) at both Guy's and St. Thomas' Hospitals and London Bridge Hospital, between February 2011 to December 2017. Treatment regimens were slightly varied but standard therapy was clarithromycin 750 mg OD, rifabutin 450 mg OD and clofazimine 100 mg OD. Hospital notes were used to capture demographic data, disease characteristics and therapy details including indications and duration of therapy. Objective measures of response included at least one of; reduction in CRP or faecal calprotectin, improvement in endoscopic or radiological appearances. Statistical analysis was performed using GraphPad Prism.
Results: In total, 62 patients were prescribed AMT over the study period, 21 were excluded due to insufficient outcome data. 21/41 (51%) were male and median age was 28 (range 18–63) at the time of commencing therapy. The cohort had moderate to severe Crohn's disease with 26 (63%) having stricturing or penetrating disease and 18 (44%) with previous surgery. Thirty-one (76%) had previously received biologic therapy. AMT was commenced in 26 (63%) patients due to failure of conventional therapy, 3 (7%) in patients where conventional therapy was not appropriate and the remaining due to patient preference. AMT was well tolerated with only 5 (12%) patients stopping therapy due to adverse effects. Nineteen patients (46%) demonstrated at least partial benefit, corroborated by objective evidence in 13/19 (68%). Response was not associated with disease phenotype and duration, previous therapy or use of clofazimine. Those patients who responded had a longer duration of therapy (median 24 months compared with 14 months; *p* = 0.04) than patients who did not respond.
Conclusions: Our study demonstrates that in a cohort of patients in which the majority failed conventional treatment, AMT was well tolerated and a response was seen in 46%. Patients who responded were on AMT a median 24 months which supports the current recommendation of a 24-month duration of treatment. Limitations include a small, heterogenous cohort of patients.

Reference

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P551

Use of preoperative total parenteral nutrition is associated with clinical and laboratory remission in severe active Crohn's disease

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Background: Crohn's disease (CD) patients with active penetrating and stricturing disease have a high prevalence of malnutrition that has been shown to increase post-operative complications. The effect of 1–3 months of pre-operative exclusive total parental nutrition (TPN) in active CD patients is not well established. We investigated the efficacy of exclusive TPN in active CD patients.
Methods: From our IBD Centre database (prospectively collected data) we identified all patients with complicated, active CD who were candidates for bowel resection between January 2016 and October 2018. CD location and activity were recorded based on the modified Montreal classification. Inclusion required exclusive preoperative home TPN without additional oral intake for the 1–3 months prior to surgery. The Harvey–Bradshaw Index (HBI), body mass index (BMI), C-reactive protein (CRP) and albumin levels were recorded at baseline and at the end of TPN therapy.
Results: Seventeen pre-operative CD patients (58.8% male, 41.2% female) on exclusive TPN were identified. The mean age of the cohort was 31.5 ± 11.8 years with median disease duration of 8 years (IQR 3–12). Mean duration of pre-operative TPN treatment was 69 days (range 24–110). Most patients had ileocolonic (35.3%) or terminal ileal CD (23.5%), and the stricturing and/or stenotic (B2) phenotype (94.1%) was the most common. During TPN treatment, 70.6% were on stable doses of medication (immunomodulators and/or biologics) and 29.4% had no medical treatment. All 17 patients had significant clinical improvement in all disease activity indices at the end of pre-operative TPN (baseline vs. post TPN): HBI 16.3 ± 7 vs. 6.1 ± 6.1 (p = 0.001); BMI 19.7 ± 3.3 vs. 20.8 ± 3.2 (p = 0.017); CRP 58.5 (IQR 33–149) vs. 12.5 (IQR 6–30) (p = 0.001); and albumin 2.8 ± 0.6 vs. 3.7 ± 0.5 (p = 0.001). Two patients (11.7%) no longer required bowel resections after completion of exclusive TPN.
Conclusions: Exclusive pre-operative TPN was associated with weight gain, decreased inflammatory biomarkers, and improved clinical disease activity markers and nutrition. While these initial results are encouraging, additional studies are needed before a recommendation can be made regarding longer duration of exclusive pre-operative TPN for severe, refractory CD to decrease disease activity and improve nutritional status before elective surgery.

P552

Gastroenterologists' perceptions on use of medical cannabis for IBD

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Background: The use of medical cannabis (MC) for numerous medical indications is expanding. Current evidence does not support the efficacy of MC for reducing inflammation in IBD patients. Even so, many gastroenterologists encounter the issue of recommending use of MC to IBD patients.
Methods: A computerised survey was conducted to 250 gastroenterologists in Israel. 84 (34%) physicians completed the questionnaire.
Results: Out of 84 physicians whom completed the questionnaire, 59 (70%) were male, 34 (40%) were under age 50, 71 (85%) were adult gastroenterologists, and 53 (63%) work mainly in a hospital. Forty-four per cent, 41% and 15% of physicians think that MC is very effective, mildly effective and not effective at all, respectively. Physicians will commonly, rarely and never recommend MC in 42%, 35% and 22%, respectively. Older physicians (above age 50) were significantly more likely to have a positive attitude towards MC in both questions, p = 0.003, p = 0.004. Despite clear recommendations stated by the Israeli Gastroenterological Association, 48% of physicians did not know the initial dose recommended for MC. Fifty-two (62%) physicians say that at least 60% of their prescriptions were to patients already using unauthorised cannabis, and only 10 (12%) initiate MC as opposed to 88% who prescribe MC due to the patients request. Female gastroenterologists were significantly more likely to initiate MC, p = 0.007. When asked if you would continue prescribing MC as long as the patient requests or when the patient is in mucosal remission, 35% and 20% would continue, 38% and 31% would consider and 27% and 49% would stop prescribing MC, respectively. When presented with a clinical scenario of a patient in deep remission, and requests to increase the dose, 32% would increase the dose, 49% would maintain the dose, and only 18% would stop prescribing MC altogether. In one tertiary Israeli medical centre, ninety-one patients are currently receiving MC. 85% of patients have Crohn's disease, and the others ulcerative colitis and IBD-U. Fifty-eight per cent of patients are between ages 20–40, and 2 patients over the age of 70 are currently receiving MC. In the younger age groups, 20–30 and 30–40, smoking is the most popular way of administration as opposed to oil in the older age group (above age 50).
Conclusions: The use of MC for IBD patients is encountered by many IBD physicians. Different doctors hold completely different attitudes regarding this treatment. Age above 50 and female physicians generally had a more positive attitude towards the use of MC. Guidelines and clear recommendations are needed.

P553

Efficacy, safety and cost-efficiency of adalimumab 80 mg every other week in previously intensified IBD patients under treatment with adalimumab 40 mg every week

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Background: Dose escalation is often recommended for loss of response in patients with inflammatory bowel disease (IBD) under maintenance treatment with anti-TNF, but in normal conditions this strategy considerably increases the cost. A new presentation of Adalimumab (ADA) 80 mg has been approved in our hospital with the same price per unit as the ADA 40 mg presentation. The aim of this study was to evaluate the efficacy, safety and cost-efficiency of ADA 80 mg every other week (eow) in IBD patients under previously intensified treatment with ADA 40 mg every week.
Methods: A prospective and observational study was performed. Inclusion criteria were all IBD patients under intensified maintenance therapy with ADA 40 mg every week. Physicians informed all patients the reasons (cost and convenience) for changing to a ADA 80 mg eow dose and asked for their consent. So far we have evaluated a period of 1 month, although the complete follow-up period will be 12 months. The Harvey–Bradshaw index (HBI ≤4) and the Mayo partial index (Mayo partial index ≤2) were used to evaluate clinical remission in Crohn's disease (CD) and ulcerative colitis (UC)

patients, respectively. Adverse events were monitored. Faecal calprotectin (FC) and C reactive protein (CRP) were collected at baseline (week 0, before first dose of subcutaneous injection of ADA 80 mg) and after 1 month. Biological remission was defined as clinical remission and FC < 250 μg/g and CRP < 5 mg/dl. A descriptive analysis was performed and data are shown as percentage, median and range. Cost efficiency analysis was also performed.

Results: We offered to 18 consecutive IBD patients the possibility of participating in the study, but only 16 agreed to participate. We included 15 CD and 1 extensive UC with a median age of 40. 56.3% were male, 37.5% non-smokers and 31.3% ex-smokers. In CD, 46.7% had ileal disease, 13.3% colonic disease and 40% ileocolonic disease. 46.7% CD patients presented fistulising behaviour. At baseline, 86.7% of patients were in clinical remission and 92.3% were in clinical remission after 1 month. Median FC concentration at inclusion was 210 (range 6–1900) and 1 month later 91 (range 10–3754). Median CRP concentration at inclusion was 0.14 (range 0–19) and 0.21 (range 0.01–2.94) at month 1. 60% of patients at month 0 and 53.3% at month 1 were in biological remission. No adverse events were registered. After 1 month in total we had saved more than 13.000 euros and if all patients complete 1 year of treatment we predict savings of more than 150.000 euros with our new schedule of treatment.

Conclusions: Changing to a single dose ADA 80 mg eow is an efficacy, safety and cost-efficient strategy in IBD patients under intensified maintenance therapy with ADA 40 mg every week.

P554

Point of Care detection of anti-infliximab antibodies in inflammatory bowel disease patients treated with the biosimilar SB2: performance comparison with ELISA

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Background: Promonitor® Quick ANTI-IFX is the only rapid test available for Point of Care (POC) testing of anti-infliximab (IFX) antibodies. The qualitative test is based on Lateral Flow (LF) technology to detect free antibodies to any IFX in human whole blood (capillary or venous), serum or plasma. Detection of anti-Remicade® and anti-Inflectra® (CT-P13) antibodies was previously shown to be equivalent in the capillary (finger prick whole blood) and systemic circulations (regular serum collected by venipuncture for therapeutic drug monitoring (TDM). However, detection of antibodies to Flixabi® biosimilar (SB2, Biogen) had only been proved by ELISA and data were lacking in a LF format. In this study, we compare the performance of the POC LF test to detect anti-Flixabi antibodies with the standard ELISA technique for TDM in IBD patients treated with Flixabi.

Methods: Trough (n = 202) sera collected at the Erlangen University Hospital (Germany) were analysed, corresponding to 76 IBD patients (46 Crohn's disease, 26 ulcerative colitis and 4 indeterminate colitis) treated with Flixabi only. Samples were frozen for subsequent testing with ELISA (Promonitor® ANTI-IFX, Progenika, Spain) and with the POC test (Promonitor Quick® ANTI-IFX, Progenika, Spain). The LF test uses the same format as the bridging ELISA. The POC test (LoD=23 AU/ml) results were read visually at 30 min after adding 15 μl of serum, whereas ELISA (LoD=5 AU/ml) quantitative results were categorised as positive or negative to allow comparisons with the POC test.

Results: The rapid test correctly detected anti-Flixabi antibodies and showed an almost perfect agreement with the reference ELISA method. 124 out of 202 samples were tested positive for anti-IFX antibodies with the POC test, whereas 144 samples were positive with the ELISA. Positive and negative per cent agreements between ELISA and the POC test were 86.1% and 100%, respectively. Fourteen (70%) out of the 20 discrepancies found were due to anti-Flixabi antibody concentration below the LoD of the POC test. Positive and negative agreements were 95.4% and 100%, respectively (124 LF-positive and 130 ELISA-positive sera) within the common measurement ranges of both techniques. The remaining 6 discrepancies (positive with ELISA and negative with LF) corresponded to samples of 2 patients who were confirmed as true positives by radioimmunoassay.

Conclusions: The strong agreement reported here between the Promonitor® Quick ANTI-IFX POC LF test and the standard ELISA method reinforces that the rapid test is suitable for TDM of any IFX drug.

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Deep remission and mucosal healing in IBD patients under immunosuppression with azathioprine and 6-mercaptopurine

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Background: Mucosal healing and deep remission (DR) are therapeutic targets in inflammatory bowel disease (IBD). We aimed to characterise DR in patients with Crohn's Disease (CD) and ulcerative colitis (UC) under monotherapy with immunomodulators.

Methods: Out of a total of 432 patients observed in 2017–2018, 45 were under azathioprine or 6-mercaptopurine monotherapy for a period ≥3–6 months. Patients who underwent surgery, patients previously treated with anti-TNF and patients who started anti-TNF were excluded. DR was defined by: clinical remission (CR) in patients without endoscopically documented ulcers / erosions. Imaging activity was also evaluated in patients with CD.

Results: Mean age was 37.9 ± 12.4 years and 53.3% were men. Of the 45 studied patients, 33 had CD (76.8%) and 12 UC (23.2%). In the group with CD Montreal Classification was evaluated (A2–90.9%, L1–39.4%, B1–78.8%), and in this group the prevalence of perianal disease and penetrating phenotype was 27.3% and 12.1%, respectively. In UC 75.0% had extensive colitis-E3. The mean age of diagnosis was 28.9 ± 11.0 years and the mean duration of the disease was 8.9 ± 6.8 years. The majority of patients were under azathioprine (93.3%). Mean duration of treatment was 5.15 ± 3.98 years. CR was obtained in 37 patients (CD-89.7%, CU-66.7%) and DR in 25 (DC-57.6%, CU-50.0%). Age of diagnosis, early-onset and duration of immunomodulatory treatment were not associated with DR. In CD, ileal disease, penetrating phenotype, and perianal disease showed no significant association with DR. The need for topical/oral corticosteroids after initiation of treatment was significantly associated with lower mucosal healing rates (p = 0.033).

Conclusions: Despite the high rate of clinical remission under immunomodulator in monotherapy, about half of the patients did not achieved deep remission. The need for corticoid was associated with a lower probability of mucosal healing.

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The prevalence of metabolic bone disease in patients with IBD- preliminary results from POLIBD study

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Background: The most common bone metabolic diseases in IBD patients are osteopenia and osteoporosis. The more rare ones are osteomalacia and avascular necrosis. There are many mechanisms underlying the poor metabolic state of the bones in these patients. The occurrence of osteopenia and osteoporosis in this group of patients differs depending on the study population with values ranging in case of osteopenia from 22 to 77 per cent and osteoporosis from 17 to 41%. Authors decided to analize the occurance of osteoporosis and osteopenia in patients hospitalised in our Clinic from 2016 to 2018.
Methods: We measured bone mineral density (BMD) of patients with IBD with dual- energy-X-ray-absorptiometry (DEXA scans). We divided the patients into 2 groups: the first one with ulcerative colitis (UC -29 patients, 19 women, 10 men) and the second one with Crohn's disease (CD - 55 patients, 30 women, 25 men). Both groups were subdivided depending on age - under 30 years old (we measured T-score for this group) and over 30 years old. (We measured Z- score for this group.)
Results: In the group of UC patients the mean T-score for 11 patients under 30 years old was 0.7363, –0.856 for women, –0.2 for men. Osteopenia occurred in four young women and no ostepenia was diagnosed among men. There was no osteoporosis in UC patients under 30. In the group of UC patients over 30 years old (18 patients, 10 women, 8 men) the mean Z-score was –1.07, –0.48 for women, –1.825 for men. Osteopenia was observed in 2 women and 5 men, osteoporosis in 4 men. In the group of CD patients the mean T-score for 28 patients under 30 years old was 0.844, –0.65 for women, –1.087 for men. Osteopenia occurred in 8 young women and 2 young men. There was one case of osteoporosis in CD patients under 30. In the group of CD patients over 30 years old (27 patients, 15 women, 12 men) the mean Z-score was –0.641, –0.73 for women, –0.514 for men. Osteopenia was observed in 2 women and 8 men. There was no osteoporosis in this group of patients.
Conclusions: The highest prevalence of osteopenia in young group of patients was observed in 4!4% women with UC, and in 53% women with CD. No osteoporosis was observed there.
In the older group of patients with IBD (over 30 years old) the highest risk of metabolic bone diseases - both osteopenia and osteoporosis - was in men's group with UC - 62.5% had osteopenia and 25% had osteporosis. Men over 30 years old with UC are at the highest risk of developing metabolic bone diseases in the IBD patients.

P557

Sustained remission in inflammatory bowel disease patients after discontinuing infliximab; the ongoing reluctance to stop biologics

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Background: Biologic therapy, including infliximab is the current gold standard treatment of both Crohn's disease (CD) and ulcerative colitis (UC). Long-term treatment is associated with adverse effects and significant healthcare budget burden. Previous studies into the discontinuation of biologic treatment for patients in clinical remission have shown 40–49% relapse rates by 24 month follow-up. The aim of this study was to critically evaluate the clinical/biomarker/financial outcome of biologic discontinuation in IBD patients from 2006 to 2018.
Methods: A single-centre retrospective analysis of all patients discontinuing infliximab treatment due to disease remission defined by clinical, endoscopic and biomarkers (C-reactive Protein or Faecal Calprotectin) response. The mean length of infliximab received before discontinuation was 38.5 months. Data were gathered on patients' biomarkers, endoscopy scores and clinical status at baseline, 3, 6, 12, and 24 months. Combination drug therapies and changes in medications were documented and a cost analysis performed.
Results: The study identified 30 patients discontinuing infliximab due to disease sustained remission. Data on 22/30 patients were available at 24 months, 91% (20/22) remained in clinical remission. Of the original cohort, 13.3% (4/30) patients had relapsed, resulting in restarting biologic treatment. Of the relapse patients, 75% had CD, 25% UC. After discontinuation 50% (n = 2) took no other medications for IBD. Cost analysis showed €379 351.56 per annum saving from discontinuation of infliximab.
Conclusions: This study showed low relapse rates compared with other studies. Demographics were similar in relapse patients vs. the sustained remission cohort. Discontinuation of infliximab for patients in remission was safe and offered substantial savings to the healthcare budget.

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Iterative ileocolonic resection for Crohn's disease: a prospective multi-centric cohort study of the GETAID Chirurgie

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Background: Iterative ileo-colic resection (IICR) for Crohn's disease is often required for patients. Previous retrospective studies highlighted an increased overall and surgical morbidity. However, large recent data are lacking on this frequent situation. The aim of this study was to compare perioperative characteristics and results between primary ileo-colonic resection (PICR) and IICR for Crohn's disease in a prospective multi- centric cohort.

Methods: From 2013 to 2015, 567 patients undergoing ileocolonic resection were prospectively included in 19 centres of the GETAID chirurgical. Perioperative characteristics and postoperative results of both groups (431 PICR, 136 IICR) were compared. Uni- and multivariate analyses of the risk factors of overall 30-days postoperative morbidity was carried out in the IICR group.

Results: IICR patients were less malnourished (27.2% vs. 39.9%, p = 0.007), with more stricturing phenotype (69.1% vs. 54.3% p = 0.003) and were older (11% > 65 years vs. 4.2%, p = 0.03). Preoperative treatment (steroids, anti-TNF) were not different between the two groups (p = 0.514). Laparoscopic approach was less frequently used for IICR (45.6% vs. 84.5%, p < 0.01) with an increased conversion rates (27.4% vs. 14.6%, p < 0.01). Operating time was significantly longer for IICR (155.9 vs. 138.9 min, p = 0.02). IICR patients presented less internal fistula (25% vs. 37.6%, p = 0.007), without differences in stoma rates (17.6% vs. 21.8%). Overall postoperative morbidity was 29.1%, increased in the IICR group (36.8% vs. 26.7%, p = 0.024), with more ileus (11.8% vs. 3.7%, p < 0.001), without difference in anastomotic leakage (AL) rate (8.8% vs. 8.4%) or prolonged length of stay (LOS) (IICR: 9.30 days ± 6.9 vs. PICR: 10.2 days ± 23.0, p = 0.499). Uni-and multi-variate analyses did not identify specific risk factors of overall postoperative morbidity in the IICR group and anti-TNF treatment was not associated with increased morbidity (41.3 vs. 40.2%, p = 0.460). After PRIC the post-operative outcomes were not modified by the number of surgical procedures (second (n = 97) vs. third or more (n = 39): conversion (p = 0.568), overall morbidity (p = 0.513) or intra-abdominal septic complication (p = 0.087).

Conclusions: IICR is more technically challenging but half of patients can be operated through a laparoscopic approach. Increased morbidity is linked to post-operative ileus. Anastomotic leakage and intra-abdominal sceptic complications are not different. Iterative ileo-colic resection should not be considered as a factor in favour of stoma creation.

P559

Real-life experience with long-term maintenance of golimumab in ulcerative colitis patients

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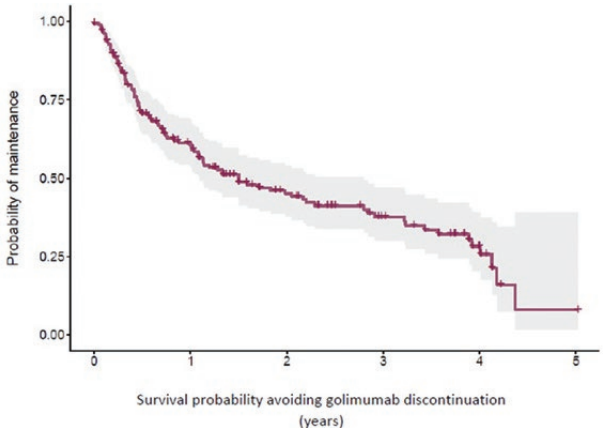
Background: PURSUIT trial demonstrated the long-term efficacy of golimumab (GLM) in ulcerative colitis (UC). However, the long-term maintenance and safety of GLM in clinical practice has not been evaluated.

Methods: The aim is to assess the probability of maintenance of GLM in UC in real-life and the possible factors associated to long-term maintenance. This multi-centre cohort study included consecutive patients with moderate-to-severe UC treated with golimumab induction doses and who had at least 12 months of follow-up. We recorded baseline demographics including prior or concomitant use of inmunosupressors (IS) or steroids (CE), prior exposure to anti-TNF, and reason of withdrawal of last anti-TNF. During follow-up we evaluated the cumulative probability of maintaining GLM, and the rates of hospitalisations, surgeries and adverse events (AE). Cox regression models were used to identify predictors of GLM discontinuation.

Results: A total of 193 patients were analysed (102 male (53%), 8 proctitis (4%), 75 (39%) left-sided UC and 110 (57%) extensive UC). Of all, 101 (53%) were anti-TNF naïve and 51 (27%) and 38 (20%) had previously received 1 and ≥2 anti-TNFs, respectively. The preceding anti-TNF was discontinued due to primary failure, secondary failure, AE, or other causes in 29%, 53%, 13% and 5% of patients, respectively. At baseline 187 patients (98%) received GLM induction doses of 200–100–100/50 mg at weeks 0-2-6. Subsequently, 101 patients (53%) and 87 patients (46%) started maintenance with 50 or 100 mg golimumab doses every 4 weeks, respectively. After a median follow-up of 43 months (IQR 11–66), GLM was discontinued in 108 (56%) patients due to primary failure in 63 (58%), secondary failure in 34 (32%) and AE in 11 (10%) patients. Eighty-two (43%) patients needed dose escalation during follow-up (median 20 months, (IQR 6–25). During follow-up 31 patients (16%) referred AE, 32 (16.5%) needed hospitalisation and 11 (6%) surgery. The survival probability of maintenance of GLM during follow-up is shown in Figure 1.

Figure 1. Cumulative probability of avoiding golimumab discontinuation during follow-up.



Multi-variate analysis retained shorter disease duration as a predictor of maintenance with GLM ($p = 0.008$). The number of previous anti-TNF drugs or the cause of withdrawal of these, the concomitant use of IS, and the disease extension were not associated with GLM maintenance.

Conclusions: After a median follow-up of 43 months 40% of patients with refractory UC patients maintained GLM. Shorter disease duration was predictive of persistence with GLM. Long-term GLM therapy was safe and achieved low rates of hospitalisations and surgeries.

P560

Multi-centric randomised study comparing interventional vs. non-interventional treatment for anal fistulas in patient with Crohn's disease and adalimumab treatment

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Background: Anal fistulas negatively impact prognostic in patients with Crohn's disease. Recommended initial treatment associates surgical drainage with seton insertion, and biotherapy to control luminal and anal disease activity. After this preliminary treatment, options concerning fistula tract treatment are still debated. Especially surgical tract closure efficacy has been rarely evaluated, and not always in patients under biotherapy.

Methods: In this prospective, multi-centric study, all patients with an anal fistula having responded to an initial treatment by drainage and seton insertion, plus adalimumab injections (ADA) were randomised between sole seton ablation or surgical closure of the tract by any technique (glue, flap, LIFT, etc.). Patients were included when local conditions indicated inflammatory remission (no abscess, minimal drainage) after at least a 3 month treatment with ADA, without active luminal disease. Main end-point was fistula closure at 12 months (Present criteria). Secondary end-points were ano-perineal symptoms PDAI score, quality of life IBDQ score, continence Wexner score, and perineal RMN evaluation at 6 and 12 months.

Results: Sixty-four patients (24M, 40F), mean age 36 years (19–63) have been randomised (31 sole seton ablation vs. 33 seton ablation plus surgical fistula tract closure). Fistulas were classified as simple and complex in respectively 16 (25%), and 48 patients (75%) (including 8 ano-vaginal).

At 3, 6, and 12 months, fistula healing was obtained in, respectively 56%, 59%, and 59% of the patients, without any significant difference between sole seton ablation or fistula closure. In patients with simple and complex fistulas rates were respectively. 69%, 80%, and 80%, and 51%, 52%, and 52% ($p = 0.035$ at 12 months between simple and complex fistulas), with no difference between the two arms in any category of fistulas.

Initial and 12 month mean PDAI score were 11 [9–20] and 6 [8–18] ($p < 0.0001$) after seton ablation, and 12 [7–21] and 8 [5–16] ($p < 0.0001$) after fistula closure, without any difference between the two arms. At 12 months RMN demonstrated no hyperfixation after gadolinium injection in 82% of the patients with a closed fistula, without any difference between the two arms. At 12 months Van Assche and Wexner scores were not different between the two arms. IBDQ did not change during follow-up and was not different between the two arms.

Conclusions: In patients with Crohn's disease and an anal fistula, having responded to initial treatment with surgical drainage and ADA injections, healing rates at 12 months were not different after closure of the fistula tract or simple seton ablation. Globally at 1 year under ADA treatment, healing rates for simple and complex anal fistulas were, respectively, 80% and 50%.

P561

Impact of ustekinumab TDM on clinical practice: a multi-centre, prospective, cross-sectional observational trial—mUST-Decide

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Background: Therapeutic drug monitoring (TDM) is an important part of the management of biologics used in the treatment of IBD. Current understanding of ustekinumab (UST) TDM is limited and its value in clinical practice is unknown. We hypothesised that addition of UST TDM to clinical practice would alter clinical decisions in the treatment of Crohn's disease (CD).

Methods: We enrolled 112 consecutive UST-treated CD patients across 11 sites in Canada from April 2017 to January 2018. HBI, CRP, baseline characteristics and clinical decisions were recorded for 110 subjects at the single study visit, faecal calprotectin (FCP) was performed (local lab, standard of care) and blood was drawn for TDM (Sanquin, UST RIA). TDM results were provided at the end of the study, and sites recorded a hypothetical clinical decision with UST TDM ± FCP. Congruency of the actual (D1) and hypothetical decisions (D2 (clinical + TDM), D3 (clinical +TDM and FCP)) were assessed using McNemars paired χ^2 test. A four- member expert panel examined all cases (3 experts/case) and made decisions by majority consensus – all D1 first, then all D2, then all D3. Experts were provided with additional training on UST PK data and interpretation, but decisions were not protocolised.

Results: Patients enrolled in the study were highly refractory (90% aTNF exposed, median 16.2 years of CD) but 70% were in clinical remission (HBI <5). At a population level, no differences could be detected before and after the introduction of TDM alone ($p = 1.0$), or TDM + FCP ($p = 0.86$). However, at a patient level, 39% of D2 decisions changed and 50% of D3 changed (see table). Examining the expert panel decisions at a population level, no differences could be detected before and after the introduction of TDM alone ($p = 0.16$), while decisions with TDM + FCP were significantly different ($p = 0.0006$). At the patient level with TDM alone, 23% of individual

decisions changed and 67% of decisions were different when incorporating TDM + FCP. No new safety signal was observed, no patient samples were positive for ADAb to UST.

Table. Summary of clinical decisions at a population and patient level.

	Site level				Expert Panel			
	Clinical decision (D1)	Clinical + UST TDM (D2)	Clinical decision (FCP group) (D1)	Clinical + UST TDM + FCP (D3)	Expert decision (ED1)	Expert + UST TDM (ED2)	Expert decision (FCP group) (ED1)	Expert + UST + FCP (ED3)
N =	110	110	72	72	110	110	72	72
Action	31 %	31 %	39 %	40 %	43 %	46 %	44 %	71 %
No Action	69 %	69 %[a]	61 %	60 %[b]	57 %	54 %[c]	56 %	29 %[d]
Action → no action		16 %		21 %		2 %		8 %
No action → action		16 %		22 %		6 %		35 %
Change of action		8 %		7 %		15 %		24%
Decisions changed		39 %		50 %		23 %		67 %
Decisions without agreement					4.5 %	8.2 %	4.2 %	5.5 %
p-values for McNemars: [a]p = 1.0 [b]p = 0.86 [c]p = 0.16 [d]p = 0.0006								

Conclusions: At a population level, introduction of UST TDM into routine clinical practice did not significantly impact clinical decisions for clinicians or experts, but adding FCP significantly altered clinical decisions for experts, but not clinicians. The divergence in impact of TDM and FCP between clinicians vs. experts highlights a need for greater education. Further study to clarify the use and impact of these tests in a proactive setting is warranted.

P562

Treatment of older inflammatory bowel disease patients; steroid use and escalation to steroid sparing therapy

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Background: Steroid therapy is essential in treatment of IBD. However, both prednisone and budesonide are not effective in maintaining remission and associated with systemic side effects. Therefore, more than one steroid course per year is a threshold for escalation to steroid-sparing therapy in all age groups. Nevertheless, medical treatment of older patients with IBD is often not optimised. The aim of this study was to assess steroid use and escalation rates in older IBD patients in an academic centre in the Netherlands.
Methods: Consecutive IBD patients (CD, UC and IBD-U) were included at the outpatient department of a university hospital. Disease activity was assessed through HBI or PMS (remission: HBI <5 or PMS <2), steroid use (oral prednisone and oral budesonide) was classified per year for the last 3 years (no steroid use, steroid use < 14 (1 course) or 15–52 weeks (more than one course)). Steroid sparing therapy was defined as the introduction or use of immunomodulators/biologicals. Adherence to treatment escalation guidelines (prednisone) and adjusted treatment escalation guidelines (prednisone and budesonide) was present when steroid sparing therapy was introduced after >1 course of steroids. Fisher exact test and binary logistic regression were used, a P value of <0.05 was considered statistically significant.
Results: 355 patients were included: 197 patients aged ≥65 years and 158 patients aged <65 years (mean age 70.82 (SD 4.59) vs. 40.85 (SD 13.36); 54.8% vs. 41.8% male (p = 0.019), 50.8% vs. 69.0% CD (p = 0.001); 76.7% vs. 76.0% remission (p = 0.899)). Older patients were less likely to receive steroids over the past 3 years (29.1% vs. 48.8%, p = 0.000) and to currently receive steroid sparing agents (36.0% vs. 65.6%, p = 0.000). No difference was observed in adherence to treatment escalation guidelines (87.5% vs. 100%, p = 0.444), but older patients were less likely to be treated according to adjusted treatment escalation guidelines (59.5% vs. 85.7%, p = 0.011). Age, corrected for sex and IBD type, was an independent predictor for non-adherence to adjusted treatment escalation guidelines (age category ≥70; OR 5.598, 95% CI 1.201–26.087).
Conclusions: IBD patients aged ≥65 years had a lower rate of both steroid and steroid sparing therapy use compared with younger patients. However, while remission rates did not differ between age groups, age was an independent predictor of non-adherence to adjusted treatment escalation guidelines: older patients were less likely to receive steroid sparing therapy after more than one course of oral prednisone or oral budesonide. Additional studies are necessary to determine the safest treatment regimen for this possibly frail population.

P563

Thiopurine adverse events in patients with inflammatory bowel disease in the UK: inflammatory bowel disease BioResource cohort

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Background: The Inflammatory Bowel Disease (IBD) BioResource is a research database recruiting patients with Crohn's disease (CD), ulcerative colitis (UC) or IBD type Unclassified (IBDU) from 83 hospitals UK-wide. In total, 17 470 subjects have been recruited to date. Data have been collected on disease phenotype, treatment, adverse events and treatment response.
Methods: **The aim of this study was** to describe the prevalence of adverse events related to thiopurine exposure among the IBD Bioresource cohort. A descriptive, retrospective analysis of the IBD BioResource database has been performed to determine the incidence of short- and long-term adverse events related to the use of thiopurines in the treatment of inflammatory bowel disease. All patients who have had exposure to thiopurine therapy (azathioprine or 6-mercaptopurine) were included.
Results: In total, 10 092 (57.8%) patients within the IBD BioResource cohort have had some exposure to thiopurine therapy during their disease course, either as monotherapy or in combination with anti-TNF. 9480 patients (94.0%) have been treated with azathioprine (AZA) and 2335 patients (23.1%) have been treated with 6-mercaptopurine (6MP). Of the 9480 patients who have been treated with azathioprine, 4167 patients (44.0%) remain on this therapy. 2369 patients (24.9%) ceased azathioprine due to adverse events. Of the 2335 patients, 1723 treated with 6MP had previously been treated with AZA and been intolerant. 684 patients (29.3%) ceased 6MP due to adverse events. 951 patients (40.7%) remained on 6MP at the time of recruitment to IBD Bioresource. The most commonly reported adverse events were nausea and vomiting (9.6%), followed by deranged liver function tests (5.1%), non-specified patient intolerance (2.4%), flu like symptoms (2.3%) and abdominal pain (2.3%). The incidence of clinically serious side effects was low. Pancreatitis was reported in 2.2% of patients; and leucopoenia (total WCC <3 or neutrophil count <2) was seen in 3.7%. 83 (0.8%) patients developed lymphoma after a mean of 2.89 years on thiopurine treatment 27 out of 83 were also on anti-TNF

Conclusions: Thiopurines are a safe treatment option for the management of inflammatory bowel disease. In this large national UK cohort, serious clinical adverse events related to thiopurine exposure were not common. Despite this low rate of serious adverse events, thiopurines were ceased due to side effects in 25.11% of patients.

P564

Significant reduction of admission time at the IBD infusion unit by an e-health pre-admission assessment and order system for intravenous therapy

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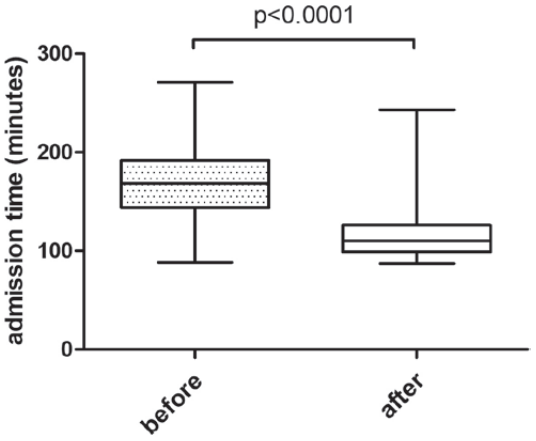
Background: The regularly administration of intravenous (IV) therapy negatively impacts on the work productivity and social functioning of patients with inflammatory bowel disease (IBD). The advent of new IV therapies leads to an increased workload at the IBD infusion unit and pharmacy, demanding a more efficient organisation. E-health tools may optimise patient time consumption and workflow at the IBD infusion unit and pharmacy. Our aim was to assess the feasibility, adoption and impact on time consumption of an automatic online pre-admission assessment and order system for patients with IBD.
Methods: We developed an online platform, directly linked to the electronic agenda of the IBD infusion unit, enabling a pre-admission order of IV therapy. This system sends an automated email to the patient the day before the admission. Using the secured link in this email, the patient is required to answer several red flag and open questions about their health status since the previous infusion. These answers are reviewed by the healthcare provider and, if approved, the IV therapy is ordered and prepared for subsequent administration at arrival on the infusion unit. All patients treated with IV therapy at the IBD clinic of our hospital were invited to participate in this program, which was GDPR (General Data Protection Regulation) approved. Time consumption was prospectively evaluated in patients with maintenance infliximab treatment (1 h infusion) before and after implementation in June 2018.
Results: In total 172 IBD patients (n = 77 male, n = 119/51 Crohn/ulcerative colitis, n = 112/60 infliximab/vedolizumab) were invited to the program, 150 (87%) of which accepted to participate and 22 (13%) declined. The most important reason to decline participation was the lack of email access, which can be attributed to the median age of this subgroup (median age 73 years (IQR 65–75) vs. 46 years (IQR 36–56); $p \leq 0.0001$). Inclusion rates were not influenced by gender, disease type or treatment duration. The effective adoption of the e-health system (number of IV therapies ordered online) increased from 42% in the first month to 59% in the fifth month. The use of the e-health system reduced the median admission time at the infusion unit significantly from 169 min (IQR 153–192) to 108 min (IQR 101–122) ($p < 0.0001$) in infliximab-treated patients (Figure 1).
Conclusions: The use of an e-health pre-admission assessment and order system for IV therapy in IBD is feasible, well adopted and leads to a significant reduction in admission time.

Figure 1 Admission time at the day clinic before and after implementation of e-health tool.



P565

Infliximab therapy intensification upon loss of response: what should be the cut-off for trough levels?

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Background: Loss of response (LOR) to infliximab occurs in approximately 30% of IBD patients. At time of LOR, lower infliximab trough levels (TL), in the absence of anti-drug antibodies (ATI), have been associated with the need for therapy escalation. TL of 3–7 μg/ml have been defined as a clinical therapeutic window. Nevertheless, few studies have examined the outcome of infliximab-therapy intensification based on TL and ATI. Hence, our aim was to evaluate the impact of TL on therapeutic efficacy of dose intensification in IBD patients experiencing LOR to infliximab in the absence of ATI.
Methods: This was a retrospective observational study of IBD patients receiving scheduled infliximab therapy at two tertiary centres between 2013–2017. Only patients who received infliximab dose intensification upon LOR after induction period were included. ATI positive patients were excluded. TL and clinical scores before therapy intensification and after 6, 12 months were obtained prospectively. The main outcome was clinical remission. Receiver-operating-characteristic-analysis was performed for TL using clinical remission as a classification variable.
Results: Forty-eight IBD patients (31, 64% Crohn's patients) were included in the study; 23 (49%), 29 (60%) reached clinical remission by 6, 12 months of scheduled infliximab therapy. TL below 4.8 μg/

ml before dose intensification were best associated with clinical remission, both at 6 (AUC=0.77, p = 0.0001, 91% sensitivity, 56% specificity) and 12 months (AUC=0.74, p = 0.001, 83% sensitivity, 53% specificity).

Conclusions: In IBD patients experiencing LOR to infliximab in the absence of ATI, infliximab dose intensification is significantly more effective when pre-escalation TL are below 4.8 µg/ml. Thus, dose escalation is probably unlikely to be successful when TL are above 4.8 µg/ml.

P566

The cost for IBD care during the first 5 years after diagnosis

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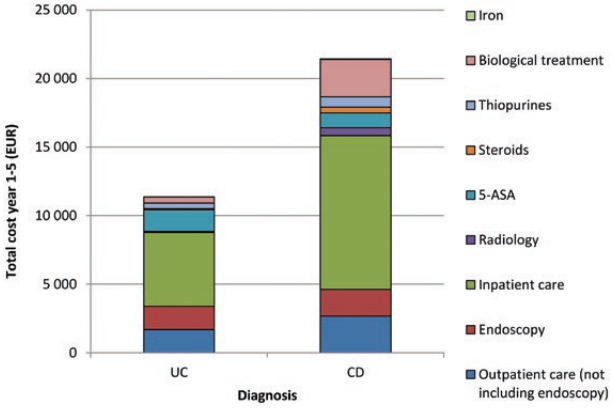
Background: Detailed studies regarding healthcare costs for IBD only exists for the first 2 years after diagnosis, when comparing contemporary treatment. Previous studies report that the first year tend to have very high costs, whereas the cost decreases rapidly the following years. The introduction of biological treatments has caused concern that this pattern will change. In combination with an increased incidence of IBD, this highlights important questions regarding financial resources allocation to IBD care.

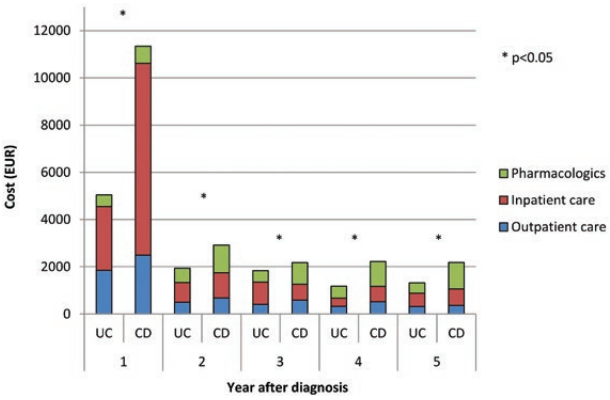
Methods: Patients diagnosed with IBD during the years 2005–2009 in the Uppsala region of Sweden (the ICURE cohort) were included in a healthcare economic study, aimed to describe the direct cost of IBD care. All medical records were analysed with regards to inpatient and outpatient care, pharmacological treatment, endoscopy and radiology during the first 5 years after diagnosis. All costs were recalculated according to the prize level of 2017. Values in SEK were converted to EUR at a ratio of 1:0.097.

Results: A total of 548 patients (UC: n = 363); CD: n = 185) participated in the study. The total cost for year 1–5 was 11 230 EUR for UC and 21 550 EUR for CD (p < 0.001).



Total cost year 1–5.

The cost was estimated to 5 070 EUR during the first year of disease for UC and 11 790 EUR for CD (p < 0.001). During year 2–5 the cost decreased to 1 500 EUR/year for UC and 2 240 EUR/year for CD.



Yearly cost.

Pharmacological treatment was 22% of total cost. There was no significant difference between men and women, but children (<17 years) had more expensive outpatient care (UC and CD) and inpatient care (CD) compared with adults. Patients in need of surgery had significantly higher costs each of the 5 years during follow-up.

Conclusions: The earlier reported pattern with high cost during the first year and rapidly decreasing costs during the following years seems to continue. Surgical treatment of IBD is the dominating cause of high costs, despite the introduction of biological treatments. Admission to an inpatient ward for IBD is mainly due to surgical treatment, but there are also high costs that can be attributed to non-surgical inpatient care. With the introduction of anti-TNF biosimilars, pharmacological costs can be reduced unless a larger percentage of the patients are treated with biological drugs.

P567

Could an escalation of therapy or intervention (ETI) calculator be used to triage appointments for patients with ulcerative colitis?

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Background: Conventional follow-up for ulcerative colitis (UC) places demands on health services. Demand might be better managed by targeting appointments at those patients who need therapeutic decisions. The aim was to further validate the TrueColours UC (TCUC) Escalation of Therapy or Intervention (ETI) calculator in an IBD outpatient clinic setting.

Methods: TCUC is a comprehensive, web-based program that works through email prompts, allowing patients to enter disease-specific data. In previous work, a logistic regression model using the SCCAI (Simple Clinical Colitis Activity Index) and IBD Control-8 (quality of life), collected through TCUC, was used to create an ETI calculator. This calculator produces a probability of escalation of therapy or other intervention at an outpatient appointment (OPA). See Figure 1.

SCCAI	Points	+	IBD CONTROL	Points	=	TOTAL POINTS	Probability of Escalation
0	0		0	24		0	0.01
1	7		1	22		13	0.05
2	14		2	21		34	0.25
3	21		3	20		47	0.50
4	29		4	18		59	0.75
5	36		5	16		80	0.95
6	43		6	15		100	0.99
7	50		7	14			
8	57		8	12			
9	64		9	11			
10	71		10	9			
11	79		11	8			
12	86		12	6			
13	93		13	5			
≥14	100		14	3			
			15	2			
			16	0			

Figure 1. UC Escalation of Therapy Calculator for SCCAI and IBD Control-8

From June to November 2018, a sample of 207 patients with UC under standard hospital follow-up, actively using TCUC was examined. For each OPA, the probability of escalation was calculated using their most recent SCCAI and IBD-Control reports. Clinic letters were assessed for the outcome of escalation of therapy or intervention.

Results: Of the 207 patients, 48 had a total of 53 OPAs over the 6-month period. Most, 33/53 (62%), OPAs resulted in no treatment escalation; 16/53 (30%) had escalation and 4/53 (8%) had de-escalation of therapy. De-escalation included stopping 5-ASA suppositories (n = 1), prednisolone enemas (n = 1), mycophenolate (n = 1), or methotrexate (n = 1). By setting the threshold for a timely OPD at a 5% estimated probability of treatment escalation, 13/16 (81%) escalation events would have been correctly identified. Of the 3 patients that would have been missed, the escalations involved increasing the dose of oral 5-ASA (n = 2) or flexible sigmoidoscopy (n = 1). By setting the estimated probability of escalation at 25%, only 9/16 (56%) would have been correctly identified. Of the 4 further patients that would have been missed, the escalation events involved starting topical therapy (n = 2), increasing the dose of azathioprine (n = 1), or increasing the frequency of vedolizumab (n = 1).

Conclusions: Models that predict the likelihood of the need for escalation of therapy or intervention during an outpatient appointment, based on remotely collected PROMs, have the potential to improve outpatient clinic resource utilisation. Using the ETI calculator, up to 62% of planned outpatient appointments could have been deferred if the agreed threshold for an appointment was a 5% chance of treatment escalation or intervention.

P568

Bowel ultrasonography is useful to evaluate disease activity in ulcerative colitis patients

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Background: Colonoscopy (CS) is the gold standard for evaluating disease activity in ulcerative colitis (UC). However, CS is invasive and especially so for patients with severe UC. We therefore evaluated the usefulness of bowel ultrasonography (BUS), as a non-invasive and potentially cost-effective alternative to CS.

Methods: UC patients followed at Kagawa Prefectural Central Hospital from September 2014 to August 2018 were included in this study. One gastroenterologist performed BUS, and the UC-BUS Grade was scored from 0 to 4 at six segments of the large bowel: caecum, ascending colon, transverse colon, descending colon, sigmoid colon and rectum based on colonic wall thickness, structure and irregularity. Right after BUS, a different gastroenterologist performed CS and the Mayo Endoscopic Score (MES) was scored from 0 to 3 at the six segments of the large bowel mentioned above. The Spearman's rank correlation was calculated at each of the large bowel segments.

Results: A cumulative total of 230 UC patients (73 women and 157 men) were prospectively included. The median patient age at examinations was 45.5 years (range, 13–82 years). The highest MES in the six segments was as follows: MES 0: 61 patients, MES 1: 60 patients, MES 2: 54 patients and MES 3: 55 patients. The success rate of ultrasound visualisation was 100% (230/230) in the caecum, ascending colon, transverse and sigmoid colon, and 99.6%(229/230) in the descending colon, and 96.5% in the sigmoid colon. Spearman's rank correlation was 0.32 (caecum), 0.56 (ascending colon), 0.52 (transverse colon), 0.55 (descending colon), 0.61 (sigmoid colon), 0.52 (rectum) and 0.56 (all segments) (p < 0.0001 in all segments).

Conclusions: BUS is useful to evaluate disease activity in all the segments of the large bowel of UC patients.

P569

A national, retrospective, observational study on the use of 5-aminosalicylates (5-ASA) in Crohn's disease (CD)

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Background: 5-ASA is an established first-line therapy for CD, though there are few recent studies on its use in routine clinical practice. The aim of this database investigation was to provide real-world evidence on the use of 5-ASA utilising data from the UK Clinical Practice Research Datalink (CPRD).

Methods: Adult patients (aged ≥18) at the time of first prescription of 5-ASA (index date) with a diagnosis of CD, having been prescribed a 5-ASA at any time between 01 January 2006 and 07 May 2018, were included for analysis. Outcomes included continuation rates, treatment patterns, and resource use.

Results: Of 21456 patients with CD, 9492 (44.2%) had been prescribed 5-ASA, with the majority (5761; 60.7%) starting on oral 5-ASA as monotherapy (Table). Of the total population on 5-ASA, 58.3% (5537) did not require a dose change, 67.6% (6416) did not require supplementary treatment (eg, corticosteroids, immunosuppressants, etc.) during 5-ASA treatment, and 4.6% (436) required a switch to another treatment. Resource use was significantly decreased in the year after 5-ASA initiation compared with the year before 5-ASA initiation (specialist referrals [285 vs. 110], hospitalisations [2475 vs. 1567] and hospitalisation days [19645 vs. 11574]; [all p < 0.001]). Significantly fewer patients required GI surgery during 5-ASA treatment than before treatment (5.3% [501] vs. 7.6% [721]; p < 0.001). In this type of study potential confounding factors, such as evolution or modification of the disease by treatment, are likely to be present and need to be considered. Patients remained on 5-ASA for a mean of 6.4 years (SD 6.1; median 4.7 years, IQR 1.2–10.1) before discontinuation. 77.4% (7347) of patients were still on 5-ASA at year 1, 68.1% (6464) at year 2, 48.5% (4604) at year 5, and 25.5% (2416) at 10 years. Longer retention on 5-ASA was associated with: a shorter time from CD diagnosis to first 5-ASA script (correlation: p < 0.001); use of an oral 5-ASA formulation at initiation (correlation: tablets: p < 0.001; granules: p = 0.008); and dose optimisation (increase: 89.3 months, decrease: 111.4 months vs. 45.5 months for no change; both p < 0.001).

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	n (%)
Number of patients with CD prescribed 5-ASA	9492
Male	4197 (44.2)
Female	5295 (55.8)
Mean age at index date (years) (SD)	42.7 (17.2)
Duration of disease at index date, months Mean (SD) Median (IQR)	 30.9 (89.6) 1.3 (-0.4-32.0)
5-ASA monotherapy (all formulations combined) at index date	5977 (63.0)
5-ASA combination therapy at index date, with:*†	3515 (37.0)
Corticosteroids	3245 (92.3)
Prednisolone	2712 (83.6)
Budesonide	375 (11.6)
Immunomodulators	817 (23.2)
Azathioprine	713 (87.3)
Oral 5-ASA at index date	9110 (96.0)
Mean 5-ASA dose at index date (oral and rectal combined) (SD)	2213 mg (1062)
Supplementary treatment during 5-ASA treatment	3076 (32.4)
Corticosteroids	2411 (78.4)
Prednisolone	2015 (65.5)
Immunomodulators	759 (24.7)
Azathioprine	643 (20.9)

*patients can be prescribed multiple treatments at a time; †data on biologic use were not available in CPRD as biologics are predominantly prescribed through secondary care

Conclusions: These data indicates that 5-ASA is used as a long-term treatment for CD, as evidenced by continuation rates extending beyond 10 years in a quarter of patients, and this is linked to relatively low levels of hospitalisations, surgery and supplementary treatments requirements. Moreover, patients that started 5-ASA earlier after diagnosis stayed on therapy significantly longer.

P570

Kock pouches in the 21st century: a descriptive study of short-term (30-day) outcomes in a national cohort of 177 patients

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Background: In 1972, Professor Nils Kock in Gothenburg Sweden developed the continent ileostomy (Koch pouch or KP) as an alternative to permanent end ileostomy. However, the KP was largely supplanted by the ileal pouch-anal anastomosis (IPAA). In the 21st century, KP's are rarely performed, and often only in highly select patients who are a not candidate for an IPAA. Presently, there are only single institution case series with which to guide surgeons' and patients' expectations for postoperative outcomes including length of stay, readmission and complication rates. Thus we aimed to report surgical outcomes in a large national retrospective cohort using the National Surgical Quality Improvement Project (NSQIP).
Methods: Using the NSQIP Participant User File from 2005–2017 we identified patients who underwent a KP (CPT 44386). Baseline characteristics, operative variables, and postoperative outcomes are reported. Figures represent frequency (proportion) or median (interquartile range).
Results: Over an 11-year period, a total of 907146 colorectal operations were performed; of these, we identified a sample of 177 patients who underwent Kock pouch procedures. The median age was 56 (46–76), 50.2% were women, and the median body mass index was 25.3 (22–29.6) kg/m^2. Any comorbidity was present in 105 (59%), with a median of 1 (0 – 2) comorbidities. A total of 13 (7.3%) and 16 (8.5%) were on steroids or had recent weight loss, respectively, and the median albumin was 3.8 (2.9–4.1) mg/dl. Most patients were ASA class 2 (78, 44%). Operative time was 198 (129.5–298.5) min, and 127 (72%) had other procedures by the same surgical team, while only 24 (14%) had concurrent procedures by a different surgical team. In terms of short-term outcomes, reoperation was required in 19 (10%) of patients, the post-operative length of stay was 8 (5–14) days. Readmission occurred in 14 (7.9%) of patients. VTE occurred in 4 patients (2.3%). Overall any complication of any severity occurred in 67 (38%) patients. The 30-day mortality rate was 3.4% (6 patients).
Conclusions: The Kock pouch procedure, despite its technical complexity, has an acceptable short-term safety profile, and remains an option for a selective group of motivated patients who cannot have IPAA and/or defer end ileostomy.

P571

Effectiveness and safety of Ustekinumab for induction of remission in patients with Crohn's disease: a multi-centre Israeli study

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Background: Background: Ustekinumab was demonstrated to be effective in treatment of Crohn`s disease in UNITI studies that used intravenous induction followed by subcutaneous maintenance. Several real-world evidence (RWE) studies addressing the efficacy of ustekinumab given subcutaneously were published. However, RWE data regarding effectiveness of the currently approved ustekinumab regimen are lacking. Our aim was to assess the safety and efficacy profile of ustekinumab for induction of remission in a large national patient cohort.
Methods: A prospective multi-centre study was conducted. Patients with active Crohn`s disease (CD) that were treated with ustekinumab were followed for 24 weeks. Patients who completed the induction protocol (week 0/8/16) or discontinued the treatment before Week 24 for adverse events or primary non-responders, were included. Induction dose was 260 to 520 mg (intravenous) according to body weight and then 90 mg subcutaneously every 8 weeks. Primary end-points were clinical response (reduction of ≥3 points in Harvey–Bradshaw score) and corticosteroid-free clinical remission at Week 24.
Results: A total of 106 CD patients from 8 Israeli medical centres were included. Median age was 38 years (range 21–74) with median

disease duration of 13 years; 64 (60%) were female patients. Eighty-five (80%) previously experienced at least two prior biological agents (anti-TNFs and vedolizumab) and only 1 patient (0.94%) was anti TNF naïve. Sixteen patients (15%) were after ileo-colic resection. Out of 106 patients, 10 (9.4%) patients discontinued treatment due to non-response and 4 (3.7%) due to adverse events, mostly worsening of arthralgia. Ninety-one patients continued treatment through Week 24. Clinical response was observed in 38 patients (36%). Ustekinumab induced significant decrease in mean CRP levels ($p < 0.004$). Twenty-one patients out of 32 (66%) achieved steroids-free remission at Week 24. Extra-intestinal manifestations (EIMs) at baseline included articular involvement in 32 patients (30%), skin manifestations in 8 patients (7.5%), biliary in 1(0.1%) and ocular in 1 patient (0.1%). Improvement of most probably arthralgia was observed at Week 24 in 23/32 patients (71%). Twenty-four patients (23%) reported of active perianal disease at the beginning of the study and 5(20%) of them improved at Week 24. Adverse events were reported in 12 (11%) patients, most common being arthralgia, weakness and skin eruptions.

Conclusions: In a large real-world Israeli cohort of anti-TNF- experienced CD patients, ustekinumab was effective and safe in induction of clinical remission and steroid-free clinical remission.

P572

Half of children with acute severe colitis have predominant single faecal bacterial species, mostly Escherichia coli: Microbiome results from the PRASCO trial

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Background: Acute severe ulcerative colitis (ASC) is one of the few medical emergencies of gastroenterology. We previously reported the clinical results of the PRASCO randomised controlled trial in which oral antibiotics (AB) improved disease activity after 5 days of treatment in children with ASC. This suggests that the microbiome is implicated in the aetiology and progression of ASC. We thus aimed to explore the microbiome of children enrolled in the PRASCO trial.

Methods: In the PRASCO trial, 26 children with ASC were randomised: 11 received IV corticosteroids (IVCS) and 15 received four oral AB's (amoxycillin, doxycillin/ciprofloxacin, metronidazole, vancomycin) in addition to IVCS. Stool samples were collected at regular intervals during admission. Metagenomic sequencing was performed using Illumina Nextera XT library preparation kit on a HiSeq platform. After filtering low quality and human reads using the KneadData pipeline, species-level taxonomic abundances were inferred for all samples using MetaPhlAn2.

Results: At baseline before treatment, 14/26 (54%) children harboured more than 30% of a single species: 9 (35%) with *Escherichia coli*, 2 (7.7%) *Haemophilus* species, and 1 (3.8%) each with *Klebsiella pneumoniae*, *Barnesiella intestinihominis* or *Parabacteroides* sp. (none with *Fusobacterium varium*). interestingly, of the 15 children in the AB arm, 11 (73%) had a transient relative bloom of >50% Enterobacteriaceae (mainly *E. coli*) after treatment, compared with only 3/11 in the IVCS only arm ($p = 0.02$). Despite this, disease activity at Day 5 was lower in the AB arm and time to remission was shorter ($p = 0.049$). When analysing all samples, several species of Lachnospiraceae family and *Clostridium bartlettii* were significantly and positively associated with remission. *C. bartletti* and *R. torques* (previously observed to be depleted in IBD and known butyrate producers) were lower in children with more severe disease.

Conclusions: This is the first report of microbiome pattern in ASC, showing provocative results. Over half of children with ASC have gut microbiomes highly enriched (>30%) at baseline with a specific species, mostly Enterobacteriaceae. This association may suggest that some ASC episodes are triggered by yet unknown enteric infections. While our antibiotic cocktail transiently exacerbated this enrichment it reduced disease activity, possibly due to niche availability after treatment, which can subsequently be filled by butyrate-producing microbes. In addition, the enrichment is relative to other species; it is possible that the absolute count was much lower in the AB group. Dysregulation of butyrate production may be associated with ASC in children.

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P573

Real-world effectiveness and safety of vedolizumab and anti-TNF in biologic-naive ulcerative colitis patients: Results from the EVOLVE study

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Background: This study aimed to compare the real-world clinical effectiveness and safety of vedolizumab (VDZ), a gut-selective anti-α4β7-integrin, and anti-tumour necrosis factor (TNF) agents in biologic (bio)-naïve ulcerative colitis (UC) patients.

Methods: A retrospective chart review study was conducted in adult (≥18 years), bio-naïve UC pts treated with VDZ or anti-TNF (June 2014 to February 2018) in Canada, Greece and the USA. Data were collected from treatment (Tx) initiation to earliest of death, chart abstraction date or 6 months post-Tx discontinuation. Cumulative rates of clinical response, clinical remission, mucosal healing, Tx persistence and dose escalations were estimated over 24 months (Kaplan–Meier method). Incidence rates (per 100 person-years [PYs]) of UC exacerbations, colectomy, serious adverse events (SAEs) and serious infections (SIs) were assessed. A Cox proportional hazards model was used to compare outcomes with adjustments for baseline confounders: age, sex, albumin, C-reactive protein, disease location and duration, UC-related hospitalisations (prior 12 mo) and disease severity; adjusted hazard ratios (HR) with 95% confidence interval are reported.

Results: Overall, 527 UC patients (VDZ: 325; anti-TNF: 202 [adalimumab: 58, infliximab: 120, golimumab: 24]) from 37 sites were included (median [min–max] follow-up [mo]: VDZ, 16.1 (3.0–47.0); anti-TNF, 20.0 [3.5–50.6]). Baseline characteristics are shown in Table 1.

Table 1. Baseline characteristics of real-world biologic-naive ulcerative colitis patients treated with vedolizumab and anti-TNF agents

Baseline characteristics	Vedolizumab N=325	Anti-TNF N=202	P-value[1]
Mean (SD) age	45.4 (17.6)	39.4 (15.5)	**<0.001**
Sex [male], n (%)	190 (58.5)	101 (50.0)	0.58
Median (min-max) disease duration, (years)	5.0 (0.06-35.0)	2.0 (<0.05-49.0)	**<0.0001**
Disease location, n with available data	282	172	0.07
Extensive colitis (proximal to hepatic flexure)	122 (43.3)	93 (54.1)	
Left sided (distal to splenic flexure)	138 (48.9)	66 (38.4)	
Ulcerative proctitis	22 (7.8)	13 (7.6)	
Disease severity[2], n with available data	230	140	0.38
Moderate, n (%)	117 (50.9)	74 (52.9)	
Severe, n (%)	26 (11.3)	23 (16.4)	
Steroid-dependent, n with available data	275	159	0.45
n (%)	104 (37.8)	66 (41.5)	
Concomitant immunosuppressive use, n (%)	68 (20.9)	43 (21.3)	0.92
Albumin, n with available data	163	95	0.56
<35 g/l, n (%)	97 (59.5)	60 (63.2)	
≥35 g/l, n (%)	66 (40.5)	35 (36.8)	
CRP, n with available data	209	128	**<0.01**
<5 mg/l, n (%)	106 (50.7)	45 (35.2)	
≥5 mg/l, n (%)	103 (49.3)	83 (64.8)	
Prior colectomy (since diagnosis), n (%)	1 (0.3)	2 (1.0)	0.27
UC-related hospitalisations (12 months prior), n (%)	41 (12.6)	47 (23.3)	**<0.01**

CRP: C-reactive protein; GI: gastrointestinal; Max: maximum; Min: minimum; Max: maximum; SD: standard deviation; UC: ulcerative colitis.
[1]Statistical tests were conducted for patients with available data. For continuous variables, the Kolmogorov-Smirnov test was conducted to evaluate normality; if normal, a t-test was used to test for differences between VDZ and anti-TNF patients, otherwise Wilcoxon-Mann–Whitney test was conducted. For categorical variables, a Chi-square test was conducted unless cells had <5 observations, then Fisher exact was used. [2]Derived based on available medical record data of standard disease measures within 6 months of treatment initiation: Mayo Score, Partial Mayo Score, Physician Global Assessment.

At 24 months, cumulative rates of clinical response (91% vs. 86%), clinical remission (79% vs. 66%) and mucosal healing (92% vs. 84%) were high in VDZ and anti-TNF patients, respectively, and did not differ significantly between groups. Higher Tx persistence (75% vs. 54%; $p < 0.0001$) and similar rates of dose escalations (25% vs. 31%; $p < 0.05$) occurred in VDZ vs. anti-TNF patients. The incidence rate (per 100 PYs) of UC exacerbations (28.3 vs. 43.9) and SAEs (4.9 vs. 10.4) were significantly ($p < 0.05$) lower in VDZ vs. anti-TNF patients but similar for colectomy (1.8 vs. 2.2) and SIs (1.9 vs. 2.2). Adjusted HR for outcomes are shown in Table 2.

Table 2. Clinical effectiveness and safety of vedolizumab and anti-TNF agents in real-world biologic-naïve ulcerative colitis patients.

	Vedolizumab N=325	Anti-TNF N=202	P-value[1]	Adjusted Hazard Ratio (95% CI)[2]
Clinical Effectiveness Outcomes[3], %				
Clinical response, n with available data	293	174		
12 months	76.5	74.3	0.99	1.1 (0.9-1.4)
18 months	84.3	81.9	0.99	1.1 (0.9-1.4)
24 months	90.8	85.7	0.82	1.2 (0.9-1.5)
Clinical remission, n with available data	301	179		
12 months	57.3	56.5	0.94	1.1 (0.8-1.4)
18 months	70.3	63.4	0.57	1.1 (0.9-1.5)
24 months	79.0	66.2	0.37	1.2 (09-1.5)
Mucosal healing, n with available data	220	153		
12 months	56.2	56.6	0.95	1.0 (0.7-1.4)
18 months	79.0	73.0	0.77	1.0 (0.8-1.4)
24 months	92.0	84.4	0.67	1.0 (0.8-1.3)
Treatment persistence, n with available data	323	202		
12 months	82.5	65.0	**<0.0001**	**2.2 (1.5-3.2)**
18 months	79.1	60.3	**<0.0001**	**2.1 (1.5-3.0)**
24 months	75.1	53.8	**<0.0001**	**2.0 (1.4-2.9)**
Dose escalation[4], n with available data	325	202		
12 months	16.3	26.4	0.01	0.7 (0.4-1.0)
18 months	20.5	27.8	0.03	0.7 (0.5-1.1)
24 months	24.7	30.5	0.04	0.8 (0.5-1.1)
Clinical and Safety Outcomes (Incidence Rate, per 100 Person-Years [95% confidence interval])				
UC exacerbation[5,6]	28.3 (23.4-34.3)	43.9 (36.0-53.6)	**0.02**	**0.7 (0.5-0.9)**
Colectomy[5]	1.8 (0.9-3.5)	2.2 (1.0-4.6)	0.82	0.9 (0.3-2.9)
SAE[7]	4.9 (3.2-7.4)	10.4 (7.4-14.7)	**<0.01**	**0.5 (0.3-0.8)**
SI[7]	1.9 (1.0-3.7)	2.2 (1.1-4.4)	0.67	0.8 (0.2-2.7)

CI: confidence interval; SAE: serious adverse event; SI: serious infection; UC: ulcerative colitis.
[1]P-values generated from Kaplan-Meyer analyses using the unadjusted log-rank test for 'Clinical Effectiveness Outcomes' and Wald Chi-square test for 'Clinical and Safety Outcomes'. [2]Hazard ratios (vedolizumab [VDZ] vs anti-TNF) for both outcomes and clinical/safety outcomes were generated using adjusted Cox proportional hazards models for confounders: age, sex, albumin, C-reactive protein (CRP), disease location and duration, UC-related hospitalisations in prior 12 months, and disease severity; patients with unknown disease duration were excluded (n=72 [VDZ=41, anti-TNF=31]). [3]Cumulative rates of clinical response, clinical remission and mucosal healing were assessed using pre-defined hierarchical algorithms of standard disease measures as reported in in the medical records and were calculated for patients with ≥1 assessment. [4]Increase in VDZ frequency or anti-TNF dose and/or frequency for ≥2 consecutive infusions/injections. [5]Assessed exposure time for UC exacerbation and colectomy spans from treatment initiation to earliest of 6 months post-treatment discontinuation or chart abstraction date. [6]UC exacerbations defined as documentation of a 'flare-up' in the medical chart or as a reason for healthcare professional visit, emergency department visit, hospitalisation or initiation of non-biological therapy. [7]Assessed exposure time for SAE and SI rates include up to five half-lives post-treatment discontinuation, where applicable (VDZ: 18 weeks; infliximab: 6.8 weeks; adalimumab and golimumab: 10 weeks).

Conclusions: VDZ and anti-TNF have similar rates of clinical effectiveness in bio-naïve UC patients in real-world clinical practice. Bio-naïve UC patients receiving VDZ are significantly more likely to persist with Tx and experience fewer exacerbations and SAEs than anti-TNF patients.

P574

IBD patients should be stratified to guide out-of-hospital monitoring: ICHOM-derived outcomes from a dedicated IBD telephone clinic

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Background: The prevalence of IBD in western countries is high. Once diagnosed most patients are monitored in hospitals. Out-of-hospital (OOH) monitoring through various electronic portals offers patient-centred care. Some IBD patients are at risk of complications from disease progression or drug therapy, but many have a low risk of adverse outcomes and may be safely monitored OOH. Several tools to deliver OOH care are described. In contrast, guidance to select low-risk patients for OOH and their outcomes using validated patient-reported outcomes such as International Consortium for Health Outcomes Measurement (ICHOM) are lacking. We selected low-risk patients for telephone OOH and describe their outcomes.

Methods: Over 18 months, 1083 IBD patients from 3 non-complex IBD clinics were stratified according to pre-specified criteria formulated with patient input and offered OOH care. Inclusion criteria were (a) age ≥ 18 years, (b) confirmed diagnosis of IBD ≥ 1 year, (c) low risk of developing IBD-related complications, (d) clinical remission (see Figure 1). Exclusion criteria were i) learning/language difficulties ii) pregnancy, iii) awaiting IBD MDT discussion. Patient-reported outcomes, quality of life and healthcare utilisation as defined from the ICHOM standard set were prospectively collected at the index telephone consultation.

Pragmatic clinical remission definition:	**Low risk of complication definition**
One or more of the following for ≥ 6 months prior to the index appointment:	None of the following:
i) MAYO Index ≤ 1 or Simple Colitis Clinical Activity Index ≤ 2 (ulcerative colitis)	i) On biologic medical therapy
ii) Harvey Bradshaw Index ≤ 3 (Crohn's disease),	ii) On immunomodulatory medications for <12 months or no shared care protocol in place with GP
iii) No change in IBD medications with no new symptoms reported	iii) Family history of bowel cancer in first degree relative, or personal history of IBD-related colonic dysplasia
iv) Physician documentation of remission status	iv) Primary sclerosing cholangitis
	v) Complex fistulating or stricturing Crohn's Disease

Figure 1. Remission and risk stratification definitions.

Results: 362/1083 patients were eligible for telephone clinics; 115 (32%) patients were transferred. Patient demographics, IBD subtype, current medication (nil, 5-ASA or immunomodulator therapy), outcome data and follow-up interval are shown for the 115 patients presented below (see Table 1):

	Ulcerative colitis [n=89]	**Crohn's disease** [n=26]
Age – median [range], years	51 [38-63]	52 [41-69]
Gender – no. [%]	M – 39 [44]; F – 50 [56]	M – 13 [50]; F – 13 [50]
Disease duration - median [range], years	14 [6-25]	16 [7-21]
Montreal classification subtype:		
E1, no. [%]	19 [21.3]	
E2, no. [%]	28 [31.5]	
E3, no. [%]	42 [47.2]	
L1, no. [%]		5 [19.2]
L2, no. [%]		6 [23.2]
L3, no. [%]		10 [38.4]
Perianal +/- L1/2/3, no. [%]		5 [19.2]
Medications:		
Nil, no. [%]	18 [20.2]	8 [30.8]
Aminosalicylate only, no. [%]	53 [59.6]	9 [34.6]
Immunomodulator, no. [%]	18 [20.2]	9 [34.6]
Activity Score:		
UC – SCCAI, median [range]	0 [0-1]	
CD – HBI, median [range]		0 [0-2]
ICHOM Outcomes:		
Bowel Symptoms, no. [%]	12 [13.5]	3 [11.5]
Fatigue, no. [%]	13 [14.6]	11 [42.3]
Pain, no. [%]	11 [12.4]	7 [26.9]
Normal Activity, no. [%]	89 [100]	26 [100]
Steroid Use, no. [%]	4 [4.5]	1 [3.8]
Emergency Visits, no. [%]	2 [2.2]	1 [3.8]
Next appointment in telephone clinic, no. [%]	79 [88.7]	23 [88.5]
Follow up duration, median [range], months	6 [6-12]	6 [6-6]

HBI – Harvey Bradshaw index; SCCAI – Simple clinical colitis activity index

Table 1. Results.

Conclusions: IBD patients with a low risk of complications and durable clinical remission, showed good outcomes with OOH telephone monitoring. Healthcare utilisation and recent steroid use as defined by ICHOM outcomes were low. Selecting the right patients for OOH monitoring may be the preferred strategy to show beneficial patient-reported and clinical outcomes and maintain adherence to telephone monitoring. Our findings should encourage patient stratification based on presumed risk and disease activity.

P575

Simple novel tacrolimus enemas are very effective in severe refractory proctitis

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Background: Many patients with UC and Crohn's rectal disease do not respond to standard simple molecules or biologic therapies. Oral and suppository tacrolimus have been proven effective in randomised controlled trials, but are often poorly tolerated or complex to formulate. Tacrolimus is highly topically active in a short time, has minimal systemic toxicity when administered rectally, and is soluble in water; we have therefore tested a very simple tap-water based enema formulation.

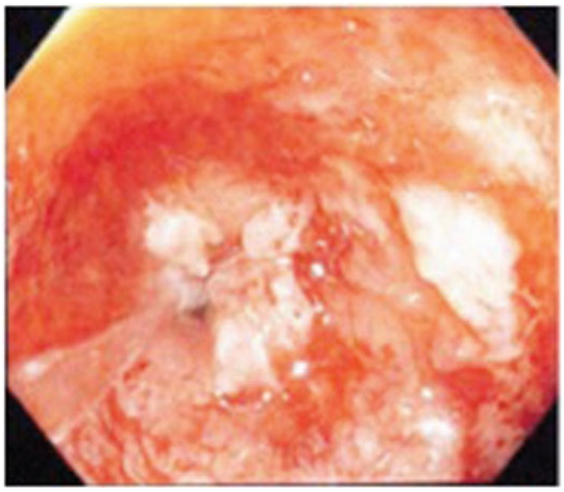
Methods: Tacrolimus powder was emptied from standard 1 mg capsules into a 60 ml syringe, 60 ml warm tap water was added, and a catheter used to deliver the solution rectally. Data of all treated patients with IBD-related refractory proctitis were reviewed by two physicians (SRF, FCM) independent to the treating physician (MAK). with respect to clinical, biochemical and endoscopic response, and adverse reactions (ADRs) recorded.

Results: Patient characteristics: 17 patients [12 UC and 5 Crohn's disease, 9 female, median age 31 (IQR 26–38)] with refractory rectal disease were treated. Four patients had endoscopically impassable inflammatory strictures. All patients had failed immunosuppressive therapy, most had failed both a thiopurine (88%) and biologic therapy (71%). Treatment: Tacrolimus enemas for active disease were used in a dose of 1–4 mg, according to tolerance, followed by 1–3 mg three times weekly maintenance, for a median duration of 20 weeks (IQR 14–72). Most patients were maintained on concomitant immunosuppression.

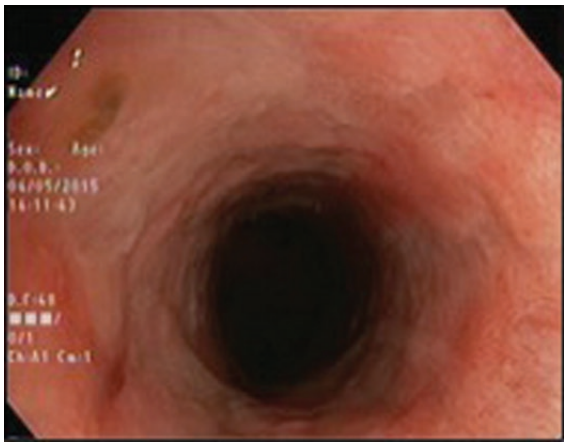
Corticosteroids	2 (12%)
5-ASA	6 (35%)
Thiopurine	14 (82%)
Biologic agent	6 (35%)
Other	4 (24%)

Concomitant therapy with tacrolimus enemas.

Sixteen (94%) patients showed clinical and biochemical, and 79% endoscopic, improvement. In all four patients with strictures the inflammation resolved and the stricture became endoscopically passable without dilatation.



Distal end of a rectal stricture, with pin-hole lumen, in a patient who has failed immunosuppressive therapy. Prior to tacrolimus enema therapy.



Mid stricture in the same patient after tacrolimus enema therapy. The inflammation has resolved and the stricture dilated to allow colonoscope passage.

Three (18%) patients had a flare of their disease while receiving tacrolimus therapy. 94% tolerated therapy well. No patient experienced major adverse events, 3 (18%) experienced minor ADRs including pruritus and nausea.

Conclusions: This novel tacrolimus formulation of water-based enemas is easy to prepare, very effective, well tolerated, and safe. Tacrolimus enemas should be included in the treatment armamentarium for refractory proctitis.

P576

Therapeutic drug monitoring as predictive marker of mucosal healing in Crohn's disease patients treated with anti-TNF: a prospective multi-centre study

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Background: Anti-TNFs are currently the most commonly used drugs for Crohn's disease (CD). Therapeutic drug monitoring (TDM) is a promising strategy to optimise the healthcare resources in case of loss of response during anti-TNF treatment, yet a proactive management of TDM is being debated. The primary aim of this prospective study was to evaluate if trough levels (TL) of adalimumab (ADL) or infliximab (IFX) could be used as a marker of therapeutic response, particularly of mucosal healing (MH). The secondary aim was to evaluate if a point-of-care (POC) assay has the same results in detecting TL as an ELISA-based test.

Methods: CD patients naïve to anti-TNFs who started a treatment with ADL or IFX in monotherapy in 2017 at Pisa and Genoa University Hospitals were prospectively included in this study. At Weeks 14, 22, and 54 TL were evaluated on serum samples drawn before drug administration, by using an ELISA-based test (Promonitor®, Grifols, Spain) and a POC assay (Bühlmann, Switzerland). At Week 54 MH (defined as the disappearance of ulcers) and clinical remission (CR) (defined as a Harvey–Bradshaw Index (HBI) <5) were evaluated. TL analysed with the two methods were correlated using Spearman's rank correlation coefficient (r) and the concordance between methods was assessed through Cohen's Kappa (k). Statistical correlation between TL and MH or CR was performed using t-test and ROC curves.

Results: At the moment 35 patients (21 ADL and 14 IFX) patients were enrolled. At Week 54 MH was reached in 25 patients (71%), while CR in 28 patients (80%). A correlation between MH at Week 54 and ADL TL evaluated at Weeks 14, 22 and 54 was found ($p < 0.05$, $p < 0.01$, $p < 0.01$, respectively); ROC curve at Week 22 showed the best performance, with a cut-off of 8.06 µg/ml (AUC 0.857, sensitivity 78.6%, specificity 100%). A trend of correlation between TL and MH was found for IFX , but the difference was not statistically significant. The TL values obtained with the 2 different methods showed a good correlation: r was 0.868, and k was 0.711 ($p < 0.001$ for both).

Conclusions: TL assessment, especially at Week 22, could be very useful in the management of CD patients naïve to anti-TNFs treated with ADL. The good correlation with MH has an important clinical implication, as far as the disappearance of ulcers should be the target of anti-TNF therapy. Moreover, POC assay has showed the same efficacy than ELISA and is quicker and easier to perform. In this perspective, a proactive management of TDM could be suggested, especially if the same results could be extended to IFX-treated patients. The study is currently ongoing, and the final results would suggest a wider use of TDM in CD patients.

P577

Drug Induced Liver Injury (DILI) secondary to biologic therapy in IBD: ECCO- CONFER Series

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Background: Drug-induced liver injury (DILI) in IBD patients is mostly attributed to thiopurines and methotrexate. Less has been reported about biologics-related DILI in IBD patients with existing data restricted to case reports.

Methods: We retrospectively collected data on a multi-centre cohort of IBD patients with DILI attributed to biologics. This was a part of the European Crohn`s and Colitis Organisation (ECCO) initiated CONFER (Collaborative Network for Exceptionally Rare case reports) project. A call was made to all ECCO members to report DILI following initiation of biologics. Data were recorded on a standardised case report form and analysed with descriptive statistics.

Results: Eighteen patients with DILI attributed to biologics have so far been reported in this cohort (M: F –10:8, CD: UC- 10:8, Median age 33 years). DILI was attributed to infliximab in 15 patients, vedolizumab in 2 and adalimumab in 1. Seven patients were on concomitant immunomodulators (5 thiopurines, 2 methotrexate). Coexistent axial or peripheral arthropathy was recorded in 6 patients. Patients had a median of 3 doses (range 1–22) prior to development of DILI. Median time to DILI following last exposure to biologics was 51 days (range 12–84 days). Predominant hepatocellular pattern of liver function tests was noted in 9 patients, predominant cholestatic in 2 and mixed picture in the remaining 7. Antinuclear antibodies were present in 11/18 (3 of these anti smooth also muscle Ab positive) with elevated IgG in 9 patients. Liver biopsy was performed in 9 patients with 6 suggesting drug toxicity, 2 showing additional features of autoimmune liver disease and one showing co-existent steatohepatitis. The biologic was discontinued in all but 2 patients. Six patients had steroids following liver injury. Complete recovery of liver function was seen in 13, and partial in 3 patients following discontinuation of biologics in a median time of 35 days. Alternative biologics were started for IBD in 13 patients (10 switched from infliximab to vedolizumab, 2 from infliximab to adalimumab, and one from infliximab to ustekinemab),) with no recurrence of DILI. In a median follow-up of 17 months, 2 patients were formally diagnosed to have autoimmune liver disease requiring additional immunosuppression.

Conclusions: DILI is reported in patients receiving biologics for IBD predominantly with Infliximab with development of autoimmunity in a subset of patients. Majority recover on stopping the offending agenda with no recurrence on switching the biologics. Results should be interpreted with caution as causality could not be certain given the retrospective nature of the study. A larger cohort is required to study DILI related to biologics in IBD.

P578

Therapeutic strategies in the approach of paradoxical psoriasis in IBD: experience of a centre

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Background: Induction of psoriasis with the use of TNFα antagonists, also used in its treatment, is a phenomenon described in inflammatory bowel disease. We intended to analyse predictive factors for the development of this entity and results of the different strategies in its treatment.
Methods: Analysis of a cohort under treatment with anti-TNFα between 2005 and 2018. Patients who developed paradoxical psoriasis following onset of anti-TNFα, confirmed by Dermatology were compared with the group without occurrence of cutaneous lesions with treatment. Statistical analysis was performed using SPSS.
Results: 291 patients were treated with anti-TNFα, of which 18 (6.2%) developed paradoxical psoriasis. Of these, 13 (72%) were female, with a mean age of 36 years. The majority were under infliximab (n = 14, 78%) and had Crohn's disease (n = 16, 88%). Extra-intestinal manifestations were present in 9 patients (50%) and the mean time until the development of paradoxical psoriasis was 2.8 years (1 month-10 years). Only 3 patients (16.6%) had active disease and 9 (50%) had perianal disease. From the studied variables, female gender and history of extra-intestinal manifestations were associated with the development of psoriatic lesions ($p < 0.05$). Topical and/or systemic therapy was used, with anti-TNFα being initially maintained, in 14 patients, with improvement of cutaneous lesions in 10 (partial improvement in 6). Anti-TNFα discontinuation was necessary in 7 patients: 2 due to recurrence of psoriasis after reintroduction of anti-TNFα; 2 for recurrence after switch and 3 for absence of skin lesions resolution despite systemic therapy. Swap to ustekinumab was made in 7 patients: complete resolution of the lesions was observed in 6 patients and partial improvement in 1 patient partial, whom maintaining adjuvant systemic therapy. Intestinal remission was maintenance/attainment in all patients.
Conclusions: In this cohort the development of paradoxical psoriasis in inflammatory bowel disease under anti-TNFα was 6.2%, with a higher prevalence in females and in the presence of extraintestinal manifestations. Definitive anti-TNFα suspension was required in 7 patients (38.8%) and the swap strategy was effective in most cases.

P579

Wearable Devices Can Predict Disease Activity in inflammatory bowel disease Patients

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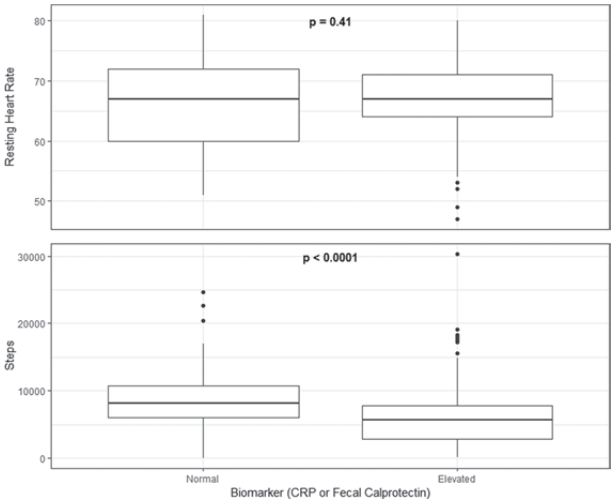
Background: Proactive disease monitoring in inflammatory bowel disease (IBD) represents an opportunity to improve care. Certain biomarkers, including C-reactive protein (CRP) and faecal calprotectin (FC), are sensitive biomarkers for active inflammation in IBD. As part of an ongoing prospective study on the use of biosensors in IBD, we aimed to determine the feasibility of predicting a patient's disease activity based on data collected by wearable devices.
Methods: As part of a yearlong prospective study on the use of biosensors in IBD, outpatients and inpatients with IBD were provided a Fitbit (San Francisco, CA) and a proprietary smartphone app (Litmus Health, Austin, TX) for data collection and completion of patient-reported outcomes. Daily steps, heart rate (HR), and sleep data were collected with the Fitbit device using their research API. Baseline disease activity status was recorded using the Simple Clinical Colitis Activity Index or the Harvey–Bradshaw Index as well as baseline CRP and FC values. We also collected subsequent clinic visit data and when ordered, subsequent CRP/FC values. The predictive ability of Fitbit data for the subsequent CRP/FC values was determined by calculating the AUC for each metric. Groups were compared using the Student's t-test for parametric data, and Wilcoxon rank sum for non-parametric data.
Results: Out of 194 IBD patients included in our biosensor study, 39 patients (13 CD, 26 UC; median age 44 years (range 22–67); Fitbit duration median 296 d (range 23–365)) had subsequently obtained CRP or FC values and were eligible for this analysis. The median number of subsequent biomarkers per patient was 1 (range 1–7).
Patients had lower daily steps (mean 6062 vs. 8541, p < 0.001) over the week before the elevated CRP or FC, but there was no difference in daily resting heart rate (mean 66.9 vs. 66.3, p = 0.42). Number of daily steps was predictive of having an elevated biomarker drawn within 7 days (AUC for steps = 0.70, 95% CI = 0.65–0.75) (Figure 1).
Conclusions: We demonstrate for the first time the use of passive biosensor data to predict elevated biomarkers of inflammation in IBD. Physical activity as measured by steps was decreased prior to a subsequent elevated CRP or FC, suggesting that this passively collected measure is predictive of disease activity in IBD. These results inform our ongoing prospective work to develop disease monitoring and management strategies.



Steps and resting heart rate in IBD patients with elevated or normal biomarkers.

P580

Improvement in disease activity is associated with less disability in a prospective study of paediatric transition patients with IBD

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Background: The transition from paediatric to adult healthcare in patients with inflammatory bowel disease (IBD) occurs at an important time in a child's psychosocial development and can impact education, employment, social integration and result in significant disability. A structured transition may limit disability and reduce the impact of disability over time. Our aims were to assess the change in disability over time in paediatric transition patients, who underwent a structured transition, using the validated Inflammatory Bowel Disease Disability Index (IBD-DI) and to assess the responsiveness of this index to change.
Methods: 59 patients (aged 18–25) that had recently transitioned to adult care at the University of Calgary, were identified from a cohort of 200 patients recruited to undertake the IBD-DI. A research coordinator administered the IBD-DI with a repeat assessment at 12 months. Demographic and clinical data including measures of disease activity were collected from participants as well as medical chart and database review. Baseline IBD-DI scores were compared using the Mann–Whitney-U test. The Wilcoxon signed rank test with calculation of an effect size and standardised response mean were used to analyse change in IBD-DI scores over time, in groups based on change in disease activity.
Results: Baseline mean IBD-DI scores for the 59 transition patients was 20.69 ± 13.19 (range 0 to 54.41) and did not differ significantly from 141 adult patients (mean age 41.39) with mean scores of 24.90 ± 14.18 (range 1.47 to 70.59) (p = 0.08.) 50 out of 59 participants completed the follow-up assessment at 12 months. Disease activity over time improved in 5 patients, worsened in 5 and were stable in 39 patients. One patient had missing disease index measures and clinical status could not be classified. There was a significant reduction in IBD-DI scores for those with clinical improvement (–17.94, ES >–1, p = 0.04) and a significant increase in IBD-DI scores in those that with clinical deterioration (+23.53, ES >1, p = 0.04). There was a reduction in the IBD-DI scores over the 12-month time period, in patients with stable disease activity, (–2.68, ES=0.20, p = 0.15), however, this was not statistically significant.

Table 1. Mean change in IBD-DI and effect size based on whether disease improved, was stable or worsened.

Disease Activity	Improved (n = 5)	Stable (n = 39)	Worsened (n = 5)	Overall (n = 50)
IBD-DI-Baseline	36.647 (10.926)	19.042 (13.201)	23.824 (13.851)	20.625 (13.511)
IBD-DI-12 months	14.706(10.757)	16.365 (12.624)	47.353 (10.263)	19.382 (15.198)
Change in IBD-DI	–17.941 (11.737)	–2.677 (11.470)	23.530 (11.532)	–1.242 (14.893)
ES	>–1.0	–0.203	>1.0	–0.060
SRM	13.09	4.64	–40.78	2.15
p value	0.043	0.147	0.042	0.390

Conclusions: Transition patients have similar disability scores as compared with an adult cohort. There was a significant reduction in IBD-DI scores for those with clinical improvement. The IBD-DI demonstrates significant responsiveness to changes in disease activity over time, a factor that was not evaluated in the initial validation study of the index.

P581

Complementary and alternative therapies for inflammatory bowel disease

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Background: Use of complementary and alternative medicines is common in patients with inflammatory bowel disease (IBD); with previous studies showing rates between 21–60%. Certain non-prescribed therapies have gained popularity in recent times in social and other media (cannabis oil) and we wished to explore the use of this, and other products in our patient population. The aim of this study was to evaluate the use of non-prescribed complementary therapies in patients with IBD in a tertiary setting.
Methods: Patients with ulcerative colitis (UC), Crohn's disease (CD) and undetermined IBD (IBD-U) were recruited from out-patient gastroenterology clinics at Tallaght University Hospital over a six-week period. They completed a self-administered, anonymised survey. Participants were asked about supplement use (prescribed and non-prescribed) and to give a subjective assessment of the impact these had on their symptoms.
Results: Of 166 consecutively approached IBD patients, 150 completed the survey, giving a response rate of 90.3%. Thirty-five per cent of respondents were prescribed dietary or vitamin supplements. Thirty-nine per cent reported use of non-prescribed therapies. Of these, 32/58 (55%) felt these therapies had a positive impact on IBD symptoms. Thirty-four had used probiotics; 13 of these patients reported improved symptoms (Table 2). Cannabis-based products were the second most commonly used supplement for IBD symptom-control (9.3%). Respondents also confirmed use of aloe vera (12%) turmeric (11%), acupuncture (9%), aromatherapy (5%) and hypnosis (2%).

Table 1. Baseline patient characteristics.

Baseline characteristics	All patients (n = 150)	UC (n = 46)	CD (n = 97)	IBD-U (n = 7)
Sex, n (%)				
Female	84(56%)	23(50%)	59(61%)	2(29%)
Male	66(44%)	23(50%)	38(39%)	5(71%)
Age (years), mean ± SD	45.4 ± 15.1	50.1 ± 17.6	43.4 ± 13.5	42 ± 13.6
Duration of disease (n = 134), years	11.8 ± 8.9	10.3 ± 8.3	12.9 ± 9.1	6.5 ± 8.6
Previous surgery (n = 148)	49(33%)	5(11%)	43(44%)	1(14%)
Regular analgesia (n = 150)	74(49%)	22(49%)	48(49%)	4(57%)
Prescribed supplement use	52(35%)	9(20%)	40(41%)	3(43%)
Non-prescribed medications	58(39%)	18(39%)	37(38%)	3(43%)

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Table 2. Use of alternative and complementary medicines in IBD.

	Current or Previous Use	Use for IBD Symptoms	Improvement in IBD-related Symptoms
Probiotics	34(23%)	17(50%)	13(38%)
Cannabis	17(11%)	14(82%)	12(71%)
Aloe Vera	18(12%)	13(7%)	4(22%)
Fish Oil	34(23%)	9(26%)	7(21%)
Acupuncture	13(9%)	9(69%)	5(38%)
Turmeric	17(11%)	6(35%)	5(29%)
Hypnosis	3(2%)	3(100%)	0(0%)
Aromatherapy	8(5%)	2(25%)	2(25%)

https://planner.smart-abstract.com/ecco2019/submission/en/abstract/13054/content#

Conclusions: These results support previous studies which have shown that the use of complementary and alternative medicine is prevalent among IBD patients. Further studies are crucial to determine their role in IBD.

P582

Effectiveness and nephrotoxicity of long-term tacrolimus administration in patients with ulcerative colitis

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Background: Tacrolimus (TAC) is a calcineurin inhibitor used for the management of refractory ulcerative colitis (UC), and it is effective for inducing remission. A number of studies have assessed the short-term efficacy of TAC. However, there are few reports on the effectiveness of long-term administration. TAC is also known to cause adverse effects including acute renal toxicity, but there are few studies focussed on renal function in UC. The aim of this study was to evaluate the long-term effectiveness, and monitor changes in renal function during prolonged TAC use in patients with UC.

Methods: Data were compiled from 49 moderate to severe active UC patients treated with TAC in Juntendo University. We adjusted the trough level with a range of 10–15 ng/ml for the initial 2 weeks and subsequently a range of 5–10 ng/ml. Their medical records were retrospectively reviewed. Clinical outcomes were assessed at 6 months, 1 year and 2 years after initiating TAC. We also monitored the chronological changes in renal function by following the estimated glomerular filtration rate (eGFR) and serum creatinine level during TAC administration. Plasma trough TAC level and dose were compared with renal function.

Results: Thirty-six patients were treated with TAC for over 3 months. Relapse-free survival at 6, 12 and 24 months were 83%, 77% and 47%, respectively, and there were no patients who needed surgery. On the other hand, renal function was reduced in 38.9% patients showing a 30% decrease in the eGFR relative to baseline. We found that even after a long-term administration of TAC, eGFR tended to improve in most cases upon discontinuation, but in some patients, there was a significant decrease. Moreover, irreversible renal dysfunction was more likely to occur in cases where eGFR was reduced more than 30%.

Conclusions: Long-term administration of TAC appeared to prevent the relapse of UC. This study seem to demonstrate the potential use of TAC as an effective option in the long-term medical management of patients with UC. On the other hand, it tended to increase the risk of nephrotoxicity. In most cases, renal function may improve upon discontinuation or reducing the dose, but in some patients, long-term TAC may cause irreversible renal damage. There is a need for careful monitoring of renal function during TAC dosing.

P583

Outcome of treat to target strategy in paediatric patients with Crohn's disease and ulcerative colitis on adalimumab

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Background: Treat to target strategy has been proposed in adult IBD to improve Quality of Life, symptoms and to treat inflammation. There are little data in the paediatric population for this approach. The aim of this study was to look if set goals (reduced PCDAI/PUCAI and Mayo/SES-CD) were achieved.

Methods: We conducted a retrospective analysis of children with IBD who received Adalimumab (ADA) in our institution. Data were collected to evaluate mucosal healing for UC from colonoscopy results, using Mayo Scoring and for CD using SES-CD. We also compared These data with activity scores (PUCAI and PCDAI), CRP and Faecal Calprotectin, (FC).

Results: A total of 24 patients were identified, 20 (Group 1) with Crohn's disease (CD), 4 (Group 2) with ulcerative colitis (UC); Male n = 14, age range 2–13 years, median 9 years. Group 1: there were 20 patients, Male n = 13, age range 3–13 years, median 9 years. SES-CD was assessed in 9 patients pre-treatment with ADA, median score was 2.5 with a range from 0 to 8; In 10 patients 1 year after treatment SES-CD score dropped to a median of 1 with a range between 0 and 5. Pretreatment median FC (n = 15) was 574 mg/kg with a range of 66–6000 mg/kg and post treatment FC was (n = 18) 108 mg/kg with a range of 11–1491 mg/kg. Median CRP pre-commencing (n = 19) was 9 mg/l with a range of 5–166 mg/l. Post treatment (n = 19) the median was 5 mg/l with a range of 0.3–8 mg/l. 70% of patients had a drop of PCDAI to <10 at 1 year follow-up. Group2: 4 children were identified, Female n = 3, age range 2–10 years, median 5 years. Mayo pre commencing (n = 4) median was 2.5, range 1–3, post (n = 2) was median of 0.5 with range of 0–1. FC precommencing (n = 3) median was 1966 mg/kg with a range of 217–3000 mg/kg and was decreased to 15 mg/kg with a range of 15–1173 mg/kg (n = 14).

CRP precommencing median (n = 4) was 40 mg/l with a range of 8–81 mg/l and after (n = 4) it was 5 mg/l with a range of 2–6 mg/l. PUCAI was found to be <10 after 1 year of follow-up in 50% of the children with UC.

Conclusions: This study suggests that setting a target and monitoring SES-CD in CD and Mayo scoring in UC improves clinical outcomes (PCDAI and PUCAI), more in Crohn's disease than Ulcerative colitis. Treat to target should become routine clinical management in paediatric IBD patients.

P584

Combining faecal calprotectin and sigmoidoscopy can predict mucosal healing in paediatric ulcerative colitis

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Background: Treatment target of inflammatory bowel disease is evolving. Currently, mucosal healing (MH) is regarded as endoscopic treatment target and 'treat-to-target' strategy, which emphasises proactive assessment and optimising treatment, is commonly applied at the clinical setting. Although colonoscopies are essential for the strategy to be successful, there are some obstacles such as bowel preparation and using sedative drugs especially for paediatric patients. In this study, we tried to verify the usefulness of sigmoidoscopy, which is less invasive endoscopic procedure, combined with faecal calprotectin to assess MH.
Methods: Total of 58 paediatric patients who are diagnosed with ulcerative colitis and followed up at Severance Children's Hospital from March 2015 to May 2018 were enrolled. Clinical data, laboratory findings including faecal calprotectin and endoscopic data were collected from the medical record. The predictive power of sMH (muscle healing of sigmoid colon and rectum) combined with faecal calprotectin to predict MH of entire colon was analysed.
Results: Mean age of enrolled patients was 16.13 ± 2.88 years. Among 58 patients, 34 (58.6%) were females and 18 (31.0%) were in MH status. Median faecal calprotectin level was 486.5 μg/g. Faecal calprotectin cut-off value for the prediction of MH, identified by receiver-operating characteristic analyses, was 148 μg/g with an area under the curve of 0.808. Sensitivity, specificity, positive predictive value and negative predictive value of sMH in predicting MH were 1, 0.82, 0.72 and 1, respectively. When we combined sMH with faecal calprotectin less than cut-off value, sensitivity, specificity, positive predictive value and negative predictive value were 0.56, 1.0, 1.0 and 0.83, respectively.
Conclusions: For patients with low-faecal calprotectin level, sigmoidoscopy might be sufficient enough to assess MH.

P585

Efficacy of iDose dashboard forecast for individualising Infliximab therapy: an Indian experience

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Background: Infliximab (IFX), a monoclonal antibody, is widely used in Inflammatory bowel disease (IBD) refractory to conventional immunosuppressive agents. Standard of care dosing of IFX in IBD is associated with significant loss of response, both primary and secondary. The loss of response is attributed to its highly variable and complex pharmacokinetics affecting IFX clearance. Dashboards based on Bayesian algorithms using multi-variate determinants of IFX concentration are proposed for individualised dosing. We aimed to assess the accuracy and efficacy of the iDose dashboard system.
Methods: The IFX levels estimated in our laboratory in IBD patients as a part of clinical service from April 2016 to October 2018 were compared with that forecasted by the iDose dashboard software. A total of 41 data points (estimated IFX level) were available from 29 patients. Patient's clinical history, demographic details, laboratory findings such as albumin and CRP were entered in the software and the predicted IFX level was compared with the estimated level. In addition, dashboard guided dosing strategy was prescribed in 5 patients who did not respond to standard dosing schedule and the clinical outcome was followed.
Results: Of 41 (73%) data points, 30 showed concordance in IFX level. An iDose guided dosing was clinically useful to achieve target IFX level and therapeutic response in 4/5 patients. The dosing interval was increased from 4 weeks to 7 weeks in one patients (with cost saving); in 3 patients the dosing was optimised with multiple drug estimations and iDose prediction with clinical remission and reduction in fistula output. One patient was switched to adalimumab due development of antibodies
Conclusions: There was 73% concurrence between the iDose dashboard predicted and observed infliximab level. This approach optimised the infliximab therapy by individualised IFX dosing and duration. It has potential to save cost.

P586

Comparative effectiveness of vedolizumab and ustekinumab as induction therapy in anti-TNF refractory Crohn's disease: a multi-centre retrospective cohort study

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Background: Anti-tumour necrosis factor (TNF) agents are effective in Crohn's disease (CD), but up to 30% of patients fail to respond or develop intolerance and require alternative biological therapy. Both vedolizumab and ustekinumab are licensed to treat anti-TNF refractory CD patients. Clinical trials of vedolizumab and ustekinumab in anti-TNF refractory patients suggest comparable efficacy, but no real-world data exist to guide clinicians' decision-making.[1,2] We conducted a multi-centre retrospective cohort study to assess the comparative effectiveness of vedolizumab and ustekinumab in treating anti-TNF refractory CD.
Methods: CD patients from four hospitals who were commenced on vedolizumab or ustekinumab following exposure to anti-TNF therapy were included. Disease activity was monitored serially by calculation of Harvey–Bradshaw index (HBI) for up to 4 months. Faecal calprotectin (FC) at baseline and subsequent visits were recorded if available. Clinical response was defined as a decrease in HBI ≥3 and remission by HBI <5. We compared the effectiveness of ustekinumab and vedolizumab.
Results: After exclusion of patients without evaluable data, 51 patients commencing vedolizumab and 25 commencing ustekinumab therapy were included. Baseline characteristics (age, disease location, behaviour, smoking status and baseline FC) were comparable in both cohorts. Clinical response, remission and steroid-free remission rates were comparable between vedolizumab and ustekinumab at 2 and 4 months (Table 1). There was a significant reduction in HBI for

vedolizumab at 2 months (1.8, 95% CI 0.50 to 3.13, p = 0.008) and ustekinumab at 4 months (3.4, 95% CI 1.84 to 4.96, p = 0.0001).

Table 1. Results at 2 and 4 months for vedolizumab and ustekinumab.

		Vedolizumab	Ustekinumab	Fisher's Exact Test (P value)
Response	2 months	37%	44%	0.623
	4 months	49%	60%	0.465
Remission	2 months	18%	28%	0.372
	4 months	27%	40%	0.302
Steroid-Free Remission	2 months	12%	20%	0.489
	4 months	25%	36%	0.422

Significance set at p = 0.05. Fisher's exact test demonstrates no significant difference between treatments at 2 and 4 months.

Results at 2 and 4 months for vedolizumab and ustekinumab. Significance set at p = 0.05. Fisher exact test demonstrates no significant difference between treatments at 2 and 4 months.

Conclusions: In a multi-centre cohort of anti-TNF refractory CD patients, vedolizumab and ustekinumab appear equally effective in the short-term. Our observations warrant longer-term follow-up and further validation in independent cohorts.

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P587

Quality of care indicators in inflammatory bowel disease: local pilot study

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Background: Recommendations have been established for an optimal care of inflammatory bowel disease (IBD) patients.[1–3] The aim of this study was determine whether patients were receiving appropriate care.

Methods: 40 consecutive patients with IBD from the outpatient Clinic of Bern University Hospital with at least 2 years of follow-up were retrospectively included in this pilot study. Clinical, laboratory and endoscopic data were collected from the patient files. Frequency of surveillance measures such as metabolic bone disease prevention, colon cancer and dermatological screening were also considered.

Results: The study population consisted of 40 patients 30 with Crohn's disease, 10 with ulcerative colitis (UC). 60% of patients with distal UC were receiving topical aminosalicylate therapy and oral aminosalicylates were appropriately dosed in 86% of the case. Unfortunately, 73% of patients have been treated with corticosteroids for longer than 3 months, however 96% of patient there was an attempt to start steroid sparing medications (azathioprine /6MP, MTX, Anti-TNF agents). Of the patients treated with either 6MP or AZA 75% were appropriately dosed. 78% of patient received adequate treatment to prevent metabolic bone disease. 90% of patients meeting indications for surveillance colonoscopy for dysplasia could undergo colonoscopy at the appropriate interval. 60% of patient did undergo a dermatological screening at least every 2 years.

Conclusions: According to current guidelines, there is room for improvement in the management of IBD patients. In particular, for the use of corticosteroids. In all other criteria, a satisfactory proportion of patients met the conditions for quality of care. A larger retrospective study, with extended criteria and clinical outcome analysis is required to build a valuable structure for quality assessment of our daily clinical practice.

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P588

Tacrolimus suppositories: a safe and effective treatment for treatment-refractory proctitis

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Background: Treatment-refractory proctitis is a miserable condition, with intractable urgency, tenesmus and often very high stool frequency and bleeding. These symptoms are both disabling and often highly distressing for patients, and yet because this patient group has been excluded from most biologic trials, the optimal treatment approach is unclear. Indeed, even surgery—the standard treatment for medically refractory UC—will initially leave most of the active disease behind. As such these patients can be extremely difficult to manage. Several small studies have suggested that topical tacrolimus can be an effective treatment in this cohort of patients. Here, we report our initial experience in a real-world setting.

Methods: Tacrolimus suppositories (2 mg) were made-to-order by a 'specials' pharmaceutical company (Martindale). Eligible patients with endoscopically-confirmed treatment-refractory proctitis (moderate–severely active) were identified from an outpatient setting and treatment (rectal tacrolimus 2 mg b.d. for 4 weeks) was initiated by gastroenterologists with an interest in IBD. Serum tacrolimus levels were checked once. Treatment response was assessed using a combination of PRO2 (rectal bleeding and stool frequency components of the Mayo score) and physician's global assessment.

Results: Between 2015 and 2018, 21 patients were treated with a total of 35 courses of topical tacrolimus. Twenty had UC and 1 had Crohn's disease. These patients had highly refractory disease (Figure 1), and 17 (81%) had required hospital admission and/or systemic steroids within the preceding year. The average number of immunomodulators and/or biologics previously used was 1.5 per patient. After 4 weeks of topical tacrolimus, 13 patients (62%) achieved clinical remission (PRO2 = 0), and a further 3 (14%) showed a clinical response (PRO2 decrease by >2 points) (Figure 2). Five patients (24%) did not respond. Serum tacrolimus levels were generally low (median 5.7 ng/ml) but did significantly correlate with clinical response (p = 0.002). In responders the average time to the next relapse was 9 months, and re-treatment with tacrolimus suppositories was clinically effective in 87% of cases. No side-effects were reported.

Figure 1. Previous treatments used.

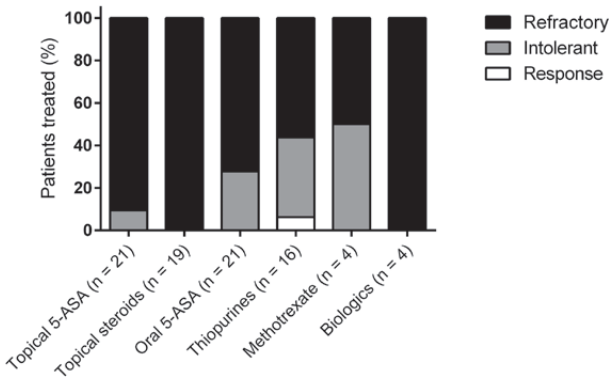
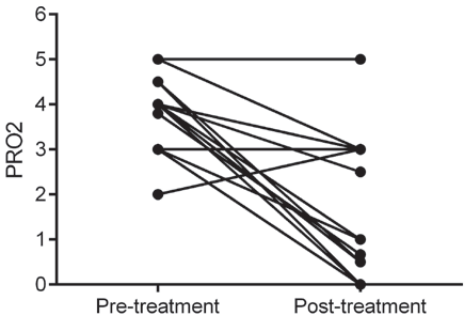


Figure 2. PRO2 scores before and after treatment.



If patients received more than one course of tacrolimus suppositories the mean pre- and post-treatment PRO2 scores are presented.

Conclusions: Tacrolimus suppositories are a safe and effective treatment for most patients with treatment-refractory proctitis.

P589

A population pharmacokinetic model to improve mucosal healing upon golimumab induction therapy in patients with ulcerative colitis

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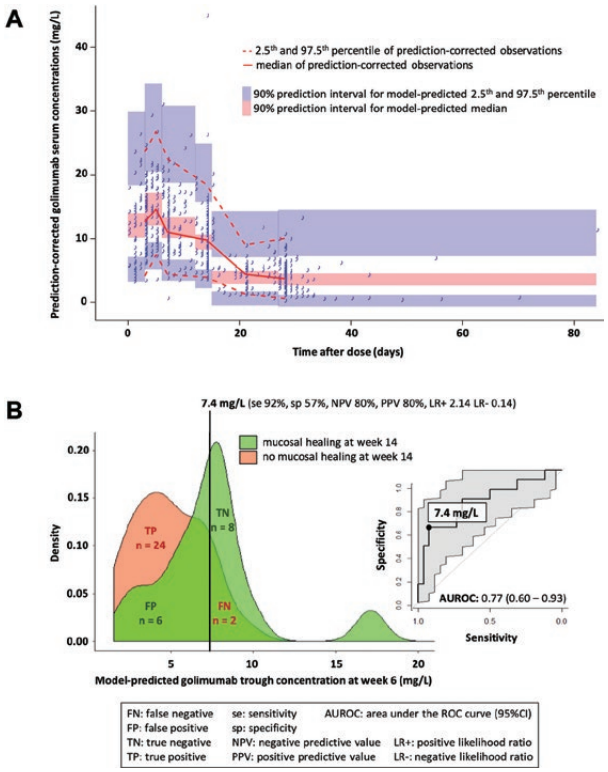
Background: From the PURSUIT programme, it is known that golimumab (GLM) trough concentrations (TC) >2.5 mg/l at week (w)6 of induction therapy are associated with clinical response in patients with ulcerative colitis (UC).[1] No TC threshold has been established for mucosal healing (MH; Mayo endoscopic score ≤1). A population pharmacokinetic (popPK) model may support dose optimisation to improve attainment of a predefined TC target.

Methods: GLM concentration–time data of 56 patients with UC (335 venepuncture and 296 dried bloodspot (DBS) samples) were obtained from 2 study centres (University Hospitals Leuven, Belgium and Ljubljana University Medical Centre, Slovenia).[2,3] A popPK model was developed using NONMEM 7.4. Exposure during GLM induction therapy was linked to MH at w14.

Results: A two-compartment popPK model with linear absorption and elimination showed good predictive capacity (Figure 1A). The estimated popPK parameters (typical value [%RSE]) were absorption constant (0.511 day^{-1} [8%]), apparent clearance CL/F (0.407 l/day [6%]), volume of distribution in the central compartment (9.16 l [5%]) and peripheral compartment V_p/F (3.21 l [22%]) and inter-compartmental clearance (0.464 l/day [13%]). Antibodies to GLM and higher alkaline phosphatase increased GLM CL/F, while prior biological use was associated with a larger V_p/F, all predicting lower GLM exposure. Still, 48% and 147% of the interindividual variability (IIV) on CL/F and V_p/F remained unexplained. A total of 14/40 patients (35%, 16/56 no endoscopy data available) achieved MH after GLM induction therapy. These patients had higher model-predicted GLM TC at w6 (median 7.6 mg/l, interquartile range [5.8–8.0]) compared with patients not achieving MH (4.7 mg/l [3.3–6.8]) (p = 0.005). A GLM TC threshold at w6 >7.4 mg/l predicted MH (Figure 1B). In addition, the estimated area under the GLM concentration–time curve (AUC) from w0 to w6 was higher when MH was achieved (p = 0.010).

Conclusions: With the currently approved induction dosing of GLM, only 10/40 (25%) reached the proposed 7.4 mg/l TC target at w6, suggesting underexposure in a substantial proportion of patients. This popPK model shows good predictive capacity and may be implemented in a therapeutic drug monitoring software tool to allow better targeting of the here established exposure targets (TC and AUC) in individual patients. Still, Bayesian updating of individuals' PK parameters using early DBS samples is recommended given the remaining large IIV.



(A) Prediction-corrected visual predictive check. (B) Density plot and receiver-operating characteristic (ROC) curve of pGLM TC at w6 as a predictor of MH at w14.

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P590

An interim analysis of real-world safety data from an ongoing, non-interventional, observational study of patients with inflammatory bowel disease treated with CT-P13, an infliximab biosimilar, in the context of usual care with reference infliximab

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Background: CT-P13 (Inflectra®/Remsima®) is an infliximab biosimilar of the reference product Remicade® (IFX-RP). We report an interim analysis of preliminary safety data for CONNECT-IBD, an ongoing, non-interventional, observational cohort study evaluating CT-P13 in the context of usual care with IFX-RP in the treatment of patients with Crohn's disease (CD) or ulcerative colitis (UC) in a real-world setting.

Methods: Patients were recruited during usual care at 150 academic and community sites in 13 European countries. Adult CD or UC patients prescribed CT-P13 or EU-sourced IFX-RP at the investigator's discretion and according to the approved label were eligible. This interim analysis reports primary outcomes (drug utilisation patterns and long-term safety) for patients who received CT-P13 either as their first biologic or as continuing treatment (CT-P13) or who switched from IFX-RP to CT-P13 (Switched) based on data collection from April 2015 to December 2017. Data were analysed descriptively.

Results: This analysis included 1957 patients (CT-P13, *n* = 1825; Switched, *n* = 132; Table 1). Of these, 1264 had CD, 692 had UC and 1 had missing diagnosis. Demographics and baseline characteristics were similar between groups. In total, 626 treatment-emergent adverse events (TEAEs) were reported in 438 (22.4%) patients: CT-P13 (22.2%) and Switched (25.0%). Incidences of TEAEs, serious TEAEs (12.1% vs. 12.1%) and TEAEs leading to discontinuation of study drug (8.1% vs. 6.8%) were balanced between CT-P13 and Switched groups, respectively. A higher percentage of Switched (2.3%) vs. CT-P13 (0.9%) patients discontinued from study due to AEs; however, this was likely driven by the smaller number of patients in the Switched group. Majority of patients reported TEAEs of mild-to-moderate intensity (overall: mild, 7.3%; moderate, 9.2%; severe, 5.8%). TEAEs and TEAES of special interest are summarised (Table 2). Two deaths were reported, both unrelated to study drug. Among the limitations were the difference in CT-P13 (*n* = 1825) vs. Switched (*n* = 132) group size and AE reporting which, due to the observational study design, had limited clinical details.

Table 1. Disposition, population characteristics and drug utilisation patterns for patients receiving CT-P13.

	CT-P13 (n=1825)	Switched from IFX-RP to CT-P13 (n=132)	All patients (N=1957)
Disposition, n (%)			
Ongoing in treatment phase	1342 (73.5)	68 (51.5)	1410 (72.0)
Ongoing in follow-up phase	1578 (86.5)	75 (56.8)	1653 (84.5)
Age, median (range), years	38 (18–87)	38 (18–69)	38 (18–87)
Male, n (%)	946 (51.8)	69 (52.3)	1015 (51.9)
History of fistulating disease, n (%)	382 (20.9)	35 (26.5)	417 (21.3)
Disease duration, median (range), months	73.0 (0–593)	111.5 (2–432)	75.0 (0–593)
Baseline dose			
n	1614	119	1733
Median (range), mg	350.0 (0–1040)	400.0 (5–1000)	360.0 (0–1040)
Baseline infusion frequency, n (%)			
Once every 7 or fewer weeks	464 (25.4)	49 (37.1)	513 (26.2)
Once every 8 weeks	1021 (55.9)	59 (44.6)	1080 (55.1)
Other	136 (7.4)	11 (8.3)	147 (7.5)
Missing	204 (11.1)	13 (9.8)	217 (11.0)

IFX-RP=infliximab reference product (Remicade®).

Table 2. Most frequently (≥2.0%, all patients) reported all-causality TEAEs and TEAE S of special interest for patients receiving CT-1)13[a].

	CT-P13 (n=1825)	Switched from IFX-RP to CT-P13 (n=132)	All patients (N=1957)
Number of TEAEs	582	44	626
Patients with ≥1 TEAE, n (%)	405 (22.2)	33 (25.0)	438 (22.4)
Drug ineffective	81 (4.4)	3 (2.3)	84 (4.3)
Hypersensitivity	59 (3.2)	6 (4.5)	65 (3.3)
Skin reaction	38 (2.1)	3 (2.3)	41 (2.1)
Opportunistic infection	36 (2.0)	4 (3.0)	40 (2.0)
Patients with ≥1 TEAE of special interest, n (%)	127 (7.0)	17 (12.9)	144 (7.4)
Serious infections (including opportunistic infection and excluding tuberculosis)	43 (2.4)	6 (4.5)	49 (2.5)
Infusion-related reactions	42 (2.3)	2 (1.5)	44 (2.2)

[a] Treatment-emergent: event started or worsened in severity after the start of CT-P13 (or IFX-RP) treatment until the end of the observation period for the study.
IFX-RP=infliximab reference product (Remicade®); TEAE=treatment-emergent adverse event.

Conclusions: Results from this interim analysis of CT-P13 in a real-world setting were consistent with the known safety profile of infliximab and did not identify new safety information to change the benefit–risk profile of CT-P13.

P591

Low donor microbial engraftment after combined endoscopic and oral faecal microbiota transplant (FMT) in patients with antibiotic dependent pouchitis

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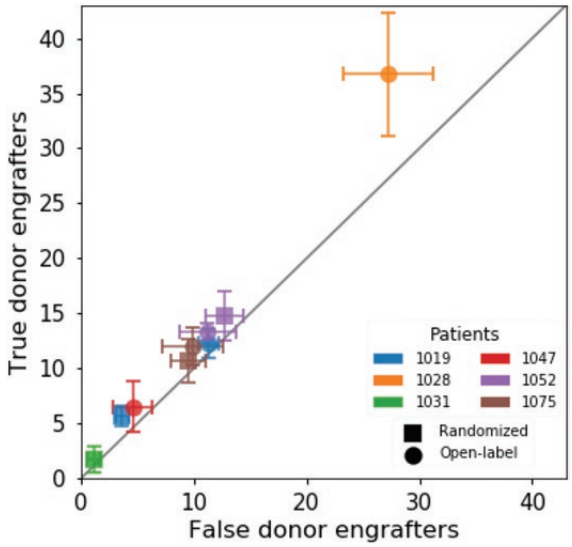
Background: A significant number of pouch patients develop antibiotic dependent pouchitis (ADP) after ileo-anal pouch anastomosis. Microbial dysbiosis, which can only be controlled with antibiotics, is thought to be a major driver of clinical symptoms in ADP. The objective of

this placebo-controlled proof-of-concept faecal microbiota transplant (FMT) study was to evaluate safety, efficacy and donor microbial engraftment of an intensified FMT approach in patients with ADP.

Methods: Patients with ADP (defined by the continuous need for antibiotic therapy to control symptoms) in clinical remission as defined by a modified pouch activity index < 4 were randomised to either active endoscopic FMT (eFMT=24 g FMT) or placebo eFMT followed by daily active encapsulated oral FMT (oFMT; 6 FMT capsules/day=4.2 g FMT) or identical placebo capsules for 14 days. Antibiotics were discontinued before randomisation. In case of relapse patients could participate in an open-label active eFMT and oFMT. FMT and matching placebo were provided by a stool bank (OpenBiome). Endpoints were safety, clinical remission without need for antibiotics during 16 weeks of follow-up, quantitative changes of faecal calprotectin (FCP) and engraftment of donor FMT. For engraftment analyses, 16S rRNA sequencing of stool samples collected before and after FMT was performed.

Results: Six patients were randomly assigned to receive active or placebo FMT. All patients experienced relapse with increase of diarrhoea and urgency either during or shortly after completion of FMT. Five patients continued with open-label active FMT and 80% (4/5) experienced a relapse with concomitant increase of FCP during or shortly after completion of FMT. No FMT-related safety events were observed. Due to the unexpected low efficacy of FMT, the steering committee decided to halt enrolment to assess for FMT engraftment. FMT engraftment was sustained in 1 out of 6 subjects (Figure 1). This patient (1028) did not relapse and remained off of antibiotics for the study period of 16 weeks.



Engraftment of active donor endoscopic followed by oral FMT in 6 patients in the randomised or open-label portion of the trial. Three patients received active FMT twice in both portions of the trial.

Conclusions: Low donor FMT engraftment is the most likely reason for the low clinical efficacy of FMT in this pilot study in patients with ADP. Thus, before embarking on larger clinical trials with FMT in patients with ADP or other forms of pouchitis it is mandatory to explore approaches for superior FMT engraftment. This study was funded by Litwin IBD Pioneers Initiative.

P592

Towards a Food Pharmacy: increased dietary quality reduces CRP and improves quality of life in IBD patients in remission

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Background: Evidence is emerging that a Mediterranean diet (MeD) can modulate the immune system and restore the gut epithelial barrier, thereby ameliorating inflammatory Bowel disease (IBD) -related complaints and quality of life (QOL). Therefore, we evaluated the effect of MeD during 6 months on QOL and inflammation. A MeD is characterised by use of olive oil as main culinary fat and a high intake of fruits, vegetables, legumes, nuts and fish, and a low intake of red meat.

Methods: A prospective case–control study evaluating the effect of a MeD on QOL and inflammation was performed. IBD patients with quiescent disease (defined as faecal calprotectin (FCP) < 150 mg/g and/or a SES-CD <5 (Crohn's disease (CD)) / MAYO <1 (ulcerative colitis (UC) / IBD-Unclassified (IBD-U)) were enrolled at the IBD unit of the Leiden University Medical Center. Patients with a healthy diet or eating disorder were excluded. Patients willing to change their lifestyle were included in the Voeding Leeft program, which is closely comparable to a MeD within the context of a healthy lifestyle. Support was provided during three instruction and feedback days and using an online platform. The following parameters were measured at baseline and 6 months: the short IBD questionnaire (sIBDQ), fatigue score (1–10), Harvey–Bradshaw index (HBI) for CD and partial mayo score (PMS) for UC and C-reactive protein (CRP). The MDSS (Mediterranean Diet Serving Score) was used to score how much the patients' diet resembled a MeD, on a scale from 0 to 24.

Results: In total, 94 patients were included in the study. Thirty-eight patients (intention to treat population, ITT) were included in the intervention group. Of these, 27 patients (per protocol population, PP) completed the 6 months period. In both the ITT and in the PP, the MDSS was increased at the end of the study period. In both the ITT and PP population, the intervention increased the sIBDQ and reduced the CRP. In the ITT group, the changes in sIBDQ (r = 0.39, p = 0.035) and CRP (r = –0.65, p = 0.001) were correlated to the improvement in the MDSS. In the control group, no changes in MDSS, sIBDQ or CRP were observed.

	Intention-to-treat population			Per protocol population			Controls		
Number of patients	38			27			56		
Mean age	46.4			47.19			44.50		
% female	64%			67%			48.5%		
IBD type	13 (33.3%)UC/IBDu			9 (33.3%) UC/IBDU			31(54.4%) UC/IBDU		
	start	+6 m	p	start	+6 m	p	start	+6 m	p
MDSS	9.8	12.8	<0.001	8.8	13.1	<0.001	7.8	7.6	0.500
sIBDQ	50.8	54.7	<0.001	52.9	57.6	<0.001	56.6	57.2	0.540
CRP	3.6	2.6	<0.050	3.3	2.1	0.035	5.0	3.5	0.120
FCP	66.7	72.6	0.78	61.3	59.7	0.931	47.9	209.5	0.274
HBI	3.88	2.88	0.14	3.28	2.06	0.097	3.24	3.28	0.514
PMS	1.15	0.46	0.15	0.88	0.13	0.034	0.50	0.38	0.666
Fatigue	4.8	3.7	0.010	4.8	3.1	0.005	-	-	-

MDSS Mediterranean diet serving score; sIBDQ (QoL questionnaire); CRP C reactive protein; HBI Harvey Bradshaw index; PMS partial Mayo Score, FCP fecal calprotectin.

Conclusions: In quiescent IBD patients, over 70% of patients was able to adhere to the Voeding Leeft lifestyle program containing a MeD-like diet, for 6 months. The MeD improved QOL and reduced CRP. In the diet group, improvements in sIBDQ and reduction in CRP were related to the improvement in diet quality. These results demonstrate the value of lifestyle medicine in IBD patients.

P593

A national database study on colectomy and colorectal cancer in ulcerative colitis: what is the role of appendectomy?

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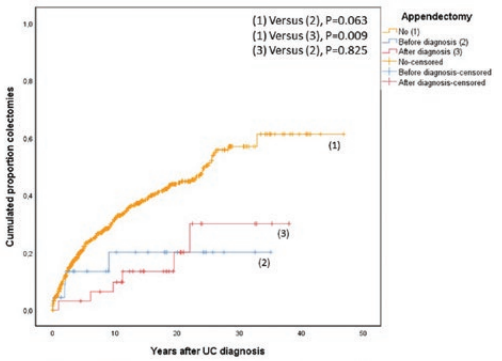
Background: Appendectomy prevents the development of ulcerative colitis (UC), and might have a positive effect on the disease course of UC. However, several studies indicated an increased risk of colectomy and colorectal cancer (CRC) after appendectomy in UC, and discourage the use of an experimental appendectomy. Nonetheless, it seems premature to draw strong conclusions, as these retrospective studies did not correct for possible confounding factors. The aim of this study was to evaluate the risk of colectomy and CRC after appendectomy in UC patients, while correcting for relevant confounders.
Methods: All included patients were retrieved from the prospective national Initiative on Crohns and Colitis Parelsnoer Institute – inflammatory bowel disease (IBD) database. From 2007, consecutive IBD patients were continuously invited to participate. For inclusion in the current study, patients had to have UC, and data on both appendectomy and colectomy and/or CRC rate had to be available. Primary outcomes were the risk of colectomy and CRC. Outcomes were compared in patients with and without appendectomy, with a separate analysis for timing of appendectomy (before or after UC diagnosis).
Results: In total, 826 UC patients (54.7% female) with a median age of 46 (range 18–89) years were included from 2007 until May 2018. Sixty-three (7.6%) patients previously had an appendectomy: 24 (38.1%) before UC diagnosis, 33 (52.3%) after diagnosis, and in 6 (9.5%) patients the timing was unknown. On baseline characteristics, patients with an appendectomy had a significantly lower rate of colectomy (19.0% vs. 37.6%; p = 0.003) and tended to have more often PSC (11.8% vs. 5.7%; p = 0.090). In multi-variate analysis, appendectomy after UC diagnosis was associated with a significantly lower risk of colectomy compared with no appendectomy (HR 0.15, 95% CI 0.04–0.59; p = 0.007), and the same trend was seen in patients with appendectomy before UC (HR 0.36, 95% CI 0.09–1.47; p = 0.156). Kaplan–Meier analysis demonstrated that appendectomy was associated with a significantly postponed colectomy, in particular when performed after UC diagnosis (p = 0.009).



Number at risk						
No appendectomy	714	306	120	28	6	0
Appendectomy before UC	23	12	7	2	0	0
Appendectomy after UC	32	27	12	4	0	0

No significant differences were found in the CRC rate for patients with and without an appendectomy (1.6% vs. 1.2%; p = 0.555).
Conclusions: An appendectomy during the course of UC is associated with an 85% decreased risk of colectomy and a postponed resection in patients who did undergo colectomy. As the colon is longer in situ the risk of developing CRC remains, emphasising the importance of endoscopic surveillance.

P594

Predictors of non-response to repeated faecal microbiota transplantation in patients with therapy refractory ulcerative colitis

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Background: Double-blind randomised studies investigating faecal microbiota transplantation (FMT) in chronic active ulcerative colitis (UC) have shown promising results so far. Factors influencing the efficacy of FMT in UC still remain unclear. FMT protocols for the treatment of UC patients vary in dose, frequency, route of application and donor stool preparation and might thus influence remission rates. The aim of this analysis was to find clinical predictors for non-response to FMT in UC.
Methods: 54 patients suffering from chronic active ulcerative colitis were treated with repeated FMT (5 times every second week) using the same protocol with the exception of donor stool preparation. Thirty patients (mean age 37 y ± 9) were treated with frozen donor stool (mixed with sodium chloride and glycerol, stored at –80°C) and 24 patients (mean age 43 y ± 14) with freshly prepared donor stool (not older than 6 h). Remission and response were determined by total Mayo score (TMS) before FMT and at Day 90. Clinical response was defined as a decrease of ≥3 points in TMS from baseline, along with either a decrease of >1 point in the rectal bleeding subscore or the absolute rectal bleeding subscore of 0 or 1. Remission was defined as a TMS <2 and an endoscopic subscore of 0 or 1. Clinical data as well as blood and stool analysis were assessed at any time point and potential predictors for non-response were calculated using regression analysis.
Results: At baseline patients had a total Mayo score of 9.0 ± 2.0 and an endoscopic subscore of 2.5 ± 1.0. 65% of patients had failed previous biologic therapy and 70% previous immunosuppressive treatment. In total 59% of patients responded to FMT, 24% achieved remission while 41% showed no response. The mean total Mayo score dropped to 5.3 ± 3.2 at Day 90. Non-response to biologics (hazard ratio (HR): 0.23 (95% CI 0.06–0.85), p: 0.03), a total Mayo score before FMT ≥9 (HR: 0.26 (95% CI 0.07–0.95), p: 0.04) and a high endoscopic subscore before FMT (HR: 0.27 (0.10–0.69, p < 0.01) were associated with lower remission rates. There was no significant difference in decrease of TMS (p = 0.51) or in remission and response rates (p = 0.97), respectively in patients receiving fresh or frozen donor stool at Day 90.
Conclusions: Failure to previous biologic treatment as well as a high total Mayo score and a high endoscopic subscore are associated with lower remission rates to FMT in chronic active ulcerative colitis.

P595

Early medical therapy and risk of subsequent perianal fistula development among paediatric patients with Crohn's disease

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Background: Crohn's disease (CD) commonly causes perianal fistulas (PF). Evidence for effective PF preventive strategies is lacking. Early steroid sparing therapy (SST) use improves other CD outcomes and decreases steroid use. We sought to determine whether early SST prevents or delays PF development among children without PF at CD diagnosis.
Methods: We identified patients with CD age 5–24 years in OptumInsight Clinformatics Data Mart (2001–2014). Diagnosis required minimum 3 CD claims within 3 years of initial diagnosis. CD diagnosis date was the first occurrence of any inflammatory bowel disease claim. We required 6 months run-in period before, and 2 years continuous follow-up after diagnosis. PF was identified by previously validated claims-based case definition (perianal/genital fistula/abscess, or seton/fistulotomy). Patients were excluded if PF <90 days after CD diagnosis. SST was defined as immunomodulator and/or anti-tumour necrosis factor (TNF) medication. Early SST use was characterised within 6 months after CD diagnosis, and only if started prior to PF. PF development was compared for those with/without early SST. Propensity score (PS) matching for patient characteristics/comorbidities was used to balance baseline characteristics. Cox multi-variate regression analysis estimated hazard ratios (HR) for PF development.
Results: We identified 2378 patients with CD (mean age 17 years, 49% female, 78% white). PF developed after diagnosis among 342 (14%). Overall, 40% initiated early SST (immunomodulator alone 28%, anti-TNF 11%); rates increased two-fold from 22% in 2001 to 45% in 2014 (trend test $p < 0.001$). There were differences in early SST use by sex (female 36%, male 43%; $p < 0.001$) and household income (greater income, higher risk SST; $p = 0.002$). Higher income was associated with lower risk of PF (HR = 0.55, $p = 0.0495$). Among patients diagnosed in later years there was a trend toward lower risk of PF with early SST (average 2001–2011: 11.5% vs. 2012–2014: 6.2%). After PS matching, 942 patients remained in each group. Early SST was not associated with risk of PF development in 3 yr after CD diagnosis (HR = 1, 95% CI = 0.75–1.34, $p = 0.98$). Antibiotic use was associated with 57% greater risk of developing PF (HR = 1.57, 95% CI = 1.18–2.09, $p = 0.002$). For each year a patient aged, risk of developing PF increased 4% (HR = 1.04, 95% CI = 1.01–1.08, $p = 0.01$). After PS matching, there were no longer differences by sex, income, or year of diagnosis.
Conclusions: We found that among paediatric CD patients without PF at diagnosis, later PF development is common. SST use soon after CD diagnosis is uncommon, but increasing. Changing trends in use of early SST may lead to decreased PF development, although this is not conclusive. Further research is needed to identify optimal treatment for PF prevention.

P596

An ongoing safety registry to identify rare and severe complications in children with paediatric-onset IBD

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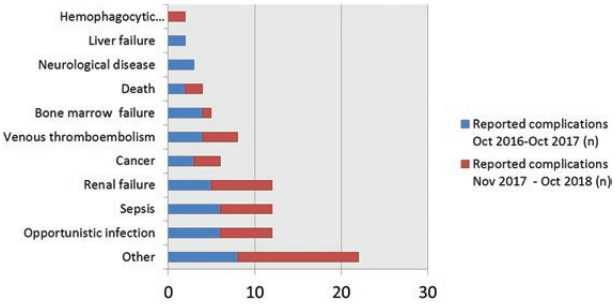
Background: Paediatric-onset IBD (PIBD) patients often present with more serious disease than adults and are exposed to intensive treatment, which may cause rare but very severe complications. Due to the rarity of these events available data are limited, resulting in prevention and treatment recommendations based on very low evidence or even absence of any recommendations. Therefore, an international study is essential to obtain data on incidence and to characterise these complications. With the setup of a safety registry for rare and severe complications in PIBD we aim to improve knowledge on incidence and risk factors of rare and severe complications.
Methods: Paediatric gastroenterologists in 26 different countries reply monthly to an electronic survey to indicate whether they have seen one of 10 predetermined complications in an IBD patient <19 years of age. It also enables the physician to report another, in their opinion rare and severe, complication. Information about disease, previous therapies and specific complications is collected for each registered complication. Additionally, participating physicians annually report the number of new and current PIBD patients under their care. The calculation of the incidence per country and region uses validated population statistics from Eurostat and the Poisson distribution for rare events.
Results: In this ongoing registry 1952 responses were received from October 2016 – October 2018 based on responses of 128 paediatric gastroenterologists (response rate 80%). A total of 88 categorised complications were reported.



Among the 7 reported cases of a venous thromboembolism were 2 cases of a venous sinus thrombosis. All were having an exacerbation of IBD and in only two patients another risk factor was present. The two reported cases of hemophagocytic lymphohistiocytosis were both using azathioprine and mesalazine, had a primary EBV infection and fully recovered. Other reported complications vary from acute psychosis to an air embolism during colonoscopy.
Conclusions: Since the start of this registry 88 rare and severe complications in PIBD patients were prospectively identified. Besides the identification of a variety of severe adverse events, this enables understanding possible causes, management and outcomes of rare but severe events in PIBD. Moreover, this may enable prevention of these events. Combined with the denominator data that are being collected this will provide data on the incidence of these severe outcomes.

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Optimising therapeutic drug monitoring of adalimumab with dried blood samples in IBD patients: an interim analysis

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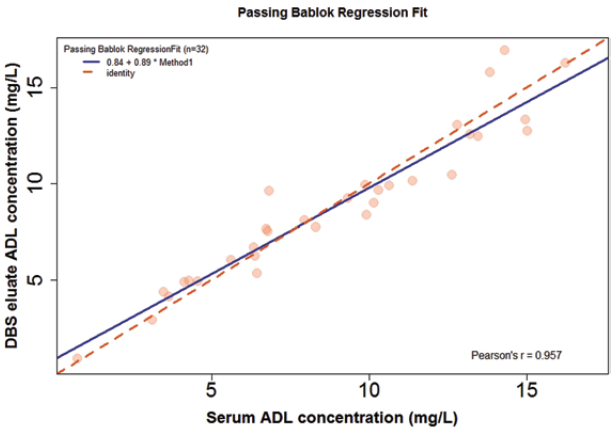
Background: Therapeutic drug monitoring (TDM) can optimise the efficacy of adalimumab (ADL) in patients with inflammatory bowel disease (IBD). Capillary blood obtained via finger prick (i.e. dried blood samples (DBS)) can be used to measure anti-TNF serum concentrations. Patients suspected of loss of response to ADL, can send in a DBS from home to check the serum ADL concentration. Dose adjustments for a patient can then be made without coming to the hospital first. We compared ADL serum concentrations and ADL concentrations measured by DBS in IBD patients.
Methods: IBD patients, receiving ADL therapy, were prospectively enrolled during a scheduled routine visit to the outpatient clinic. From each patient, blood was obtained via venepuncture and via DBS. Capillary blood for DBS was obtained with a Mitra microsampling device. Serum and DBS ADL concentrations were measured using an ELISA (Sanquin, the Netherlands) with lower limit of quantification (LLOQ) of 0.01 mg/l. A fixed haematocrit (Hct) value of 0.42 was used to convert DBS eluate results to values which can be compared with (venous) serum concentrations. Pearson's correlation coefficient was used to assess correlation between venepuncture and DBS results, and Passing-Bablok regression was performed.
Results: Thirty-three patients (Crohn's disease: 27, ulcerative colitis: 6) were evaluated in this interim analysis. Thirty-one patients received ADL maintenance treatment. One patient was excluded because ADL concentrations were below LLOQ by using either DBS or venous blood (with detectable anti-ADL antibodies). Median [interquartile range (IQR)] albumin and CRP were 43 g/l [42–45 g/l] and 1.7 mg/l [0.9–3.9 mg/l], respectively. Samples were obtained after a median [IQR] of 6 [4–10] days after the last ADL administration with a median [IQR] serum ADL concentration of 5.1 [8.3–12.7] mg/l. Patients had a median [IQR] serum Hct of 0.40 L/l [0.42–0.44 L/l]. A high correlation was found between venepuncture and DBS results (Pearson's correlation coefficient: 0.96). Passing-Bablok regression showed no proportional or systematic bias with the intercept of the regression line including zero (0.84 mg/l (95% CI -0.08–1.56 mg/l)) and the slope including 1 (0.89 (95% CI 0.79–1.01)).



Conclusions: DBS via finger prick can be used for the assessment of serum ADL concentrations. This method can facilitate broader use of TDM in the treatment of IBD patients using ADL.

P598

Safety and effectiveness of adalimumab treatment in 1523 patients with ulcerative colitis: Results from a prospective, multi-centre, observational study

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Background: In a Phase 2/3 trial and its 4-year extension, adalimumab (ADA) induced early clinical remission that was maintained with no new safety signals in Japanese patients (patients) with moderate-to-severe active ulcerative colitis (UC). We conducted an observational study to evaluate the real-world safety and effectiveness of ADA in UC.
Methods: This prospective, multi-centre, post-marketing, 52-week study was conducted between 2013 and 2018 in Japan (NCT01947816). Pts with moderate-to-severe UC who were prescribed ADA were included in the study. Subcutaneous ADA was administered at an initial dose of 160 mg, followed by 80 mg at 2 weeks, and then 40 mg every other week. The primary endpoint was the incidence of adverse drug reactions (ADRs). Effectiveness endpoints included assessments of clinical remission based on partial Mayo scores (pMS), mucosal healing, steroid-free remission, and change in C-reactive protein (CRP) levels from baseline.
Results: Of 1593 registered patients, 1523 (male, 57.6%; mean age, 41.8 years) and 1241 were included in the safety (Table 1) and effectiveness population, respectively.

Table 1. Patient demographics and baseline characteristics

Characteristics	Safety analysis population (n=1523)
Sex, male, n (%)	878 (57.6)
Age, years, mean±SD	41.8±16.1
Body weight, kg, mean±SD	57.4±11.8
Duration of UC, years, mean±SD	7.9±7.6
History of allergy, yes, n (%)	331 (21.7)
History of smoking, no, n (%)	1029 (67.6)
Prior use of medications for UC, yes, n (%)	1521 (99.9)
Prior use of biologics, yes, n (%)	408 (26.8)
Infliximab	390 (25.6)
Other biologics	23 (1.5)
Concomitant medications, yes, n (%)	
5-Aminosalicylic acid	1310 (86.0)
Corticosteroid	709 (46.6)
Azathioprine and 6-mercaptopurine	664 (43.6)
Tacrolimus and cyclosporine	72 (4.7)
Antibiotics	111 (7.3)
Other	1187 (77.9)
Disease location, n (%)	
Rectum only (no colon)	37 (2.4)
Transverse and/or ascending colon	1018 (66.8)
Other	465 (30.5)
Unknown	3 (0.2)
Partial Mayo score, mean±SD	5.0±2.1
0 to <3, n (%)	198 (13.0)
≥3 to <6, n (%)	570 (37.4)
≥6 to <9, n (%)	696 (45.7)
Unknown/not provided, n (%)	59 (3.9)

SD, standard deviation; UC, ulcerative colitis

The period of ADA administration was 266.9 ± 135.5 days (mean ± standard deviation [SD]) in the safety population. ADRs and serious ADRs were reported in 18.1% (276/1523) and 4.9% (74/1523) of patients, respectively (Table 2).

Table 2. Summary of ADRs.

	Safety analysis population (n=1523)	
	ADR	Serious ADR
All, n (%)	276 (18.1)	74 (4.9)
ADRs of interest, n (%)		
Infection	92 (6.0)	27 (1.8)
Tuberculosis*	3 (0.2)	3 (0.2)
Malignancy	7 (0.5)	7 (0.5)
Injection site reaction	10 (0.7)	0 (0)
Interstitial pneumonia	6 (0.4)	4 (0.3)
Autoimmune disease	5(0.3)	5 (0.3)
Pancytopenia	0 (0)	0 (0)
Demyelinating disease	0 (0)	0 (0)
Cardiac failure congestive	0 (0)	0 (0)

Also included in 'infection'
ADR, adverse drug reaction

Infection was reported in 6.0% (92/1523) of patients and tuberculosis was reported in 0.2% (3/1523) of patients. No cases of de novo or reactivation of hepatitis B were reported. Clinical remission was achieved in 49.7% (531/1068) of patients at Week 4 and increased to 74.4% (539/724) at Week 52. In patients who used steroid at baseline, steroid-free remission rates gradually increased over time, from 10.4% (51/489) at Week 4 to 32.9% (124/377) at Week 24 and 53.1% (171/322) at Week 52. More than 60% of patients showed mucosal healing at Weeks 24 (Mayo endoscopic sub-score [MES] 0, 29.5%; MES1, 34.4%) and 52 (MES0, 34.3%; MES1, 33.3%). The CRP levels decreased from baseline (1.2 ± 2.4 mg/dl, n = 1058) to Weeks 4 (0.6 ± 1.7 mg/dl, n = 882) and 52 (0.3 ± 0.9 mg/dl, n = 597).

Conclusions: ADA treatment was efficacious and well tolerated in patients with UC in real-world settings, without any new safety signals.

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Development of an inflammatory bowel disease-specific nutrition screening tool (IBD-NST)

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Background: Patients with inflammatory bowel disease (IBD) frequently report that their nutritional concerns are unmet. Current nutrition screening tools identify malnourished patients with low body mass index (BMI) or significant weight loss but may not identify all IBD patients at nutrition risk. This study aimed to develop and test an IBD-specific nutrition self-screening tool (IBD-NST).

Methods: IBD patients were recruited prospectively to independently complete IBD-NST and Malnutrition Universal Screening Tool (MUST). Subjective global assessment (SGA) and hand grip strength (HGS) were completed by a dietitian. The IBD-NST scored nutrition risk as low (0), moderate (1) or high (≥2), with equal importance given to BMI, unintentional weight loss, and a combination of active disease and nutrition concerns. Scores were compared with sub-optimal (15% below the mean) HGS, mid-upper arm muscle circumference (MAMC), BMI, weight loss >5% and SGA. χ^2 compared dichotomous outcomes and Receiver Operator Characteristic curves were used for prediction assessment with a cut-off of AUC < 0.7 for poor prediction.

Results: 101/116 patients (87%) were recruited, 54 (53%) were female, 61 (60%) had CD, 33 (33%) had UC and 7 (7%) had IBD-U. Mean (SD) age was 40 (14) years and BMI was 24.6 kg/m^2 (4.3). SGA identified 11/91 (12%) with malnutrition and IBD-NST and MUST identified a similar number of patients at nutrition risk (Table 1). Twelve patients were low risk for MUST but high risk for IBD-NST due to having a flare and concerns about their nutrition. Unlike SGA and MUST, IBD-NST nutrition risk was not predicted by BMI (AUC = 0.262 (SE 0.06) (95% CI 0.17, 0.40)). No statistically significant difference in suboptimal HGS was seen across BMI categories of underweight (7/9 (78%)), healthy (28/46 (61%)), overweight (14/23 (61%)) and obese (6/12 (50%)). Patients with >5% weight loss (13/101 (13%)) or suboptimal HGS (56/101 (55%)) were significantly more likely to be at nutrition risk using IBD-NST, MUST and SGA ($p < 0.05$). Patients with suboptimal MAMC (10/66 (15%)) were not significantly more likely to be at nutrition risk using IBD-NST or MUST ($p > 0.05$).

Table 1. Patients identified at nutrition risk by IBD-NST and MUST.

		MUST			
		Low	Moderate	High	Total
IBD-NST	Low	60	4	4	68 (67%)
	Moderate		9		9 (9%)
	High	12	1	11	24 (24%)
	Total	72 (71%)	14 (14%)	15 (15%)	101

Conclusions: The IBD-NST identifies more patients with high nutrition risk, and equally weights physical, disease, and nutritional identifiers of nutrition risk and places less importance on BMI than SGA or MUST. Finally, we confirm that BMI is a poor indicator of HGS in IBD supporting a reduced importance in identifying nutrition risk. Further work is required to validate the IBD-NST.

P600

Ustekinumab for Crohn's disease: a nationwide real-life observational cohort study from Finland

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Background: There is limited real-life data on ustekinumab (UST) treatment in patients diagnosed with Crohn's disease (CD). The present study is a retrospective non-interventional chart review of dosing and short-term clinical outcomes in patients with CD who were treated with UST in Finland (FINUSTE, EUPAS 24728 registration). The aim of the study was to describe the current treatment patterns and the positioning of UST, and to observe changes in clinical outcomes.
Methods: FINUSTE was performed in 13 Finnish hospitals. Eligible patients were adults with confirmed CD who were induced with intravenous UST (approx. 6 mg/kg) during year 2017. UST treatment patterns were explored in dosing frequency, mean and median dose at the induction and maintenance phase. The clinical outcomes were observed as proportion of patients achieving clinical response or remission at 16 weeks and at the end of follow-up. Remission was defined as Harvey–Bradshaw index (HBI) 4 points or less, response as HBI reduction of at least 3 points and clinical benefit as the proportion of patients in remission and/or response. For endoscopic response, the Simple Endoscopic Score for Crohn's disease (SES-CD) was used.
Results: 48 patients (54% female) initiated UST treatment for CD. The median age of the patients was 39 years with a median disease duration of 13 years. Fifty-two per cent of the patients had a stricturing, 29% inflammatory and 19% penetrating disease. More than 60% of the patients had CD-related surgeries prior to UST treatment. Out of 48 patients, only 2 (4%) were bionaïve, 25% were treated with one biologic agent and 71% with 2 or 3 biologic agents prior to UST. The average UST induction dose was 5.6 mg/kg and maintenance treatment was initiated in 88% of the induced patients. After initiation of UST, the proportion of patients on corticosteroids decreased from 48% to 25% in 16 weeks. At the end of follow-up, 11% of the patients with follow-up exceeding 16 weeks (n = 37) remained on corticosteroids. Clinical outcomes at 16 weeks and end of follow-up are described in Figure 1. Endoscopic response with ≥50% reduction from baseline in the SES-CD was observed in 67% of patients with endoscopic data (n = 9) at 16 weeks.
Conclusions: In patients with highly refractory and long-standing CD, the treatment with UST was shown to be effective in inducing short-term clinical benefit and endoscopic response, as well as allowing for significant corticosteroid tapering.

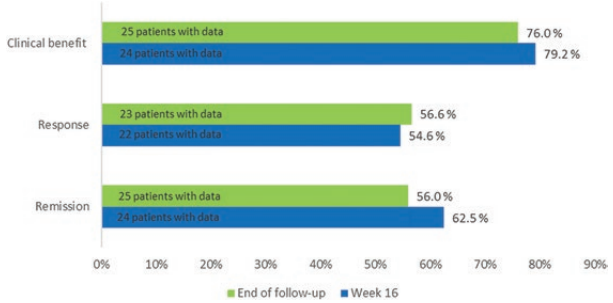

Figure 1. Clinical outcomes at Week 16 and end of follow-up (on average 8 months of follow-up).

P601

Differential cytokine profiles and drop of faecal calprotectin for prediction of primary response to infliximab induction therapy in Crohn's disease

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Background: One third of Crohn's disease (CD) patients do not achieve a clinical response after the induction therapy with infliximab (IFX). Cytokines emerge as possible biomarkers of response, as they are directly implicated in the pathogenesis of CD. Furthermore, novel cytokines have been described recently (ie, Oncostatin M (OSM)[1]). Their utility as biomarkers remains to be explored. Response to IFX seems to be well reflected by a drop in faecal calprotectin (FC).[2] We aimed to determine plasmatic cytokine profiles of active CD patients that started IFX treatment, their changes after the induction therapy, and their capacity to predict response to IFX.
Methods: Twenty-two active CD patients (68% males) receiving an induction therapy of IFX (5 mg/kg weeks 0, 2, 6) were included in the study (45% L1). Peripheral blood samples (for cytokine analysis) and faecal samples (for FC analysis) were collected on weeks 0 and 14. Fifteen cytokines (IL-1β, -2, -6, -7, -8, -10, -12p70, -13, -17, -21, -22, -23, IFNγ, TNFα and OSM) concentrations were measured by Luminex technology. FC concentration was determined by ELISA. Response to IFX was evaluated by the drop of FC based on its logarithm values (Ln FC week 0 – Ln FC Week 14). Other clinical parameters (HBI, CRP) were also considered. R statistical software, random forest predictive model, heatmap graphs and Rho Spearman (R^2) were used for data analysis.
Results: FC and HBI median values were 498 µg/g (IQR: 247, 918.5) and 7 (IQR: 5.25, 8) pre-induction; and 104 µg/g (IQR: 29, 767) and 3 (IQR: 1.25, 5) post-induction, respectively. Random forest model showed 10 pre-treatment cytokines on the top plot which were related to response: TNFα, IL-13, OSM, IL-7, IL-10, IL-8, IL-23, IL-17, IL-6 and IL-22. Among these cytokines, TNFα, IL-13 and OSM were statistically significant. Heatmap graphs showed that higher levels of IL-13 pre-treatment, low TNFα levels and the presence of OSM were significantly associated with a better IFX therapy response. The analysis of the cytokines' networks showed that most important correlations were established between IL-17, IL-1b, IL-2, and IFNγ (R^2 = 0.92; 0.82; 0.79; 0.77) where IL-13 was also present (R^2 = 0.51). TNFα and OSM belonged to different networks: TNF was associated to IL-8 (R^2 = 0.68), and OSM to IL-22 (R^2 = 0.67). This is the first study exploring the plasma concentration of OSM and its utility as biomarker in CD.
Conclusions: Determination of IL-13, TNFα, and OSM plasma concentrations could help to predict response to the IFX therapy. Networking analysis supports the idea that cytokines may be analysed in groups instead of individually. IL-13, TNFα and OSM seem to have differential and specific interconnections.

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P602

CD-TREAT a novel dietary therapy of active Crohn's disease using the exclusive enteral nutrition paradigm

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Background: Treatment with exclusive enteral nutrition (EEN) in Crohn's disease (CD) offers a nutritional therapy paradigm that could potentially be replicated by less restrictive dietary therapies, thereby improving compliance and tolerability. On this premise, we developed a food-based diet (CD-TREAT) to replicate the efficacy of EEN. Using a combination of a randomised control trial in healthy volunteers and experiments with animal models we demonstrated that CD-TREAT replicates the EEN effect on gut microbiome and ameliorates rat ileitis.[1,2] Following these pre-clinical studies, we aimed to assess the effect of CD-TREAT diet on gut inflammation and clinical efficacy, using a pilot trial in children with active CD.

Methods: CD-TREAT is a personalised diet which replicates EEN composition using solid food. The translational efficacy of an 8-week treatment course with CD-TREAT was explored in a pilot study of five children with active luminal CD. In order to assess compliance, participants were instructed to record their dietary intake daily during the intervention using a food checklist. The primary outcome was clinical response (weighted Paediatric Crohn's disease Activity Index-wPCDAI fall ≥ 17.5) or clinical remission (wPCDAI < 12.5) at 8 weeks. Secondary outcomes included changes in faecal calprotectin (FC), serum albumin and C-reactive protein (CRP).

Results: From the enrolled CD children, 80% (4/5) clinically responded to CD-TREAT (wPCDAI fall greater than 17.5) and 60% (3/5) entered clinical remission (wPCDAI<12.5). FC decreased by a mean (SD) of 918 (555) mg/kg or 55% of baseline values. One patient had raised CRP and low albumin at CD-TREAT initiation and both inflammatory markers normalised at treatment completion. There were no differences between the prescribed and actual CD-TREAT intake of the patients, indicating high compliance to the dietary treatment protocol.

Conclusions: The current pilot trial in children with active CD demonstrated, for the first time, that CD-TREAT improves disease activity and inflammatory markers as induction treatment in active CD. The high tolerability of CD-TREAT suggests that this personalised, ordinary food-based diet could replace EEN as the nutritional therapy of choice to treat active luminal CD.

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P603

Paediatric onset inflammatory bowel disease is not associated with more disability compared with adult onset disease

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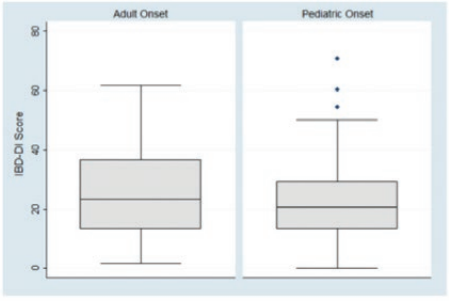
Background: A diagnosis of inflammatory bowel disease (IBD) during the paediatric years, may result in a larger burden of disability given that disease onset is coinciding with critical periods for physical and psychosocial development. The Inflammatory Bowel Disease Disability Index (IBD-DI) has recently been developed and validated to assess disability in patients with IBD. Our aims were to assess the burden of disability in paediatric onset as compared with adult onset disease using this index.

Methods: The IBD-DI was administered to a cohort of adult patients with either paediatric or adult onset IBD, matched by duration of disease at the University of Calgary. Sociodemographic and clinical parameters including measures of disease activity, the Harvey–Bradshaw Index (HBI) for Crohn's disease (CD) and Partial Mayo Score (PM) for ulcerative colitis (UC), were collected from participants as well as database review. A quantitative IBD-DI score was computed, based on a previously validated method.[1] IBD-DI scores were compared between groups and bivariate analysis of variance was used to identify factors associated with disability level.

Results: 200 patients (101 paediatric onset, 99 adult onset) were recruited. The distributions in IBD-DI scores did not differ significantly between adult onset and paediatric onset disease (25.18 ± 13.98 vs. 22.16 ± 13.91, $p = 0.13$) (Figure 1)



	Adult Onset	Pediatric Onset	p-value
Mean ± SD	25.18 ± 13.98	22.16 ± 13.91	0.13
Median (IQR)	23.43 (13.24-36.76)	20.59 (13.24-29.41)	
Min-Max	1.47-61.76	0-70.59	

Figure 1. Distribution in Inflammatory Bowel Disease Disability Index (IBD-DI) scores between paediatric and adult onset IBD.

There were also no significant differences in scores between Crohn's disease and ulcerative colitis in adult onset (26.14 ± 13.98 vs. 22.62 ± 13.93, $p = 0.27$) and paediatric onset disease (22.35 ± 13.77 vs. 21.67 ± 14.50, $p = 0.83$), respectively. Age>25 years ($p = 0.02$), female gender ($p = 0.04$), active smokers (p =0.03) and clinically active disease ($p < 0.001$) were associated with higher IBD-DI scores. IBD-DI scores correlated with measures of disease activity, PM ($r = 0.64$, $p < 0.001$) and HBI ($r = 0.65$, $p < 0.001$). Patients with paediatric onset disease demonstrated significantly higher negative influencer scores (family, $p = 0.04$) and lower positive influencer scores (family, $p = 0.02$ and health professionals, $p = 0.03$.)

Conclusions: Patients with paediatric onset IBD have a similar burden of disability compared with those with adult onset disease. They however were less likely to view family and health professional's as facilitators and more likely to view family as a barrier to their disease and disability. Factors associated with higher disability scores include age>25 years, female gender, active smokers and clinically active disease.

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P604

Biologics with or without a combination with 5-ASA in ulcerative colitis: frequency of usage and effect on the course of disease in the Swiss IBD-Cohort study

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Background: 5-ASA remains the mainstay of therapy in mild-to-moderate ulcerative colitis (UC) enabling achievement of remission in between 50–75% of all patients. Combination of immunosuppressives (IS) has been found to be associated with a better outcome when compared with monotherapy. However, concerning 5-ASA combination with biologics, clinical practice is highly variable and the evidence on potential benefit is scarce. We aimed to evaluate the course of UC in patients being treated with a combination of 5-ASA and biologics vs. biologics alone.

Methods: We analysed the prospectively collected clinical data from all UC patients currently receiving biologic treatment and participating in the nation-wide Swiss IBD cohort study (SIBDCS) with vs. without 5-ASA co-treatment.

Results: At last clinical follow-up visit amongst the 366 identified UC patients with currently ongoing biologic treatment, 170 received 5-ASA co-treatment. Regarding key baseline characteristics, including sex, duration of disease and age at UC diagnosis, there were no differences between patients with vs. without 5-ASA. More patients with 5-ASA co-treatment were under concomitant therapy with IS and/or steroids. Moreover, disease activity in the 5-ASA combination group was significantly higher. No differences across groups were identified considering most recent, maximal and average levels of faecal calprotectin and leucocyte count, CRP and haemoglobin from blood samples. The occurrence of complications, for example, cancer, dysplasia, anaemia, osteoporosis, thromboembolism or extraintestinal manifestations (EIM) was similar. However, combination lead to less intestinal surgery.

Population characteristics	Biologics only (%)	Biologics+ 5-ASA (%)	Significant
Number	196 (53.6)	170 (46.4)	No
Male	105 (53.6)	90 (52.9)	No
Female	91 (46.4)	80 (47.1)	No
MTWAI Median; IQR	5; 2–8	6; 4–10	$p = 0.009$
Immunomodulators	33 (16.8)	43 (25.3)	$p = 0.047$
Steroid	39 (19.9)	55 (32.4)	$p = 0.007$

Population characteristics

Events	Biologics only (%)	Biologics +5-ASA (%)	Significant
Complications	114 (58.2)	107 (62.9)	No
EIM	105 (53.6)	93 (54.7)	No
Intestinal Surgery	16 (8.2)	5 (2.9)	$p = 0.032$

Events

Conclusions: In our cohort, we found that UC patients under biologic therapy receiving 5-ASA co-treatment had a similar risk of complications or EIM while having a lower risk of colonic surgery. This being despite the fact that 5-ASA co-treated patients appear to reflect a subgroup of UC patients with a more severe course of disease as suggested by disease activity and co-treatment with IS and steroids. As no randomised prospective studies investigating this issue can be expected, further long-term observations in cohort studies and registries are mandatory to investigate the place of concomitant 5-ASA in UC patients receiving 'advanced' treatments.

P605

CRP reduction rate following initiation of anti-tumour necrosis factor-α induction therapy predicts secondary loss of response in patients with Crohn's disease

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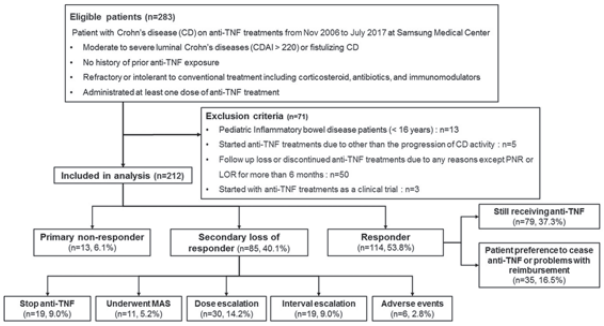
Background: The objective of this study was to identify clinical predictors of primary non-response (PNR) and secondary loss of response (LOR), in Crohn's disease (CD) patients treated with anti-tumour necrosis factor-α (anti-TNF) agents.

Methods: This retrospective, longitudinal, and observational cohort study was performed, which included 283 CD patients who received anti-TNF from November 2006 to July 2017 at Samsung Medical Center, Seoul, Korea.

Results: A total of 212 CD patients were eligible and divided into three groups: PNR, LOR, and responder groups.



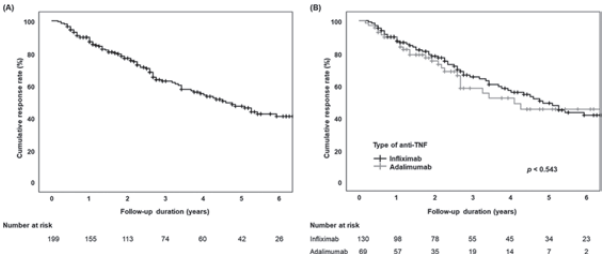
Flow chart showing the selection of patients. MAS, major abdominal surgery.

PNR occurred in 13 patients (6.1%). CRP level at initiation of anti-TNF (baseline CRP) was a possible predictor of PNR compared with non-PNR group (baseline CRP >1 mg/dl, OR = 4.34, 95% CI = 1.06–17.83).

		OR (95% CI)	*p*
Baseline age (years)	≤ 40	1.34 (0.30–5.93)	0.699
Gender	Male	2.20 (0.54–9.02)	0.272
Indication of anti-TNF	Fistulising CD		0.998
Baslein Hb (g/dl)	≤ 10	2.83 (0.72–11.04)	0.135
Baseline albmin (mg/dl)	≤ 3.5	0.77 (0.19–3.13)	0.710
Baseline CRP (mg/dl)	> 1	4.34 (1.06–17.83)	0.042
Baseline BMI (kg/m^2)	< 18.5	3.01 (0.82–11.62)	0.095

Clinical predictors of PNR in CD patients with anti-TNF.

During maintenance therapy, incidence of LOR was 12.9% at 1 year, 23.2% at 2 years, 37.3% at 3 years, and 52.1% at 5 years.



Cumulative response rate during anti-TNF maintenance therapy.

Baseline CRP and CRP reduction rate [(CRP at 12–14 weeks – baseline CRP)/baseline CRP] were possible predictors of 1 year LOR compared with responder group (baseline CRP >1 mg/dl, OR = 5.84, 95% CI = 1.95–17.53; CRP reduction rate >–70%, OR = 5.09, 95% CI = 1.61–16.05).

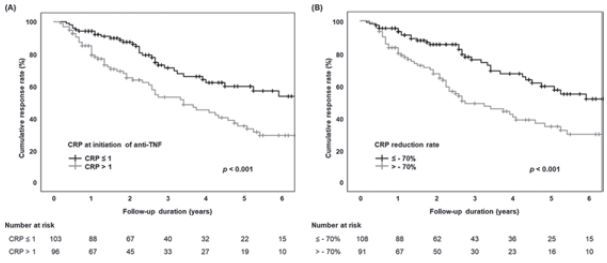
		OR (95% CI)	*p*
Baseline age (years)	≤40	1.24 (0.39–3.98)	0.715
Gender	Male	0.94 (0.32–2.78)	0.905
Disease duration (years)	>2	0.75 (0.22–2.54)	0.646
Montreal behaviour	B2+B3 (complicating)	2.02 (0.54–7.56)	0.298
Baseline Hb	≤10	2.38 (0.73–7.76)	0.151
Baseline albumin (mg/dl)	≤3.5	0.74 (0.23–2.38)	0.617
Baseline CRP (mg/dl)	>1	5.84 (1.95–17.53)	0.002
CRP reduction rate	>–70%	5.09 (1.61–16.05)	0.005
Baseline BMI (kg/m^2)	<18.5	1.54 (0.58–4.14)	0.390

Clinical predictors of 1-year LOR in CD patients with anti-TNF.

In Cox hazard proportional model, baseline CRP and CRP reduction rate were possible predictors of long-term LOR during maintenance therapy (baseline CRP >1 mg/dl, HR = 2.56 95% CI = 1.55–4.22; CRP reduction rate >–70%, HR = 2.54, 95% CI = 1.54–4.20).

		HR (95% CI)	*p*
Baseline age (years)	≤ 40	1.32 (0.74–2.33)	0.351
Gender	Male	1.14 (0.68–1.89)	0.625
Disease duration (years)	> 2	1.02 (0.57–1.84)	0.944
Montreal behaviour	B2+B3 (complicating)	1.41 (0.78–2.53)	0.253
Baseline Hb (g/dl)	≤ 10	1.25 (0.68–2.27)	0.475
Baseline albumin (mg/dl)	≤ 3.5	1.40 (0.81–2.39)	0.227
Baseline CRP	> 1	2.56 (1.55–4.22)	<0.001
CRP reduction rate	> –70%	2.54 (1.54–4.20)	<0.001
Baseline BMI (kg/m^2)	< 18.5	1.36 (0.84–2.19)	0.206

Clinical predictors of long-term LOR in CD patients with anti-TNF.



Cumulative response rate during anti-TNF maintenance therapy depending on predictors of long-term LOR.

Conclusions: Baseline CRP and CRP reduction rate might be clinical predictors for PNR or LOR to anti-TNF in CD patients and could guide proper therapeutic intervention in CD patients with anti-TNF treatment.

P606

Steroid use in inflammatory bowel disease patients on biological therapy in Montenegro

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Background: According to ECCO recommendation, corticosteroids are used in patients with ulcerative colitis (UC) and Crohn's disease (CD) to induce remission of the disease, but do not modify the course of disease and have no role in maintaining remission. Additionally, due to the large number of side effects, long-term application of corticosteroids is not recommended.

Methods: We prospectively collected data from 110 IBD (inflammatory bowel disease) patients who had undergone biological therapy in IBD referral centre in Montenegro over 12 months. We used the online Steroid Assessment Tool (SAT), as described by Selinger et al., 2017, to record steroid use in this population of patients.

Results: In this cohort, there were 57% patients with UC and 43% patients with CD. There were 73% patients who had been administered anti-TNF biological drugs (adalimumab or infliximab), and 27% who had been administered anti-integrin therapy (vedolizumab) in the current therapy. Exposure to second anti-TNF was recorded in 23% of patients. Concomitant immunosuppressive therapy (Thiopurine and Methotrexate) was used for more than 3 months by 34 patients (30.1%). At the last measurement, 18% patients had severe and 32% patients had moderate disease activity. In the last year, 42 patients (38%) had used corticosteroids (UC 28 (44%), CD 14 (30%)) and 60% of them were taking suggested medicines for bone protection (UC 20 (71%), CD 6 (36%)). 81% of patients were found to have used one course of steroid, two courses of steroids is recorded in 14% and three courses in 5% of patients. The duration of the steroid administration was mainly observed to be 3 months (79% patients). The longest duration was 6 months and it is recorded in 1 patient.

In the sub-population of patients (42) who had used steroids, 64% (27/42) did not develop corticosteroid dependency and did not relapse after 3 months (UC 15 (54%) and CD 12 (86%)); and 36% (15/42) were found to be steroid resistant/ dependent.

In the population of steroid resistant/dependent patients (15), 67% ((10/15) (69%)UC, 1(6.7%) CD)) were not able to reduce steroid below the equivalent of prednisolone 10 mg/day (or budesonide below 3 mg/day) within 3 months of starting steroids, without recurrent active disease and had a relapse within 3 months of stopping steroids.

Conclusions: We identified inappropriate excess steroid use in 15% of patients. Excess steroid exposure was significantly higher in patients with UC compared with active CD. Routine recording of steroid dependency or excess needs to be extended to all IBD patients (particularly to UC patients) not only on biologic experienced.

P607

Higher adalimumab serum levels do not increase the risk of adverse events in patients with inflammatory bowel disease

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Background: The relationship between serum adalimumab concentrations and adverse events in patients with inflammatory bowel disease (IBD) is unknown. We aimed to determine whether patients with IBD using adalimumab are at increased risk of adverse events if they have high adalimumab serum levels compared with those with lower adalimumab levels.

Methods: This was a retrospective study of 133 IBD patients with at least one measurement of serum adalimumab level available. The cohort was divided according to the median adalimumab level of 9.8 μg/ml. The primary outcome was the rate of overall adverse events between the two groups. Secondary outcomes included the rate of infections, dermatologic reactions, injection-site reactions, and other adverse events in both groups. Rates of discontinuation of adalimumab due to adverse events was also evaluated. Multi-variate logistic regression analysis was also performed to evaluate the relationship between adalimumab levels and adverse events.

Results: A total of 27 adverse events were reported in 133 patients in the overall cohort. In patients with higher adalimumab levels, there were 17 adverse events reported in a total of 66 patients, which was not significantly different than the 10 adverse events reported in 67 patients with lower adalimumab levels (25.7% vs. 14.9%, $p = 0.12$). Stratification of patients into adalimumab level tertiles did not show any difference in the rate of adverse events between the three groups. After adjustment for potential covariates, IBD patients with higher adalimumab levels did not have higher odds of an adverse event than patients with lower levels (OR 1.94, 95% CI 0.81–4.64).

Conclusions: There does not appear to be an increased risk of adverse events in IBD patients with higher adalimumab levels.

P608

Crohn's disease patients with high baseline symptoms achieve clinical remission more rapidly with Budesonide than with Mesalazine

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Background: Budesonide (Entocort®) showed non-inferiority compared with Mesalazine (Pentasa®) in Japanese patients with mild-to-moderate active Crohn's disease (CD) after 8 weeks of treatment.[1] The aim of this analysis was to compare 2, 4, and 8 weeks remission rates based on Patient-reported Outcome (PRO) in patients treated with Budesonide (BUD) or Mesalazine (MZ) grouped according to high or low level of symptoms at baseline (week 0).

Methods: In a post-hoc sub-group analysis, patients with mild-to-moderate CD on BUD 9 mg/day ($n = 54$) or MZ 3 g/day ($n = 53$) were analysed. A two item weighted PRO based on stool frequency and abdominal pain (PRO2) was calculated. The daily values were accumulated for the whole week. Patients with a baseline PRO2 above or below the median of the study population (103) were compared. Calculations for difference between BUD and MZ were done for five different outcomes which were defined as: (1) PRO2<53 (clinical remission), and clinical improvements: (2) PRO2<53 or reduction of at least 57, (3) PRO2<53 or reduction of at least 38, (4) PRO2 change from BSL of at least 57 and (5) PRO2 change from BSL of at least 38.

Results: Clinical remission [def 1] was achieved in significantly more patients starting with high BSL (>103) and treated with BUD compared with MZ after 2 weeks ($n = 5$ (19.2%) vs. $n = 0$ (0%) $p = 0.05$) and 4 weeks ($n = 6$ (22.2%) vs. $n = 0$ (0%) $p = 0.03$) of treatment. Also clinical improvements [def 2–5] were more expressed in patients starting with high BSL (data not shown). This significant difference in clinical remission between BUD and MZ was not achieved in patients starting with low BSL PRO2<103 (Week 2: ($n = 4$ (14.8%) vs. $n = 7$ (24.1%) $p = 0.51$); Week 4: ($n = 4$ (14.3%) vs. $n = 8$ (28.6%) $p = 0.33$)). There was no relevant difference between patients starting with high or low BSL after 8 weeks treatment.

Conclusions: This post-hoc sub-group analysis reveals that PRO2 is a suitable instrument to detect early improvement of symptoms. Budesonide (Entocort®) showed a more rapid onset of effect compared with Mesalazine (Pentasa®) in patients starting with high baseline symptoms.

Reference

1. Yokoyama T, *et al*. Inflamm Intest Dis 2017.

P609

Handsewn anastomosis after ileo-colic resection for Crohn's disease: a lost art?

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Background: Ileo-colic resection (ICR) is the most common surgical procedure for Crohn's disease (CD). Reconstruction is most commonly achieved with stapled side-to-side (SSTS) or hand-sewn (HS) ileo-colic anastomosis (ICA). We aimed to compare short-term complications and long-term recurrence-free survival (RFS) of CD between patients who underwent SSTS vs. HS anastomoses in our institution.

Methods: This study was a retrospective analysis. Patients who underwent ICR and ICA for terminal ileal CD from January 2012 to December 2016 were included. Surgeries were done for 26 surgeons. Patients with stoma or other types of anastomoses were excluded.

The groups were compared in a univariate analysis. Recurrence (Rutgeerts ≥i2 or active disease on CT/MRI) was assessed using Kaplan–Meier curves and a log-rank test. Cox-proportional hazard and linear regression models with propensity score inverse probability of treatment weighting were used to further evaluate postoperative outcomes and recurrence of CD. Numbers represent median or proportion as noted.

Results: Were included 59 patients in HS group and 202 in SSTS group. HS group had a longer course of disease (16 vs. 9 years, p = 0.005), were more likely to have previous surgeries (59 vs. 42%, p = 0.02), perianal disease (39 vs. 23%, p = 0.02) and redo ICA (56 vs. 33%, p = 0.001). There was no difference in use of medications. More HS patients were ASA 3 (65 vs. 40%, p = 0.004), and HS operations were longer (157 vs. 133 min., p < 0.001), with more blood loss (150 vs. 50 ml, p < 0.001), and fewer laparoscopies (41 vs. 65%, p < 0.001). Patients who underwent HS had more experienced surgeons (16 vs. 11 years, p < 0.001). HS patients had longer lengths of stay (6 vs. 5 days, p = 0.02)

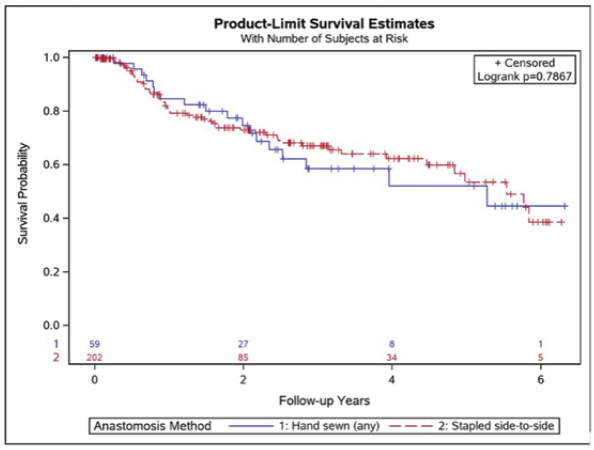
Factor	Handsewn (N=59, 22.6%)	Stapled side-to-side (N=202, 77.4%)	p-value
Follow-up (months)	34.4 (0.20 - 75.9)	30.6 (0.13 - 79.2)	0.33
Number (%) of surgeons using method at least once	13 (50%)	24 (92%)	***<0.001***
Postoperative LOS (days)	6.0[5.0 - 9.0]	5.0[4.0 - 7.0]	***0.02***
Total LOS (including readmissions – days)	11.0 [7.0 - 14.0]	9.0[6.0 - 14.5]	0.41
Any complication	29 (49.2)	78 (38.6)	0.15
Any septic complication	4 (6.8)	16 (7.9)	0.77
Anastomotic leak	2 (3.4)	3 (1.5)	0.32
Enteric leak	0 (0.0)	1 (0.50)	0.99
Abscess	3 (5.1)	13 (6.4)	0.70
Dehydration	1 (1.7)	0 (0.0)	0.23
Clavien-Dindo >= III*	4 (6.8)	17 (8.4)	0.68
ICU within 90 days	0 (0.0)	7 (3.5)	0.36

LOS: Length of stay. Statistics presented as Mean ± SD, Median [P25, P75], Median (min, max) or N (column %).
p-values: ANOVA, Kruskal-Wallis test, Pearson's chi-square test, Fisher's Exact test as appropriate.
*The table refers to the entire cohort and not the matched group.

Figure 1. Univariate analysis of perioperative variables and short-term outcomes within 30 days.

Outcomes within 30 days.

There was no difference in recurrence rates



Recurrence-free Survival Estimates (95% CI)				
Anastomotic method	**1-year**	**3-year**	**5-year**	**6-year**
HS	0.85 (0.74 - 0.95)	0.59 (0.42 - 0.75)	0.52 (0.33 - 0.71)	0.45 (0.24 - 0.66)
SSTS	0.81 (0.74 - 0.87)	0.67 (0.59 - 0.75)	0.53 (0.41 - 0.66)	0.39 (0.22 - 0.56)
p-value	0.52	0.36	0.90	0.66

P-values based on Z-test of point estimates of survival.

Figure 2. Kaplan–Meier plot for recurrence-free survival and log rank test.

RFS curve.

After propensity score weighting and adjustment for covariates, HS patients had less than 1/3 of the odds of Clavien-Dindo ≥3 complication compared with SSTS group (OR 0.29 [0.09–0.92], p = 0.03).

Conclusions: HS anastomoses, compared with SSTS anastomoses, were independently associated with a lower rate of major postoperative complications, despite being performed in more complex patients. In addition, no difference in recurrence rates between groups was observed. Thus, colorectal surgeons should be facile and confident in performing HS procedures, especially in difficult situations, lest HS become a lost art.

P610

Penetration, short- and long-term efficacy of anti-TNF-α therapy for ulcerative colitis between 2010–2016 in Hungary

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Background: Anti-TNF therapy showed high efficacy in the maintenance of remission in ulcerative colitis (UC) based on study results. However, there is still high need for long-term assessment of biological treatments based on full population analysis.

Methods: This is an observational/non-interventional, retrospective, epidemiological study using the National Health Insurance Fund social security databases and the special drug reimbursement database of patients. Study population contained all of the adult Hungarian patients suffering from UC who are observable in the database between 2010 and 2016. Patients were treated with anti-TNF therapy during the study period were eligible. Our aim was to analyse patient characteristics and therapeutic outcome of UC patients treated with anti-TNF agents in Hungary.

Results: In total, 0.24% of total Hungarian population suffered from UC in 2016. This is more than 23 000 patients. The median age of the patients with UC is 51 (male 49, female 53) in the examined period. Annual prevalence of anti-TNF therapy was increasing continuously from 1.1% to 2.1%; 497 patients with UC were on anti-TNF therapy at the end of 2016. The prevalence of infliximab and adalimumab was similar in 2016 (1.2 and 1.1%, respectively). The onset of anti-TNF therapy in UC is between 20 and 39 years, the average age is 37 years. This is 16 years less compared with the average age of total UC population. Anti-TNF therapy was started within 3 years after the diagnosis in 35% of the patients, while disease duration was more than 10 years in every third cases. Top-down therapy was applied only in 0.1% of the patients. Primary non-response was observed in 9.7% of anti-TNF therapy. Ratio of dose escalation was 13.6%. Dose escalation was equally common among patients on infliximab and adalimumab therapy; however it occurred significantly later in case of infliximab. Frequency of switch was 15.7% and 83.1% of switch was performed after dose escalation. Ratio of infliximab to adalimumab switch was 6.7%, adalimumab to infliximab switch was 0.8% in 2016. Thirty-two point four% of the patients received azathioprine and anti-TNF combination therapy in the first 5 month of anti-TNF therapy. Steroid therapy was prescribed significantly less frequently in the subsequent 2 years after starting anti-TNF.

Conclusions: Both the prevalence and incidence of UC are high in Hungary. Patients receiving anti-TNF therapy are significantly

younger than the other part of the total UC population. Our results show the steroid-sparing effect of anti-TNF in a real-life, population-based setting.

P611

A real-world assessment of golimumab effect on quality of life, healthcare resource utilisation and work productivity in patients with ulcerative colitis in Greece: interim results from the GO-LIFE study

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Background: GO-LIFE is an observational, prospective study assessing the impact of golimumab (GLM) on health-related quality of life (HRQoL) and other patient-reported outcomes in patients with ulcerative colitis (UC) in real-world clinical practice. This interim analysis presents the 6-month results.

Methods: Eligible patients had moderate-to-severe UC (total Mayo score 6–12, endoscopy subscore ≥2), inadequate response to conventional therapy and were anti-TNFa naïve. GLM was administered per label (no dose optimisation applied). Primary objective was the assessment of the clinically meaningful HRQoL improvement rate, defined as ≥16-point increase in Inflammatory Bowel Disease Questionnaire (IBDQ-32) score from baseline (BL) to 6 months. Other endpoints included assessments of the impact of GLM on: treatment satisfaction, with the Treatment Satisfaction Questionnaire for Medication (TSQM-14); UC-related healthcare resource utilisation (HCRU) during the 6-month period prior to BL vs. 6-month follow-up period; work productivity with the Work Productivity and Activity Impairment (WPAI:UC) questionnaire; and disease activity with the total/partial Mayo score (for patients without endoscopy at 6 months, only the partial Mayo score was used).

Results: Fifty patients with mean ± SD UC duration of 8.1 ± 8.1 years were included in the interim analysis; 37 (74%) patients completed the 6-month follow-up. Clinically meaningful HRQoL improvement from BL to 6 months was achieved by 27/50 patients (54%; 95% CI: 39%–68%). All TSQM-14 dimensions improved at 6 months vs. BL; mean ± SD change was significant for effectiveness: 18.0 ± 28.9 ($p < 0.001$) and convenience: 10.2 ± 21.8 ($p = 0.002$), and nonsignificant for side effects and global satisfaction:6.8 ± 24.9 ($p = 0.142$) and 6.2 ± 30.7 ($p = 0.182$), respectively. HCRU was reduced during the follow-up period vs. the 6-month period prior to BL (table). All WPAI:UC domain scores improved at 6 months vs. BL; improvement was significant for absenteeism ($p = 0.039$), work productivity loss ($p = 0.025$) and activity impairment ($p = 0.044$). For 28 patients, total Mayo score was not available (no endoscopy done) at 6 months (13 patients did not reach the 6 month visit and for 15 patients endoscopy was not available at 6 months). Clinical response was achieved by 32 (64%) patients and clinical remission by 27 (54%) patients, using the partial Mayo score.

	6-month period prior to baseline	Follow-up period (baseline to 6 months)	*p*-value
Hospitalisations, *n*	23	5	
Hospitalisation duration (days), median (min, max)	7.0 (1.0, 12.0)	5.0 (3.0, 7.0)	0.33
Emergency room visits (patients), *n*	5	3	
Emergency room visits per patient, median (min, max)	1.0 (1.0, 3.0)	1.0 (1.0, 4.0)	0.86
Outpatient admissions (patients), *n*	6	3	
Outpatient admissions per patient, median (min, max)	2.5 (2.0, 6.0)	2.0 (1.0, 3.0)	0.34

HCRU data comparison.

Conclusions: In real-world practice GLM improved HRQoL, treatment satisfaction, HCRU, work productivity and disease activity in patients with moderate to severe UC. The study was funded by Merck Sharp and Dohme S.A., Greece.

P612

Long-term outcomes of treatment intervention according to the severity of small bowel capsule endoscopy findings in patients with Crohn's disease: A Japanese single-centre cohort study

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Background: There are few studies about the influence of small bowel capsule endoscopy (SBCE) findings on clinical outcomes in patients with Crohn's disease (CD). In particular, the influence of the severity of SBCE findings on treatment intervention is unclear. The present study analysed the long-term outcomes of treatment intervention according to the severity of SBCE findings in patients with CD.

Methods: We retrospectively collected the data of patients with CD who underwent initial SBCE between January 2015 and December

2017. Patients without lesions in the small intestine and those who received new medications within 3 months after SBCE were excluded from this study. SBCE findings were evaluated using the Lewis score and Capsule Endoscopy Crohn's disease Activity Index (CECDAI). Treatment intervention was defined as additional treatment involving budesonide, prednisolone (PSL), elemental diet therapy, immunomodulators (IMs), anti-tumour necrosis factor (TNF) agents or intestinal resection. The cumulative rates of treatment intervention following the initial SBCE were estimated using the Kaplan–Meier method. Prognostic factors related to the cumulative rates of treatment intervention were evaluated using the log-rank test. In addition, Lewis and CECDAI scores were categorised into three groups (Lewis score: ≤134, 135–789 and ≥790; CECDAI score: ≤3, 4–9 and ≥10). The cumulative rates of treatment intervention were compared among the three groups of Lewis and CECDAI scores.
Results: The study included 107 patients (median age, 27.1 years; 23 female patients). The median C-reactive protein and albumin levels were 0.09 mg/dl and 4.4 g/dl, respectively. Concomitant treatments with anti-TNF agents, IMs and PSL were administered to 52, 29 and 5 patients, respectively. The median Lewis and CECDAI scores were 230.0 and 6.0, respectively. The 1-, 2- and 3-year cumulative rates of treatment intervention were 12%, 28% and 32%, respectively. In the univariate analysis, median albumin levels ≤4.4 g/dl, Lewis scores ≥230.0 and CECDAI scores ≥6.0 were significantly associated with higher rates of treatment intervention. The 2- and 3-year cumulative rates of treatment intervention according to the Lewis score were as follows: ≤134, 5% and 5%; 135–789, 28% and 31% and ≥790, 44% and 35%, respectively. Similarly, the 2- and 3-year cumulative rates of treatment intervention according to the CECDAI score were as follows: ≤3, 5% and 5%; 4–9, 28% and 29% and ≥10, 58% and 68%, respectively.
Conclusions: This study found that increases in the Lewis and CECDAI scores were associated with increases in the rates of treatment intervention in patients with CD who underwent initial SBCE. The SBCE findings may be able to predict clinical outcomes in patients with CD.

P613

Tacrolimus as rescue therapy for steroid-dependent/steroid refractory ulcerative colitis: experience from tertiary referral centre

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Background: Approximately 20–40% patients of severe UC are either refractory to steroids (SRUC) or become steroid dependent (SDUC). Tacrolimus is an oral and relatively cheap drug with minimal adverse events.
Methods: 52 UC patients diagnosed as SDUC/SRUC were started on tacrolimus 0.05–0.1 mg/kg. Clinical Mayo Score (CMS) and UCEIS were recorded prior to starting tacrolimus and after 8 weeks. 5-ASA and immunomodulators were continued if the patients were already on these drugs. Clinical response at 8 weeks was defined as CMS decrease by at least 3 points. Clinical remission was defined as CMS ≤2 and combined remission as CMS ≤2 with UCEIS <3.
Results: The mean age of 52 patients (29 males) was 35.1 ± 12.8 years. Extent of disease was E3 in 37 (71%) patients. Thirty-one were SDUC and 21 were SRUC. 7 failed treatment within 8 weeks and 4 were subjected to surgery and 3 patients were switched to infliximab. Three patients either discontinued Tacrolimus or were lost on follow-up. Forty-two patients continued Tacrolimus for 8 weeks. Mean CMS and UCEIS prior to starting tacrolimus were 6 ± 1.1 and 4.8 ± 1.1, respectively. At 8 weeks, median CMS and UCEIS were 2.6 ± 1.7 and 2.7 ± 1.3, respectively. Twenty-nine (56%) patients responded while 25 (48%) had CMS ≤ 2 and 18 out of 35 (35%) had CMS ≤2 and UCEIS <3 suggesting that they had achieved clinical and endoscopic remission. Ten patients showed partial/no response at 8 weeks. There was a significant fall in both CMS and UCEIS at 8 weeks of Tacrolimus therapy (paired *t*-test $p < 0.001$) in both SDUC and SRUC subgroups.
Conclusions: Our results show that tacrolimus was effective in inducing a clinical response in 56% of patients with SDUC and SRUC. In view of its low cost and safety profile it may be considered as first-line therapy for SDUC/SRUC.

P614

The utility as a biomarker of faecal calprotectin for predicting the clinical outcome of granulocyte and monocyte adsorptive apheresis treatment in patients with ulcerative colitis

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Background: The diagnosis and assessment of ulcerative colitis (UC) has been based on the clinical symptoms, blood parameters, and the findings of endoscopy and radiological examinations. Recently, faecal calprotectin (Fcal) was developed as a non-invasive and easy marker that could be used to detect and monitor intestinal inflammation in clinical practice. However, its value as a biomarker for predicting the clinical outcome of remission induction therapy in patients with UC is still unclear. Granulocyte and monocyte adsorptive apheresis (GMA) treatment is widely used as a remission induction therapy for UC in Japan. The aim of this study was to evaluate the utility of Fcal as a biomarker for predicting the efficacy of GMA treatment.
Methods: This multi-centre prospective observational study was conducted to assess the usefulness of Fcal as a biomarker for the prediction of remission induction in UC patients treated with GMA from October 2015 to November 2018. Fcal was measured at weeks 0, 1, 2 and the end of GMA treatment. Colonoscopy was performed at week 0 and within 24 weeks after the end of GMA treatment. Clinical activity was assessed using the partial Mayo score at the same time as Fcal was monitored. Clinical remission was defined a partial Mayo score (pMayo) of ≤2 and a score of ≤1 on all subscores. Mucosal healing was defined as a Mayo endoscopic subscore (MES) of ≤1.
Results: Twenty of the 30 patients who enrolled in this study completed GMA treatment. Nine patients achieved clinical remission, three showed a clinical response, and eight showed no response to GMA treatment. Three patients achieved mucosal healing. pMayo was more strongly associated with Fcal than the CRP level, the WBC count and the MES. The Fcal level decreased before the partial Mayo score and the rate of Fcal reduction (ΔFC) at Week 1 was approximately 50% that of the baseline value in the clinical remission group. A ROC analysis demonstrated that the ΔFC at Week 1 was the most

accurate predictor of clinical remission at the end of GMA treatment (AUC=0.83, $p = 0.01$) among the patient data, including pMayo and the CRP level at Week 1. When the cut-off value was defined as a >60% reduction in ΔFC at Week 1, the sensitivity and the specificity for the prediction of clinical remission were 77.8% and 81.8%, respectively.

Conclusions: Fcal is considered to be a useful and objective predictor of the efficacy of GMA treatment in UC patients and superior to symptomatic scores and blood parameters.

P615

Rescue infliximab for acute severe colitis: a single-centre experience

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Background: Since the late 1990s the use of biologics in inflammatory bowel disease (IBD) has become well established in clinical practice. The use of anti- tumour necrosis factor (TNF) therapy (infliximab) as 'rescue' in steroid refractory disease as an alternative to surgery or Cyclosporine has become widespread in IBD colitis. Here we report a single-centre experience.

Methods: A retrospective review of consecutive patients hospitalised with IBD flare and refractory to intravenous steroid treatment who received rescue infliximab infusion at Aberdeen Royal Infirmary, NHS Grampian, between 2009 and 2017 was performed. Cases were identified using the local biologics IBD database. Patients were followed up for a 1-year period. The project was registered as a service evaluation with the NHS Grampian Clinical Effectiveness team.

Results: In total, 47 patients received infliximab for IBD colitis as a rescue therapy during this period. Median age was 41 years (range 17–87) and 28/47 (59.6%) were female. Twenty-three of 47 (48.9%) patients had a diagnosis of ulcerative colitis (UC) and 19/47 (40.4%) Crohn's disease (CD), with the remaining unspecified IBD (IBD-U). Three of 47 (6.4%) had a subsequent change in diagnosis. Use in UC has steadily increased since accounting for over half of cases (13/24, 54.2%) since changes to the National Institute of Health and Care guidance in 2015. Primary non-response to infliximab was 12.7%, 4/47 underwent colectomy during the same admission and 2/47 were deemed unfit for surgical intervention. An additional 7/47 (14.9%) required surgery within 1 year of rescue infliximab following discharge. Dosing regimen varied with the majority (30/47, 63.8%) receiving a single dose, with no significant difference in outcome at 1 year from discharge (single dose 3/26, 8.0% vs. 2 or more doses 4/17, 23.5%, $p = 0.30$). Of the patients undergoing surgery within 1 year, 2 had serious complications following surgery; one anastomotic leak and one mortality due to pulmonary embolism. Three individuals receiving rescue infliximab had infective complications (1 × mild post-operative wound infection, 2 × hospital acquired pneumonia) and one cytomegalovirus colitis following maintenance IFX requiring colectomy. Readmission rate at 1 month for IBD-related issues was 10.6%.

Conclusions: Previous literature has suggested between 17 and 40% of patients have primary non- response to rescue infliximab typically requiring surgery in the same admission and 12 month surgery rates 36%. Our single-centre experience found with appropriate patient selection, acute and longer term surgery rates to be less than reported in current published data. This emphasises the benefits of infliximab in avoiding surgery in the acute setting.

P616

Ustekinumab for refractory paediatric Crohn's disease: experience from two UK tertiary referral centres

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Background: Crohn's disease (CD) is frequently diagnosed in childhood and follows a more aggressive course when compared with adults. In this population, anti-TNF treatments are well established, but little is known about the efficacy and safety of ustekinumab. We report our experience in its use for paediatric Crohn's disease across two London hospitals.

Methods: Paediatric patients (<18 years) commenced on ustekinumab were identified from University College London Hospital (UCLH) and The Royal London Hospital (RLH). A retrospective case note review was conducted and data collected on disease phenotype, prior treatment, prior surgery, CRP and weight. Biological response at Week 8 was defined as a 50% reduction in CRP where the baseline CRP was >5 mg/l.

Results: Ten patients with CD were commenced on ustekinumab under the age of 18. The baseline characteristics are summarised in Table 1. All patients had failed at least one anti-TNF and 8 patients had failed two. The mean CRP at baseline was 38 mg/l. Patients received intravenous drug at baseline and 8 weekly subcutaneous dosing thereafter. Two patients discontinued treatment prior to Week 16 owing to primary non-response, both requiring intestinal resection. Four patients had reached Week 16 at the time of analysis. One patient had been followed up for 29 weeks at the time of analysis. No adverse events were reported. Where paired data were available, there was a significant increase in mean weight from baseline (38.9 kg, $n = 7$) to Week 8 (42.7 kg, $n = 7$, $p = 0.003$) and Week 16 (44.0 kg, $n = 3$, $p = 0.001$). Where paired data were available, mean CRP (mg/l) improved from 38 at baseline ($n = 7$) to 22 at Week 8, and 9 at Week 16 ($n = 4$), although this did not reach significance. The biological response rate was 50% at Week 8. Both patients on steroids at baseline had discontinued these by Week 8.

Characteristic	Number
Number of patients	10
Gender, male/female	5/5 (50%/50%)
UCLH/RLH	5/5
Median age at diagnosis (range), years	8 (4-13)
Median time from diagnosis to starting ust (range), years	6 (4-12)
Montreal Classification	
Age at diagnosis, years	
< 16, A1	10 (100%)
Disease behavior	
Inflammatory, B1	5 (50%)
Stricturing, B2	4 (40%)
Penetrating, B3	1 (10%)
Disease location	
Ileum, L1	0 (0%)
Colon, L2	3 (30%)
Ileocolon, L3	7 (70%)
+ upper GI involvement, L4	2 (20%)
Perianal involvement	4 (40%)
Orofacial granulomatosis	2 (20%)
Previous biologic therapy	
Infliximab	9/10 (90%)
Adalimumab	9/10 (90%)
Infliximab and adalimumab	8/10 (80%)
Vedolizumab	0/10 (0%)
Previous intestinal resection	4 (40%)
Disease activity at ustekinumab induction	
Mean CRP (range)	38mg/l (1-86)
Corticosteroids	2/8 (20%)
Thiopurines or methotrexate	6/10 (60%)

Table 1. Baseline characteristics of paediatric patients treated with ustekinumab.

Conclusions: We report on the use of ustekinumab to treat anti-TNF refractory Crohn's disease in 10 paediatric patients. This was well tolerated with no adverse events reported. We found a mean reduction in CRP and significant weight gain at Week 8 which was sustained at Week 16, suggesting clinical benefit. Further studies are needed to establish the safety and efficacy of its use in the paediatric population.

P617

Evaluation of subclinical myocardial damage in patients with inflammatory bowel disease on treatment with biologics

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Background: Patients with inflammatory bowel disease (IBD) have a higher risk of cardiovascular disease (CVD) due to chronic inflammation. It has been suggested that inflammation leads to oxidative stress and to an increase in inflammatory cytokines leading to endothelial dysfunction and atherosclerosis. Biological therapies are the mainstay for the treatment of active IBD and can modify the disease activity and also the risk of CVD. The aim of the study is to assess the subclinical cardiac and vascular damage in IBD patients on treatment with biologics.
Methods: Pulse wave velocity (PWV), global longitudinal strain (GLS), and circulating CD34+ cells were evaluated to estimate subclinical cardiovascular involvement in 16 patients with IBD, before (T0) and after (T1) a 6-months treatment with biologics (infliximab, adalimumab, or vedolizumab). Carotid-femoral PWV was measured by routine methods. GLS was measured by speckle tracking echocardiography. Circulating CD34+ were counted by flow cytometry. In addition, markers of inflammation (ESR, CRP, and fibrinogen) and ejection franction % (EF) were also evaluated.
Results: At T1, no statistically significant differences were detected as regards ESR, PWV, EF with respect to T0; in contrast, some parameters appeared statistically improved when compared with baseline, including CRP ($p = 0.013$), GLS ($p < 0.001$), and CD34+ ($p < 0.001$). The interdependence analysis performed on the mean per cent changes showed a significant correlation between ΔPWV and ΔGLS: as ΔPWV decreases ΔGLS increases, improving ventricular performance.
Conclusions: Patients with IBD have a greater risk of developing CV disease, especially when IBD is biological uncontrolled. Biologics have a favourable effect on inflammatory status and symptoms/biological compensation, but also on CV risk as suggested by favourable change in plasma levels of CRP, circulating levels of CD34+ and GLS values. This study needs to be enhanced and reproduced on larger patients cohort to confirm this preliminary data and to address the question of whether therapy with these drugs may have a role also in favourably modulating CV risk.

P618

Vedolizumab acute infusion reactions in inflammatory bowel disease patients: results of a multi-centre retrospective observational cohort study

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Background: Vedolizumab is a fully humanised monoclonal IgG1 antibody directed towards α4β7-integrin approved for Crohn's disease and ulcerative colitis treatment. Until now, a systematic follow-up after all vedolizumab infusions is recommended. Clinical trials and post marketing studies have reported infusion reactions ranged from 0.1 to 2.3%, but specific symptoms, circumstances and severity are not always detailed. The main objective was to report systematically the frequency and severity of immediate hypersensitivity reactions (IHR) to vedolizumab in inflammatory bowel disease (IBD) patients.
Methods: We performed a multi-centre systematic retrospective review of IBD patients treated with vedolizumab in 4 French university hospitals (Lyon-Sud, Saint-Etienne, Nancy, and Grenoble). We collected patient's characteristics, symptoms, duration of treatment, concomitant drugs, history of previous IHR to other biologics, anti-drug antibodies and outcomes to identify potential risk factors of drug-induced IHR.
Results: From May 2014 to February 2018, 550 patients received a total of 6459 vedolizumab infusions. In our cohort, 7 acute infusion reactions (0.1%) could be identified but none of them occurred within 2 h of infusion. No severe reaction was reported and vedolizumab was definitely discontinued in only two cases. We failed to identify associated risk factors with the occurrence of IHR especially history of infliximab IHR, immunosuppressant concomitant use or anti-drug antibodies against vedolizumab.
Conclusions: We confirm in this multi-centre study the excellent short-term safety profile of vedolizumab especially the absence of IHR occurring within 2 h of infusion. These data support the uselessness of systematic follow-up of patients after vedolizumab infusion.

P619

Maintenance of efficacy following tofacitinib dose reduction in patients with ulcerative colitis in stable remission

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Background: Tofacitinib is an oral, small-molecule JAK inhibitor approved in several countries for the treatment of ulcerative colitis (UC). Safety and efficacy of tofacitinib 5 and 10 mg twice daily (BID) were evaluated in 2 Phase 3 induction studies (OCTAVE Induction 1 and 2, NCT01465763 and NCT01458951), a 52-week, Phase 3 maintenance study (OCTAVE Sustain, NCT01458574), and an ongoing

open-label, long-term extension (OLE) study (NCT01470612). Here, we assess maintenance of remission following tofacitinib dose reduction from 10 mg BID in OCTAVE Sustain to 5 mg BID in the OLE study, and explore potential predictors of successful dose reduction.

Methods: Patients in remission (total Mayo score ≤2 with no individual subscore >1, rectal bleeding subscore 0) at Wk52 of OCTAVE Sustain (central read) received tofacitinib 5 mg BID in the OLE study. We present remission rates (local read; as observed and with non-responder imputation) with tofacitinib 5 mg BID in the OLE study (as of 10 November 2017) among patients who achieved remission with tofacitinib 10 mg BID in OCTAVE Sustain, and evaluate characteristics of these patients, stratified by whether they subsequently maintained remission (local read; as observed) with 5 mg BID at Month (M)12 of the OLE study.

Results: Of 76 patients treated with tofacitinib 10 mg BID who were in remission at Wk52 of OCTAVE Sustain and received 5 mg BID in the OLE study, 82% and 76% (as observed) were in remission at M12 and M24 of the OLE study, respectively (table). Patient characteristics by remission status at M12 of the OLE study are shown (table). Alternatively, by duration of remission in OCTAVE Sustain: among patients in remission at baseline (BL), Wk24 and Wk52 of OCTAVE Sustain (remission ≥12 months pre-dose reduction), 91% (21/23) maintained remission at M12 of the OLE study, vs. 82% (18/22) who were not in remission at OCTAVE Sustain BL but in remission at both Wk24 and Wk52 (remission 6–<12 months pre-dose reduction), and 71% (15/21) who were in remission at Wk52 but not Wk24, regardless of BL status (remission <6 months pre-dose reduction).

Conclusions: In this post-hoc analysis, most patients with UC who achieved remission with tofacitinib 10 mg BID in OCTAVE Sustain and reduced to 5 mg BID in the OLE study maintained remission through M24 of the OLE study. Despite small pt numbers, maintenance of remission after dose reduction was numerically more likely for patients in remission for ≥6 months than for those in remission for <6 months prior to reduction. Further studies are needed to evaluate flexible dosing of tofacitinib in patients with UC.

Table. Remission at M12 and M24 in the OLE study and patient characteristics by M12 remission status among patients who achieved remission at Wk52 of OCTAVE Sustain with tofacitinib 10 mg BID and reduced to 5 mg BID in the OLE study.

Remission in the OLE study	Patients in remission at Wk52 of OCTAVE Sustain after receiving tofacitinib 10 mg BID, who reduced to 5 mg BID in the OLE study[a] (N=76)	
Remission at M12 of the OLE study[b]		
As observed, n/N1 (%)	56/68 (82)	
NRI, n/N2 (%)	56/73 (77)	
Remission at M24 of the OLE study[b]		
As observed, n/N1 (%)	32/42 (76)	
NRI, n/N2 (%)	32/52 (62)	
Patient characteristics	**OLE study M12 remission status (as observed)**	
	In remission at M12 of the OLE study[b] (N=56)	**Not in remission at M12 of the OLE study[b] (N=12)**
Male, n (%)	25 (45)	5 (42)
Age at induction study baseline (years), mean (SD)	46.0 (14.8)	42.4 (16.2)
Total Mayo score at induction study baseline, mean (SD)	8.7 (1.6)	8.0 (1.3)
Duration of remission in OCTAVE Sustain , n/N1 (%)[c]		
≥12 months prior to dose reduction (remission at Sustain baseline, Wk24 and Wk52)	21/54 (39)	2/12 (17)
6–<12 months prior to dose reduction (remission at both Wk24 and Wk52, but not at Sustain baseline)	18/54 (33)	4/12 (33)
<6 months prior to dose reduction (remission at Wk52 but not Wk24, regardless of remission status at Sustain baseline)	15/54 (28)	6/12 (50)
Endoscopic subscore at OLE study baseline, n (%)		
0	17 (30)	5 (42)
1	39 (70)	7 (58)
CRP at OLE study baseline, n/N1 (%)		
<3 mg/L	49/56 (88)	9/10 (90)
≥3 mg/L	7/56 (13)	1/10 (10)
Extent of disease at induction study baseline, n/N1 (%)		
Proctosigmoiditis	11/55 (20)	5/12 (42)
Left-sided colitis	16/55 (29)	5/12 (42)
Extensive colitis/pancolitis	28/55 (51)	2/12 (17)
Prior TNFi failure at induction study baseline, n (%)	25 (45)	6 (50)

[a]All OCTAVE Sustain remitters received tofacitinib 5 mg BID in the OLE study, per OLE study design
[b]Remission status in the OLE study was based on local read of endoscopy
[c]Remission status in OCTAVE Sustain was based on central read of endoscopy
Remission was defined as a total Mayo score of ≤2 with no individual subscore >1, and a rectal bleeding subscore of 0
BID, twice daily; CRP, C-reactive protein; M, Month; N, number of evaluable patients;
N1, number of patients with non-missing data; N2, number of patients with imputed data who could have reached the specified time point; NRI, non-responder imputation; n, number of patients in the given category;
OLE, open-label, long-term extension; SD, standard deviation;
TNFi, tumour necrosis factor inhibitor; Wk, Week

P620

Stapled end-to-side vs. side-to-side anastomosis after ileocecectomy for Crohn's disease: a propensity score-matched analysis

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Background: Ileo-colic resection (ICR) is the most common surgical procedure for Crohn's disease (CD). Anastomotic construction is most commonly achieved with stapled side-to-side (SSTS) or hand-sewn end-to-end anastomosis (ETE). Another option that combines advantages of both SSTS and ETE is the stapled end-to-side anastomosis (SETS). However, results after SETS have not previously been reported. We aimed to compare short-term septic complications and long-term recurrence-free survival (RFS) of CD between patients who underwent SETS vs. SSTS.

Methods: This study was a retrospective analysis of a prospectively maintained database. All patients who underwent resection and anastomosis for terminal ileal CD from 01/2012–12/2016 were included. Patients with a stoma, or other type of anastomosis were excluded. Surgeries were done for 27 surgeons. Groups were compared with univariate analysis. RFS (Rutgeerts ≥ i2 or active disease on CT/MRI) was assessed using Kaplan–Meier curves and a log-rank test. Cox-proportional hazard and linear regression models with propensity score inverse probability of treatment weighting were used to further evaluate postoperative outcomes and recurrence of CD. Numbers represent median or proportion as noted.

Results: A total of 383 patients were analysed: 181 with SETS and 202 with SSTS. There were no differences regarding demographics and disease characteristics, except SETS patients had less weight loss (8% vs. 15%, $p = 0.04$) and fewer phlegmons (5% vs. 10%, $p = 0.05$). SETS operations were shorter (120 vs. 133 min, $p = 0.02$), and fewer were performed laparoscopically (46% vs. 65%, $p = 0.001$). Patients who underwent SETS compared with STSS had more experienced surgeons (23 vs. 11 years, $p < 0.001$). There was no difference in any short-term outcome on univariate analysis.

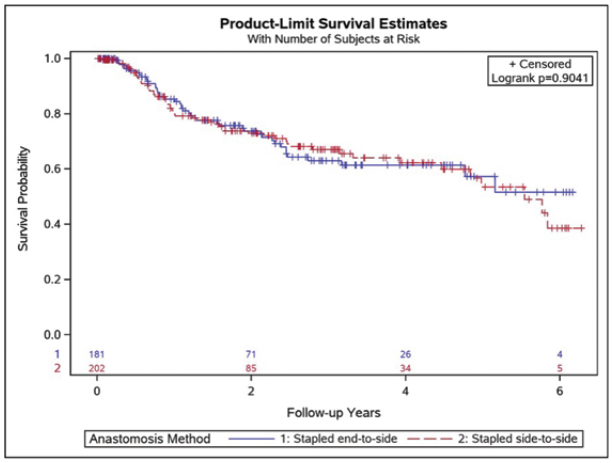
Figure 1. Univariate analysis of short-term complications within 30 days.

Factor	Stapled end-to-side (N=181)	Stapled side-to-side (N=202)	p-value
Follow-up (months)	25.6 (0.30 - 153.7)	30.6 (0.13 - 79.2)	0.24
Number (%) of surgeons using method at least once	17 (63)	24 (89)	***0.026***
Length of stay (postoperative)	6.0 [4.0 - 7.0]	5.0 [4.0 - 7.0]	0.21
Total Length of Stay (including readmissions)	9.0 [6.0 - 14.0]	9.0 [6.0 - 14.5]	0.94
Any complication	59 (32.6)	78 (38.6)	0.22
Any septic complication	8 (4.4)	16 (7.9)	0.16
Anastomotic leak	4 (2.2)	3 (1.5)	0.71
Enteric leak	1 (0.55)	1 (0.50)	0.99
Abscess	5 (2.8)	13 (6.4)	0.09
Dehydration	2 (1.1)	0 (0.0)	0.22
Clavien-Dindo >= III	11 (6.1)	17 (8.4)	0.38
ICU within 90 days	8 (4.4)	7 (3.5)	0.63

Statistics presented as Mean ± SD, Median [P25, P75], Median (min, max) or N (column %).
p-values: ANOVA, Kruskal-Wallis test, Pearson's chi-square test, Fisher's Exact test as appropriate

RFS Kaplan–Meier analysis

Figure 2. Kaplan–Meier plot for RFS and log-rank test



Recurrence-free Survival (95% CI)

Anastomosis method	1-year	3-year	5-year	6-year
SETS	0.85 (0.79, 0.91)	0.63 (0.54, 0.72)	0.57 (0.45, 0.69)	0.52 (0.36, 0.67)
SSTS	0.81 (0.74, 0.87)	0.67 (0.59, 0.75)	0.53 (0.41, 0.66)	0.39 (0.22, 0.56)
p-value	0.30	0.53	0.66	0.26

P-values based on Z-test of point estimates of survival.

showed no difference in recurrence rates. After inverse probability of treatment weighting using the propensity score and number of postoperative medications, there was no significant difference in any of the outcomes between the two groups.

Conclusions: At our centre, SETS and SSTS anastomoses in patients undergoing ICR for CD were comparable with respect to short-term complications and long-term recurrence rates. Therefore, SETS remains a viable method for reconstruction, especially in the case of bowel lumen size mismatch.

P621

Real-world effectiveness and safety of vedolizumab and anti-TNF in biologic-naive Crohn's disease patients: results from the EVOLVE study

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Background: This multi-country, retrospective chart review study assessed the effectiveness and safety of vedolizumab (VDZ) compared with anti-tumour necrosis factors (anti-TNF) agents in a real-world cohort of biologic (bio)-naïve Crohn's disease (CD) patients.

Methods: Bio-naïve CD patients (≥18 years old) treated with VDZ or anti-TNF (May 2014 to March 2018), were included from sites in Canada, Greece and the USA. Data were collected from treatment (Tx) initiation to earliest of death, chart abstraction date or 6 months post-Tx discontinuation. Using the Kaplan–Meier method, cumulative rates of clinical response, remission, mucosal healing, dose escalation and Tx persistence were estimated over 24 months (mo). Incidence rates (per 100 person-years [PYs]) of CD exacerbations, CD-related surgeries (bowel resection, strictureplasty, colectomy), serious adverse events (SAEs) and serious infections (SIs) were assessed. A Cox proportional hazards model adjusted for baseline confounders (age, sex, albumin, C-reactive protein, disease location and duration, CD-related hospitalisations in (prior 12 mo), and disease severity) was used to compare Tx cohorts; adjusted hazard ratios (HR) with 95% confidence intervals are reported.

Results: Overall, 419 CD patients (VDZ: 177; anti-TNF: 242) [adalimumab: 125, infliximab: 111, infliximab-dyyb: 3, certolizumab pegol: (3) from 37 sites were included (median [min–max] follow-up [mo]: VDZ, 15.3 (5.0–45.9); anti-TNF, 18.1 [6.0–49.8]). Baseline characteristics are shown in Table 1.

Baseline characteristics	Vedolizumab N=177	Anti-TNF N=242	P-value[1]
Mean (SD) age	51.3 (17.0)	39.8 (14.7)	**<0.0001**
Sex (male), n (%)	96 (54.2)	124 (51.2)	0.54
Median (min-max) disease duration, (years)	6.83 (0.05-54.0)	2.35 (<0.05-48.0)	**<0.0001**
Disease location, n with available data	156	205	0.05
Colonic with/without upper GI disease	38 (24.4)	63 (30.7)	
Ileal with/without upper GI disease	65 (41.6)	65 (31.7)	
Ileocolonic with/without upper GI disease	53 (34.0)	77 (37.6)	
Disease behaviour[2], n with available data	145	195	0.88
Non-stricturing, non-penetrating	77 (53.1)	109 (55.9)	
Penetrating	15 (10.3)	19 (9.7)	
Stricturing	53 (36.6)	67 (34.4)	
Disease severity[3], n with available data	114	157	0.16
Moderate, n (%)	38 (33.3)	60 (38.2)	
Severe, n (%)	8 (7.0)	18 (11.5)	
Steroid-dependent, n with available data	142	197	0.93
n (%)	24 (16.9)	34 (17.3)	
Concomitant immunosuppressive use at index, n (%)	36 (20.3)	68 (28.1)	0.07
Albumin, n with available data	74	117	**0.01**
<35 g/l, n (%)	40 (54.1)	84 (71.8)	
≥35 g/l, n (%)	34 (45.9)	33 (28.2)	
CRP, n with available data	106	139	0.11
<5 mg/l, n (%)	55 (51.9)	58 (41.7)	
≥5 mg/l, n (%)	51 (48.1)	81 (58.3)	
Prior CD-related surgery[4] (since diagnosis), n (%)	17 (9.6)	15 (6.2)	0.19
CD-related hospitalisations (12 months prior), n (%)	28 (15.8)	55 (22.7)	0.08

CD: Crohn's disease; CRP: C-reactive protein; GI: gastrointestinal; Max: maximum; Min: minimum; Max: maximum; SD: standard deviation.
[1]Statistical tests were conducted for patients with available data. For continuous variables, the Kolmogorov-Smirnov test was conducted to evaluate normality; if normal, a t-test was used to test for differences between VDZ and anti-TNF patients, otherwise Wilcoxon-Mann–Whitney test was conducted. For categorical variables, Chi-square test was conducted unless cells had <5 observations, then Fisher exact was used. [2]Disease behavior includes patients with/without perianal disease for each category. [3]Derived based on available medical record data of standard disease measures within 6 months of treatment initiation: Crohn's Disease Activity Index (CDAI), Harvey-Bradshaw Index (HBI), modified HBI, Physician Global Assessment. [4]CD-related surgeries defined as: Partial or total colectomy, small bowel, sigmoid or ileocolonic resection, hemicolectomy, total proctocolectomy with/without ileostomy, ileostomy reversal to restore bowel continence, laparoscopic strictureplasty.

Table 1. Baseline characteristics of real-world biologic-naive Crohn's disease patients treated with vedolizumab and anti-TNF agents.

At 24 months, cumulative rates of clinical response, clinical remission, mucosal healing and dose escalation were similar in both Tx cohorts (Table 2). Tx persistence rates were significantly ($p < 0.05$) greater at 12 months (86% vs. 76%) for VDZ vs. anti-TNF patients, respectively, but did not differ at 18 (79% vs. 71%) and 24 months (71% vs. 71%). Although observed incidence rates (per 100 PYs) of CD exacerbations (17.2 vs. 25.9; $p = 0.09$), CD-related surgery (1.7 vs. 6.2; $p = 0.079$), SAEs (6.4 vs. 11.7; $p = 0.16$) and SIs (1.6 vs. 3.6; $p = 0.13$) were lower in VDZ vs. anti-TNF patients, respectively, these differences did not reach statistical significance. Adjusted HR for outcomes are shown in Table 2.

Outcomes	Vedolizumab N=177	Anti-TNF N=242	P-value[1]	Adjusted Hazard Ratio (95% CI)[2]
Clinical Effectiveness Outcomes[3], %				
Clinical response, n with available data	149	208		
12 months	61.5	65.4	0.16	1.1 (0.8-1.5)
18 months	71.4	69.9	0.35	1.2 (0.9-1.6)
24 months	74.5	73.4	0.38	1.2 (0.9-1.6)
Clinical remission, n with available data	150	211		
12 months	52.3	55.1	0.48	1.1 (0.8-1.5)
18 months	62.5	61.3	0.69	1.2 (0.9-1.6)
24 months	69.7	66.4	0.80	1.2 (0.9-1.6)
Mucosal healing, n with available data	105	134		
12 months	62.5	59.7	0.59	1.0 (0.7-1.5)
18 months	78.7	74.8	0.82	1.0 (0.7-1.5)
24 months	100	90.1	0.82	1.1 (0.8-1.6)
Treatment persistence, n with available data	177	238		
12 months	85.6	76.0	**0.02**	**1.8 (1.1-3.0)**
18 months	78.8	70.7	0.04	1.6 (1.0-2.5)
24 months	71.4	70.7	0.11	1.4 (0.9-2.2)
Dose escalation[4], n with available data	177	242		
12 months	16.6	12.6	0.30	1.2 (0.7-2.2)
18 months	23.2	15.8	0.21	1.4 (0.8-2.3)
24 months	23.2	18.1	0.26	1.3 (0.8-2.2)
Clinical and Safety Outcomes (Incidence Rate, per 100 Person-Years [95% confidence interval])				
CD exacerbation[5,6]	17.2 (12.3-23.9)	25.9 (20.7-32.5)	0.09	0.6 (0.4-1.1)
CD-related surgery[5]	1.7 (0.6-4.6)	6.2 (4.1-9.3)	0.08	0.3 (0.1-1.1)
SAE[7]	6.4 (3.8-10.6)	11.7 (8.6-15.7)	0.16	0.6 (0.3-1.2)
SI[7]	1.6 (0.6-4.3)	3.6 (2.2-6.0)	0.13	0.4 (0.1-1.3)

CD: Crohn's disease; CI: confidence interval; SAE: serious adverse event; SI: serious infection.
[1]P-values generated from Kaplan-Meyer analyses using the unadjusted log-rank test for 'Clinical Effectiveness Outcomes' and Wald chi-square test for 'Clinical and Safety Outcomes'. [2]Hazard ratios (vedolizumab [VDZ] vs anti-TNF) for both outcomes and clinical/safety outcomes were generated using adjusted Cox proportional hazards models for confounders: age, sex, albumin, C-reactive protein, disease location and duration, CD-related hospitalisations in prior 12 months, and disease severity; patients with unknown disease duration were excluded (n=75 [VDZ=40, anti-TNF=35]). [3]Cumulative rates of clinical response, clinical remission and mucosal healing were assessed using pre-defined hierarchical algorithms of standard disease measures as reported in in the medical records and were calculated for patients with ≥1 assessment. [4]Increase in VDZ frequency or anti-TNF dose and/or frequency for ≥2 consecutive infusions/injections. [5]Assessed exposure time for CD exacerbation and CD-related surgery spans from treatment initiation to earliest of 6 months post-treatment discontinuation or chart abstraction date. [6]CD exacerbation defined as documentation of a 'flare-up' in the medical chart or as a reason for healthcare professional visit, emergency department visit, hospitalisation or initiation of non-biological therapy. [7]Assessed exposure time for SAE and SI rates include up to five half-lives post-treatment discontinuation, where applicable (VDZ: 18 weeks; infliximab/ infliximab-dyyb: 6.8 weeks; adalimumab and certolizumab pegol: 10 weeks).

Table 2. Clinical effectiveness and safety of vedolizumab and anti-TNF agents in real-world biologic-naïve Crohn's disease patients

Conclusions: Clinical and endoscopic outcomes in this real-world cohort suggest that VDZ and anti-TNF in CD are equally effective in a first-line biologic setting over 24 months.

P622

Child outcome in IBD pregnancy: early vs. late discontinuation of IFX therapy

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Background: Due to the unknown effect of intra-uterine exposure to biologics, women with IBD discontinue medical therapy early in pregnancy to avoid the risk of foetal exposure. We assessed the child outcome in mothers with IBD, who discontinued Infliximab (IFX) early vs. late during pregnancy.

Methods: We performed a retrospective analysis of all deliveries recorded in the Truven Health Analytics MarketScan® database from 2011 to 2015. We included only those patients on maintenance therapy with (IFX) (they received at least 3 infusions four or more weeks apart). Early discontinuation IFX group ('Early IFX') were considered all patients who discontinued IFX 90 days or more prior to delivery; late IFX discontinuation group ('Late IFX') were considered all patients who continued IFX closer to the delivery date or throughout the pregnancy. We have linked the mother's records with the available child records from inpatient and outpatient encounters. Primary outcomes include: congenital malformations, respiratory infection, developmental delay, underweight as defined by ICD-9 codes.

Results: We included 419 mothers with children in our study: 68.4% infants and 31.6% 1 year of age at the end of follow-up. Children of the mothers who discontinued IFX late in pregnancy did not show a different outcome when compared with children from mother who discontinued IFX early in pregnancy (Tables 1 and 2). One patient from the late IFX discontinuation group met the criteria for VACTREL syndrome (cardiac defects, trachea-oesophageal fistula, genitourinary malformations, renal agenesis, hemivertebra).

Outcomes	Late infliximab (n = 366)	Early infliximab (n = 73)	p-Value
Acute respiratory infections, n(%)	163 (45.6)	27 (37)	0.175
Underweight, n(%)	49 (13.4)	8 (11)	0.573
Development delay, n(%)	28 (7.6)	2 (2.74)	0.129
Congenital malformations, n(%)	20 (5.5)	2 (2.74)	0.441

MAJOR CONGENITAL MALFORMATIONS	
Late Infliximab (N=366)	**Early Infliximab (N=73)**
Hypospadias	Other specified anomalies of ureter, Other obstructive defects of renal pelvis and ureter, Other specified anomalies of kidney
Spina bifida, Hydrocephalus, PDA	Congenital hypertrophic pyloric stenosis Other specified anomalies of stomach Other specified congenital anomalies of brain OS type ASD
Specified congenital anomalies of lacrimal passages, congenital dislocation of hip, unilateral, OS type ASD	
OS type ASD, congenital dislocation of hip, bilateral	
Stenosis of pulmonary valve, congenital dislocation hip, OS type ASD	
Renal dysplasia	
Agenesis, hypoplasia, and dysplasia of lung, Renal agenesis and dysgenesis, Tracheoesophageal fistula, esophageal atresia and stenosis, Stenosis of pulmonary valve, atresia and stenosis of large intestine, rectum, and anal canal, other congenital deformity of hip (joint), hypospadias, hemivertebra, VSD (VECTRL)	
VSD	
OS type ASD, other anomalies of pulmonary artery and pulmonary circulation	
Other specified congenital anomalies of brain	
Hypospadias	
OS type ASD	
Agenesis lung, OS type ASD	
Hidden penis	
Complete transposition of great vessels, Hidden penis, Stenosis of pulmonary valve, Double outlet right ventricle, Cor triatriatum, VSD, Congenital chordee, PDA, OS type ASD	
Congenital chordee, Hypospadias	
VSD	
OS type ASD	
Congenital chordee, Talipes, unspecified, Hypospadias	
OS type ASD, PDA	

*PDA: patent ductus arteriosus, OS: ostium secundum, ASD: arterial septal defect

Early IFX and Late IFX group were similar in terms of maternal age at delivery (28.9 ± 4.81 vs. 29.4 ± 5.63, p = NS), parity, gestation, smoking and comorbidities such as HTN, obesity, pulmonary of cardiac diseases. In each Group 2/3 of patients had Crohn's disease and 1/3 ulcerative colitis. Additional medication use, steroids and/or thiopurine, before discontinuation of IFX was no significant different between the groups. However, mothers who discontinued IFX early in pregnancy were more likely to flare (12.2% vs. 1.33%, $p < 0.001$)

Conclusions: There was no difference in child outcomes if patients discontinued IFX early or late in pregnancy. These data are reassuring for mothers concerned of negative effect of intra-uterine exposure to IFX therapy.

P623

Colorectal cancer, colectomy rates and inflammatory bowel disease activity following liver transplantation in primary sclerosing cholangitis: a systematic review and meta-analysis

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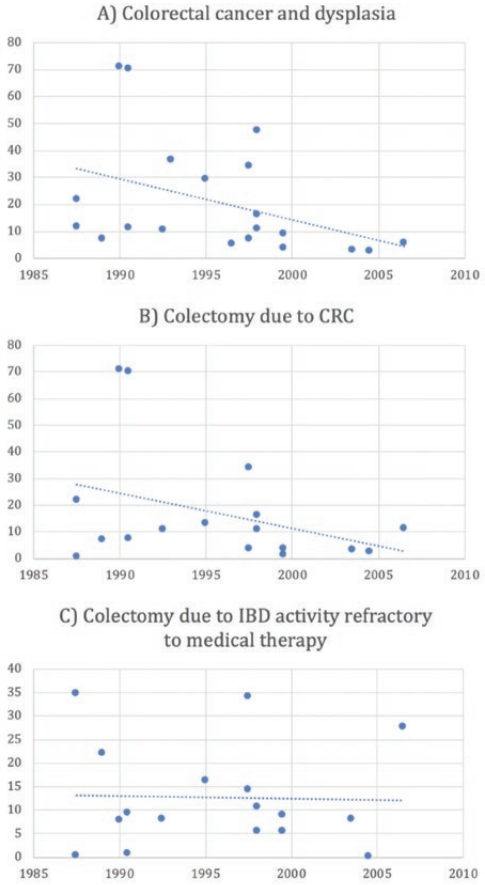
Background: Primary sclerosing cholangitis (PSC) is the classical hepatobiliary manifestation of inflammatory bowel disease (IBD) for which liver transplantation [LT] is the only curative therapy. We provide pooled incidence rates (IR) and time trends of (1) colorectal cancer (CRC), (2) colectomy, and (3) IBD activity post LT through systematic review and meta-analysis.

Methods: A systematic literature search of Medline and Embase was undertaken to identify studies that met the research objectives from 1981 to 2014. Studies were assigned to one or more of the three analytical streams (as above). The 'meta' package (R Studio (V.1.1.463)) and Revman was used to pool IRs and HRs from individual studies using a random effects model.

Results: 42 studies were included in the systematic review. Twenty studies detailing the clinical course of 1994 patients (9874 patient-years) were pooled to assess the incidence of dysplasia or CRC (combined endpoint) and CRC only; IR 14.97 cases (95% CI 9.74–23.02) and 9.21(95% CI 6.01–14.09) per 1000 person-years, respectively. Heterogeneity was considerable (I^2 = 86%). The incidence of post LT CRC was seen to be decreasing over time (Figure 1A).



Time trends in the incidence of colorectal cancer and colectomy post LT in the PSC cohort.

Colectomy following OLT was 23.18 per 1000 person-years (95% CI 16.74–32.08) (I^2 = 84%).The IR for colectomy due to dysplasia/CRC was 11.25 cases per 1000 person-years (95% CI 6.43–19.68) and seen to be decreasing over time (Figure 1B). In contrast, worsening IBD activity necessitated colectomy in 13.26 cases per 1000 person-years (95% CI 9.95–17.66), with no change over time (Figure 1C). Nine studies reported clinical course of IBD post-LT according to endoscopy findings/escalation in IBD therapy. 27.6% of patients (n = 584) experienced worsening IBD activity post LT. The effect of 5-aminosalicylates (5ASA) on risk of CRC (2 studies), colectomy (one study), and IBD activity (two studies) could not be analysed due to study heterogeneity. The effect of ursodeoxycholic acid (UDCA) on the risk of CRC after LT was examined by three studies. Due to data availability, only two studies could be pooled. UDCA increased the risk of CRC post LT; HR 2.90 (95% CI 1.37–6.11). The impact of UDCA on colectomy and IBD activity post-LT were inconclusive. No study examined biologics in context of study objectives.

Conclusions: This is the first comprehensive systematic review and meta-analysis of IBD-related outcomes post LT in the PSC cohort. The risk of CRC mandates colonoscopy surveillance, although incidence appears to be decreasing. Identifying factors affecting IBD course is of critical importance, given that IBD deterioration appears to be the principal indication for colectomy post LT.

P624

Factors that may influence the development of anti-drug antibodies to adalimumab

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Background: Anti-drug antibodies (ADAs) to adalimumab (both the originator and biosimilars) are associated with a loss in efficacy and infusion reaction. ABP 501 [EU: AMGEVITA® (adalimumab); US: AMJEVITA™ (adalimumab-atto)] is the first approved biosimilar to adalimumab. Earlier identification of ADAs would help optimise treatment with adalimumab. In this post-hoc analysis, we aim to identify factors that may influence the development of binding ADAs to adalimumab.

Methods: We analysed data from a randomised, double-blind, 26-week, active-controlled study designed to show clinical equivalence between ABP 501 40 mg and adalimumab reference product 40 mg among adalimumab-naive adult patients with moderate-to-severe rheumatoid arthritis. Validated electrochemiluminescent assays were used to detect the presence of binding ADAs to adalimumab. We fitted a logistic regression to the Week 26 ADA binding status (positive or negative) in subjects who had negative ADA at Week 12. Factors that were explored included baseline BMI (underweight, normal, overweight, or obese), albumin, glucose, platelet counts, C-reactive protein (CRP), change in CRP from baseline to Week 12, and serum pharmacokinetic (PK) trough at Week 12. A stepwise selection procedure with entry criterion of 0.3 and stay criterion of 0.2 was used in a multi-variable logistic regression. Variables with $p < 0.05$ were considered to strongly correlate with the development of binding ADA at Week 26.

Results: Of 526 subjects tested, 353 showed negative for binding ADAs to adalimumab through Week 12, with 52 subjects developing

binding ADA to adalimumab at Week 26. Average baseline BMI was 28 with 31% obese. Mean (SD) was 42 (2.8) g/l for albumin; 5.6 (1.7) mmol/l for glucose; 290.6 (84.55) 10^9/l for platelet count; 14.4 (21.45) mg/l for CRP; –7 (19.7) mg/l for change of CRP from baseline at Week 12; 7152 (2723) ng/ml for trough PK at Week 12 for ADA negative patients; 5755 (2810) ng/ml for trough PK at Week 12 for ADA-positive patients. The final multi-variable logistic regression showed that log-transformation of PK trough at Week 12 strongly correlated with the development of binding ADA at Week 26. The odds ratio (95% CI) for log-transformation of PK trough at Week 12 was 0.31 (0.17, 0.56), $p < 0.01$.

Conclusions: Baseline factors, such as BMI, albumin, glucose, platelet count, and CRP, did not correlate with the development of binding ADAs to adalimumab. A lower PK trough in ADA-negative patients may be strongly correlated to developing binding ADAs later in their course of adalimumab therapy. While further studies are needed, earlier monitoring of PK levels may provide insight into ADA formation in patients treated with adalimumab.

P625

Head-to-head comparison of three stool calprotectin tests for home use

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Background: Calprotectin-guided disease monitoring is done by periodically testing stool samples with an enzyme-linked immunosorbent assay (ELISA). Several manufacturers introduced a lateral flow–based test with software application that turns a smartphone camera into a reader for quantitative measurements. We compared three home tests (IBDoc, QuantonCal and CalproSmart) and companion ELISA tests (fCAL, IDK-Calprotectin and Calprotectin-ALP) to see if measurement pairs agreed sufficiently.

Methods: Method comparison study with 40 homogenised stool samples from patients with active or quiescent inflammatory bowel disease. Home tests were done with two iOS (iPhone 6 and 7) and two Android devices (Samsung Galaxy S6 and Motorola Moto G5 Plus). Primary outcome was test agreement (defined as percentage of paired measurements within predefined limits of difference). Secondary outcome included reading error rate (RER) per smartphone type.

Results: We performed 1440 smartphone readings and 120 ELISA tests. In the low calprotectin range (≤500 µg/g) IBDoc, QuantOnCal and CalproSmart showed 87%, 82%, and 76% agreement with their companion ELISAs. In the high range (>500 µg/g) the agreement was 37%, 19% and 37%, respectively. CalproSmart and QuantOnCal had significantly higher RERs than IBDoc (respectively, 5.8% and 4.8%, vs. 1.9%). Forty-three per cent of reading errors was on the Motorola device, in particular with the QuantOnCal application.

Conclusions: All three calprotectin home tests and companion ELISAs agreed sufficiently when concentrations are ≤500 µg/g. We recommend to always use the home test and ELISA of one and the same manufacturer. Manufacturers should explicitly evaluate and report the suitability of commonly used smartphones for quantitative calprotectin readings.

P626

Higher discontinuation rates of anti-TNF therapy in elderly IBD patients compared with a younger age group: results from a prospective registry

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Background: Increasing life expectancy and IBD incidence will result in more elderly IBD patients. There is paucity of data on safety and efficacy of anti-TNF in the elderly since this group is underrepresented in clinical studies. We aimed to compare the long-term effectiveness and safety of first anti-TNF treatment in IBD patients per age group (20–40 years/41–60 years/>60 years), by assessment of drug survival and reasons for discontinuation.

Methods: Patients on first anti-TNF treatment were identified through IBDREAM, a multi-centre prospective IBD registry in 5 hospitals in the Netherlands. Data on demographics, medical history, drug survival and adverse events were extracted from IBDREAM. STATA 11.2's competing risk regression was used to study time to drug discontinuation due to adverse events or lack of effectiveness, with discontinuation due to remission as a competing risk. The following predictors were considered in the analysis, corrected for age group: gender, IBD-type, anti-TNF type (infliximab or adalimumab), co-medication at baseline, disease duration, malignancies and surgery in medical history.

Results: A total of 895 patients were included, 679 had Crohn's disease, 200 ulcerative colitis and 16 IBD unclassified. Male represented 42%, median age at diagnosis was 26 years (IQR 19–38) and median follow-up was 46 months (IQR 18–97). 546 patients started anti-TNF at an age between 20 and 40 (61%), 268 at age 41–60 (30%) and 81 at age >60 (9%). Infliximab was the first anti-TNF in 75%, 71%, and 67% of patients, respectively, per age group. A total of 450 patients discontinued first anti-TNF therapy, 284 (52%), 133 (50%) and 33 (41%) per group. Reasons for discontinuation were adverse events in 27%, 29% and 39%, respectively per age group, lack of effectiveness in 40%, 47% and 32% and remission in 15%, 30% and 3%. Competing-risks regression analysis, with discontinuation due to adverse events/ lack of effectiveness as the outcome of interest and discontinuation due to remission as a competing event, showed a shorter drug survival in the two older groups (subhazard rate (SHR) age >60 1.46, SHR age 41–60 1.21; $p = 0.03$, both SHR compared with age <40) (Figure 1). Risk factor for discontinuation was prednisone use at baseline (SHR: 2.78; $p < 0.001$).

Conclusions: IBD patients starting the first anti-TNF agent at higher age showed a higher discontinuation rate due to adverse events or lack of effectiveness, with patients >60 years having the highest rate of discontinuation. Prednisone use at baseline was the only other predictor found for discontinuation.

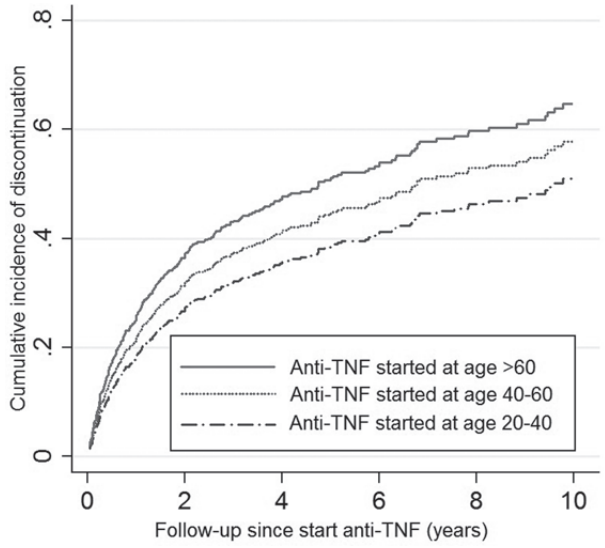

Figure 1. Cumulative incidence function of discontinuation in patients who started anti-TNF at age 20–40/41–60/>60 as estimated by the competing risk regression model.

P627

Stopping anti-tumour necrosis factor (TNF) therapy in patients with perianal Crohn's disease: Results from a population-based study

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Background: Little is known of the outcome of patients with perianal Crohn's disease (PCD) after stopping anti-TNF. Aim: To assess rate of relapse in PCD patients after stopping anti-TNF.

Methods: Consecutive PCD patients treated with anti-TNF therapies were identified from a territory wide Hong Kong IBD registry which covers 13 public hospitals in Hong Kong. Patients' disease characteristics, drug therapies and clinical outcomes were retrospectively reviewed from medical records and analysed.

Results: Sixty-three PCD patients received anti-TNF from 1997 to 2016. Median age at PCD diagnosis was 24 years (interquartile range, IQR: 20–28) and 72% were male. Median follow-up was 10 years (IQR: 6.3–14.5 years). Fifty-nine patients had complex fistulas. All had thiopurines in addition to anti-TNF. Twenty-seven patients (42.9%) achieved clinical remission, defined as complete cessation of fistula drainage, after median of 6 months (IQR: 4–10 months). Ten (15.9%) achieved radiological healing, defined as complete resolution of previous high signal tract or subtle, narrow calibre intermediate signal tract. Radiological healing lagged behind clinical healing by median of 7 months (IQR, 3–10 months). Thirty-eight patients (60%) stopped anti-TNF after median duration of 13 months (IQR: 4–24 months). Reasons for stopping included: financial reason (n = 11), loss of response (n = 10), achieving clinical remission (n = 9), side effects (including two tuberculosis) (n = 6) and patient's choice (n = 2). Twenty-one patients (55.2%) developed PCD relapse, defined as increased fistula drainage or recurrence of previously healed fistula, after stopping anti-TNF. Of which, 5 had relapse of both PCD and luminal Crohn's disease. Four had relapses of luminal CD alone. Median time to PCD relapse was 8 months (IQR: 3–14 months). Cumulative probabilities of PCD relapse were 46.5% at 12 months, 58.2% at 24 months and 71.1% at 36 months respectively. Seven out of 13 (53.8%) PCD patients with clinical remission relapsed after stopping anti-TNF. None of the PCD patients with radiologically healed fistula relapse after stopping anti-TNF. Among those who developed PCD relapse, 8 (38%) required defunctioning surgery and one required proctectomy. Twenty-seven switched to thiopurines, 6 to methotrexate, one to thalidomide and one to tacrolimus after stopping anti-TNF. Twenty-five patients (92.6%) restarted biologics (one vedolizumab, 24 anti-TNF) and 20 (80%) regained response.

Conclusions: More than half of PCD patients developed relapse after stopping anti-TNF. Majority regained response after restarting anti-TNF. Larger and longer-term studies are needed to investigate the role of deep fistula healing and de-escalating therapy in PCD.

P628

Long-term outcomes with transmural healing vs. mucosal healing in Crohn's disease: time for new treatment goals ?

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Background: While mucosal healing (MH) has been proved to predict relevant clinical outcomes in Crohn's disease (CD), little is known about the long-term significance of transmural healing (TH). The aim of this study was to prospectively assess the 1-year clinical outcomes in CD patients achieving TH following treatment with biologics, and to compare them with those in patients reaching only MH or no healing (NH).

Methods: We carried out an observational longitudinal study, evaluating 1-year outcomes in terms of steroid-free clinical remission (CR), rate of hospitalisation and need for surgery in a group of CD patients treated with anti-TNF-α for 2 years. On the basis of clinical, endoscopic, and sonographic findings, patients were divided in 3 groups: patients achieving TH, patients achieving MH only, and patients with NH.

Results: Out of 218 patients who completed a 2-year treatment course with anti-TNF-α, 68 (31.2%) presented TH (plus MH), 60 (27.5%) MH only, and 90 (41.3%) did not achieve any intestinal healing (NH). TH was associated with a higher rate of steroid-free CR (95.6%), and lower rates of hospitalisation (8.8%) and need

for surgery (0%) at 1 year compared with MH (75%, 28.3% and 10%, respectively) and NH (41%, 66.6% and 35.5%, respectively) ($p < 0.001$). Furthermore, TH was associated with longer intervals until clinical relapse (HR 0.87, $p = 0.01$), hospitalisation (HR 0.88, $p = 0.002$) and surgery (HR 0.94, $p = 0.008$) than MH. Also among patients discontinuing treatment with biologics, TH predicted better clinical outcomes at 1 year than MH ($p < 0.01$).

Conclusions: TH is an ambitious and powerful treatment goal associated, to a greater extent than MH, with improvement of all clinical outcomes. Additionally, TH is associated with better long-term clinical outcomes than MH also after discontinuation of biologics.

P629

The initial trough concentration at 36 h after starting tacrolimus is important for the personalised medicine strategy in patients with ulcerative colitis

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Background: Oral tacrolimus (TAC) is effective for inducing clinical remission in patients with refractory ulcerative colitis (UC). Therapeutic drug monitoring of TAC to achieve a high trough level as soon as possible is essential for demonstrating maximum effectiveness especially in patients with severe UC. However, high interindividual pharmacokinetics variability due to CYP3A5 genetic polymorphism may affect the efficacy of TAC therapy. Since it is difficult to examine genetic polymorphisms before TAC administration in clinical settings, an easy and practical strategy to predict optimal dose of TAC is required.

Methods: Seventy-one hospitalised patients with moderate to severe UC who received oral TAC were retrospectively analysed. The initial dose of TAC was 6 mg/day (0.08–0.15 mg/kg/day) twice daily and was administrated in a fasting condition. The initial trough concentration of TAC was measured at 36 h after starting therapy and each patient was classified as a poor metaboliser (PM; trough >20 μg/ml), intermediate metaboliser (IM; 10–20 μg/ml), rapid metaboliser (RM; 5–10 μg/ml), or ultra-rapid metaboliser (UM; <5 μg/ml). Dosage of TAC was adjusted as follows: reduce to 2–4 mg/day for PM, continue with 5–6 mg for IM, increase to 8–10 mg/day for RM, increase to 12 mg/day with coadministration of proton pump inhibitor for UM. After the first dose adjustment of TAC, trough concentration was measured once every 2 days to maintain a high trough level for 2 to 3 weeks. All responding patients were followed by tapered trough level of 5–10 μg/ml for 3 months.

Results: Proportion of metabolising phenotypes of TAC depending on the initial trough concentration was as follows: PM 13%, IM 39%, RM 24%, and UM 24%. Final required average dose of TAC for maintaining high trough level was 3.9 ± 1 mg/day for PM, 4.8 ± 1.6 mg/day for IM, 7.9 ± 2.2 mg/day for RM, and 11.5 ± 3.3 mg/day for UM. All cases reached a high trough level within a week. Time required for reaching a high trough level was 2.9 days on average. After 3 months from the treatment initiation, the response rate was 76% and clinical remission was achieved in 65% of patients. Patients with severely active compared with moderate UC had equivalent rate of clinical response (72% vs. 88%; $p = 0.15$) and clinical remission (59% vs. 82%; $p = 0.07$). Frequency of RM or UM did not differ between non-responder and responder (38% vs. 60%; $p = 0.15$, chi-squared test). The incidence of adverse events did not differ between metabolising phenotypes of TAC.

Conclusions: Personalised medicine strategy based on predicted metabolising phenotype from the initial trough level would make TAC therapy safer, easier and more effective. The influence of genetic polymorphism could be eliminated by our rapid induction method of TAC.

P630

A non-inferiority randomised clinical trial of the use of the smartphone-based health applications IBDsmart and IBDoc® in the care of inflammatory bowel disease patients

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Background: Using smartphones to communicate symptoms and biomarkers is a potentially cost-effective and quality-of-care equivalent method for managing inflammatory bowel disease (IBD). We aim to compare the management of IBD using two smartphone apps (IBDsmart for symptom monitoring and IBDoc® for faecal calprotectin [FC] monitoring) vs. standard face-to-face (F2F) outpatient care. We hypothesised non-inferiority of quality of life (QoL) and symptoms with a reduction in standard F2F appointments in the smartphone app group. Assessment was made of adherence and usability of the apps.

Methods: Adult IBD outpatients (usually seen more often than annually) were randomised to smartphone app or standard F2F care for 12 months. The smartphone app group sent their self-reported disease activity index scores (Harvey–Bradshaw Index [HBI] for Crohn's disease and Simple Clinical Colitis Activity Index [SCCAI] for ulcerative colitis) and FC scores 3-monthly and were not seen F2F unless they had a disease flare or specifically requested. Those in F2F care were seen as usual during the study period (i.e. 3 or 6 monthly). QoL was measured via the IBD Questionnaire (IBDQ) at 0, 3, 6, 9, and 12 months. At 12 months, the smartphone app group completed a system usability scale for IBDsmart and for IBDoc® and doctor usability was assessed. Australian New Zealand Clinical Trials Registry (ACTRN12615000342516).

Results: In total, 107 patients were recruited between August 2015 and December 2016 from four District Health Boards. One hundred people (73 Crohn's disease, 49 males, average age 35 years) consented and completed baseline questionnaires (50 in each group). There was no difference in IBDQ, HBI, and SCCAI between the two groups. Outpatient appointment numbers were 1.7 (SD 0.8) in standard F2F care vs. 0.6 (0.9) in smartphone app care ($p < 0.001$). There was no difference in the number of surgical outpatient appointments

or IBD-related hospitalisations. Usability: 82% completed >50% of the IBDsmart indices and 72% completed more than half of the IBDoc tests®. Patient-reported system usability scores were 81.37 (SD 14.08) for IBDsmart and 71.6 (16.76) for IBDoc®. Fifty-eight per cent of patients felt comfortable using the apps to report symptoms instead of F2F appointments. The gastroenterologist was very or somewhat comfortable using IBDsmart/IBDoc® in 78% of cases. The gastroenterologist said IBDsmart/IBDoc® adequately replaced F2F appointments in 58%. In 54% of cases, the gastroenterologist claimed there was something they were not able to communicate with patients via the apps (c.f. 10% when seeing them F2F).
Conclusions: Use of IBDsmart and IBDoc® in routine clinical care of IBD patients over 12 months is demonstrated to be acceptable, usable, and non-inferior to standard clinic-based care.

P631

Development and validation of a clinical scoring tool for predicting treatment outcomes with vedolizumab in patients with ulcerative colitis

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Background: We created and validated a clinical decision support tool (CDST) for vedolizumab (VDZ) therapy in active ulcerative colitis (UC).
Methods: To identify factors associated with corticosteroid-free remission (CSFREM; full Mayo score ≤2, no sub-score >1), logistic regression analyses were run on data from the GEMINI 1 VDZ trial for UC (derivation set; n = 620) and used to develop a CDST. Correlations between VDZ exposure, onset of action, and efficacy across predicted-probability groups were explored, and the CDST was externally validated in an observational cohort of VDZ-treated UC patients (validation set; n = 199).
Results: Factors independently associated with CSFREM were absence of previous tumour necrosis factor antagonist exposure (+3 points), disease duration ≥2 years (+3 points), baseline endoscopic activity (moderate vs. severe) (+2 points), and baseline albumin concentration (+0.65 points per g/l). Patients were stratified into low (≤26 points), intermediate (>26 to ≤32 points), or high (>32 points) probability of response groups. The higher probability group more rapidly achieved symptom activity reductions and attained higher rates of CSFREM ($p < 0.001$). In the validation set, a 26-point cut-off value showed high sensitivity (93%) for identifying non-responders. A statistically significant linear relationship was observed between VDZ exposure, probability groups, and efficacy in the derivation set ($p < 0.001$). In the validation set, only the low–intermediate probability group benefited from VDZ interval shortening for lack of response ($p = 0.02$).
Conclusions: We developed and externally validated a CDST with good discriminative performance for predicting CSFREM with VDZ in UC patients. Pending further validation, this tool could be a helpful aid in identifying patients who would benefit from VDZ interval shortening due to insufficient response. (GEMINI 1: NCT00783718).

P632

Allogenic hPDMSCs gelatum in the treatment of perianal fistulas in patients with Crohn's disease

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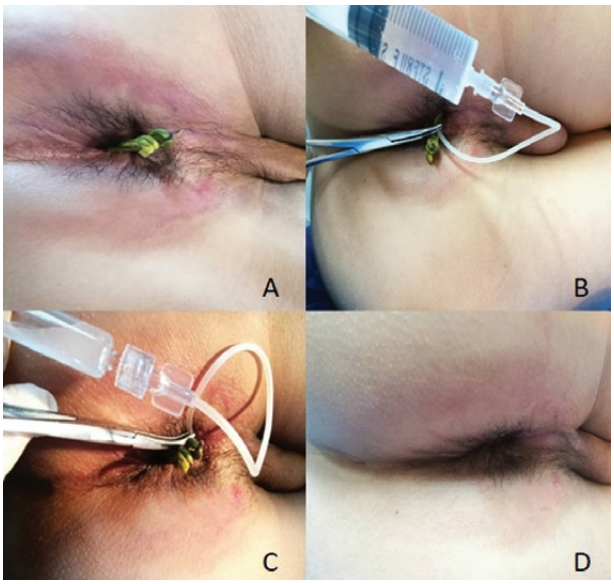
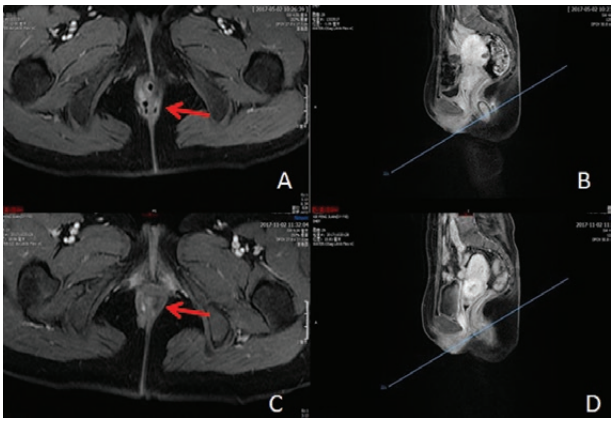
Background: Perianal fistulas in patients with Crohn's disease (CD) are still lacking in effective management modalities and mesenchymal stem cell-based therapy emerges as an attractive candidate for the treatment for perianal fistulising CD. But how to maintain the MSC activity in fistula in convenient way remain to be settled. Therefore, this pilot study aimed to assess the efficacy and safety of allogenic human placenta-derived mesenchymal stem cells (hPDMSCs) gelatum for perianal fistulas in patients with CD.
Methods: Six consecutive patients with perianal fistulising CD were enrolled. The hPDMSCs gelatum containing 1×10^6 or 5×10^6 hPDMSCs per millilitre were administrated via intrafistular injection.



The four steps of Allogenic hPDMSCs gelatum administration observe-flush fistula with NS –administrate MSCs -remove seton.
The primary outcome, fistula healing, was determined by physical examination 6, 12, and 24 weeks later; healing was defined as absence of discharge and less than 2 cm of fluid collection—the latter

determined by magnetic resonance imaging at Week 12 and 24. All procedures were performed at the Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China, from March 2017 through January 2018.

Results: Allogenic hPDMSCs were successfully injected for all patients (n = 6). A total of nine fistulas were identified, with two patients having ≥2 fistulas. Three patients received 1 × 10^6 and 5 × 10^6 hPDMSCs per fistula, respectively. After hPDMSCs injection, 6/6, 4/6, and 4/6 patients completed the 6-week, 12-week and 24-week follow-up, respectively. At Week 6, fistula healing was observed for 4/9 fistulas in 3/6 patients. At Week 12, fistula healing was observed for 3/5 fistulas in 2/4 patients. At Week 24, fistula healing was observed for 4/5 fistulas in 3/4 patients.



Pelvic MRI showed fistula closure in 24-week follow-up

No adverse events associated with hPDMSCs injection occurred.

Conclusions: Intrafistular administration of hPDMSCs gelatum seems to be a safe and effective treatment for perianal fistulas in patients with CD.

P633

Harmonisation of quality of care in an IBD centre impacts disease outcomes: importance of structure and process indicators

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Background: Optimal management of IBD requires harmonised monitoring and treatment pathways. We aimed to evaluate the quality of care at the McGill University Health Center (MUHC) IBD Center using quality of care indicators (QIs) including patient assessment strategy, monitoring, treatment decisions, and outcomes.

Methods: The MUHC IBD centre was officially established in July 2016 with a structure based on the PACE (Promoting Access and Care through Centers of Excellence) program developed by the Crohn's and Colitis Canada organisation. We retrospectively analysed the quality of care IBD patients were receiving before and after their referral to MUHC IBD specialists and up until their first visit at the newly established MUHC IBD centre. Consecutive patients were included with an outpatient visit ('index visit') at the MUHC IBD Centre from July 2016 to December 2016. Demographic variables, outpatient visits, inpatient stays including IBD-related surgery, laboratory, imaging, and endoscopy data, current medications and/or changes in medications, and vaccination profiles were captured.

Results: In total, 1357 patients (64.4% Crohn's disease (CD)) were included. At referral, a large proportion of patients were objectively re-evaluated (ileocolonoscopy: 79%, cross-sectional imaging: 15.6% of CD patients had abdomino-pelvic MRI or CT and 23.6% abdominal US, biomarkers CBC, CRP and FCAL: 89.9%, 81.9% and 16.5%, respectively). Therapeutic strategy was changed in 53.6% with 22.5% of patients starting biologics. Tight objective patient monitoring was applied also during follow-up (colonoscopy: 79%, cross-sectional imaging: 61.8% within 2 years prior to the index visit). Additional colonoscopy and imaging to evaluate disease activity was ordered in 32% and 19% within 6 months after the index visit. The frequency of therapeutic drug monitoring (TDM) was escalated following the establishment of the IBD centre. Maximum therapeutic step was accelerated with 48.8% of patients on biological therapy at the time of index visit. Treatment was changed in 17.8% of patients (active disease: 40.3%, patients in remission: 7.2%, $p < 0.01$). The need for surgery (4.3%) and hospitalisation (7.6%) were relatively low, while 16.8% of patients needed an IBD-related ER visit within 6 months after index visit.

Conclusions: Our data support that tight monitoring was applied at the MUHC IBD centre with a high emphasis on objective patient (re)evaluation, timely access and accelerated treatment strategy at referral or during follow-up. QIs mapped in this study can serve as reference data for comparison on structure, process algorithms and outcomes for IBD centres worldwide.

P634

Real-world data on the efficacy and safety of vedolizumab therapy in patients with inflammatory bowel disease: a retrospective nation-wide cohort study in Singapore

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Background: Real-world clinical data on the use of vedolizumab in patients with inflammatory bowel disease (IBD) is lacking in Asian populations. We aim to report the efficacy and safety outcomes of vedolizumab in a nation-wide cohort in Singapore.

Methods: A retrospective nation-wide cohort study of adult IBD patients from the 6 largest local hospitals who completed vedolizumab induction between 2015 and 2018 was conducted. The primary outcome measure was steroid-free clinical remission (SFCR) at 14, 24 and 54 weeks after initiation of vedolizumab therapy. SFCR was defined as complete tapering of steroids with a complete absence of symptoms in Crohn's disease (CD), and a partial Mayo Clinic score <2 in ulcerative colitis (UC). Secondary outcome measures

included endoscopic remission as defined by complete absence of ulceration in CD and Mayo endoscopic subscore ≤1 in UC; and normalisation of radiological appearance on CT/MR enterography.

Results: Fifty-three patients (28 CD, 25 UC) were included in this study, with 64.2% (34/53) anti-TNF-experienced.

Characteristics	CD (n=28)	UC (n=25)
Age, y		
Mean age at diagnosis (SD)	28.1 (19.2)	32.0 (22.1)
Smoking, n (%)		
Never	28 (100)	21 (84.0)
Ex-smoker	0 (0)	2 (8.0)
Active smoker	0 (0)	2 (8.0)
Duration of disease at initiation of vedolizumab, y (SD)	8.4 (8.5)	6.1 (5.7)
Montreal disease location, n (%)		
L1: Ileal	10 (35.7)	
L2: Colonic	6 (21.4)	
L3: Ileocolonic	10 (35.7)	
L4: Upper GI	1 (3.6)	
E1: Proctitis		2 (8.0)
E2: Left-sided colitis		6 (24.0)
E3: Pancolitis		17 (68.0)
Montreal disease behaviour, n (%)		
B1: Inflammatory	8 (28.6)	
B2: Stricturing	6 (21.4)	
B3: Penetrating	14 (50.0)	
Perianal disease	15 (53.6)	
Previous bowel surgery, n (%)	10 (35.7)	1 (4.0)
Previous anti-TNF therapy, n (%)		
Anti-TNF naïve	11 (39.3)	8 (32.0)
1 anti-TNF agent	13 (46.4)	13 (52.0)
2 anti-TNF agents	4 (14.3)	3 (12.0)
3 anti-TNF agents	0 (0)	1 (4.0)
Concomitant therapy, n (%)		
Immunomodulator	14 (50.0)	10 (40.0)
Corticosteroids	11 (39.3)	13 (52.0)
Disease activity		
Mean Harvey Bradshaw index (SD)	2.6 (2.9)	
Mean Partial Mayo score (SD)		3.6 (2.4)

Table 1. Baseline characteristics.

In CD, SFCR at Weeks 14, 24 and 54 was 39.3% (11/28), 30.0% (6/20), and 42.9% (6/14), respectively. Endoscopic remission was achieved in 30.8% (4/13) of patients at a median treatment duration of 37 weeks, and radiological remission in 22.2% (2/9) at a median treatment duration of 48 weeks. In UC, SFCR at Weeks 14, 24, and 54 was 68.0% (17/25), 66.7% (14/21), and 80.0% (8/10), respectively. Endoscopic remission was achieved in 35.3% (6/17) of UC patients at a median treatment duration of 31 weeks. Thirteen patients (6 UC, 7 CD) discontinued treatment, as depicted in the Kaplan–Meier survival analysis (Figure 1).

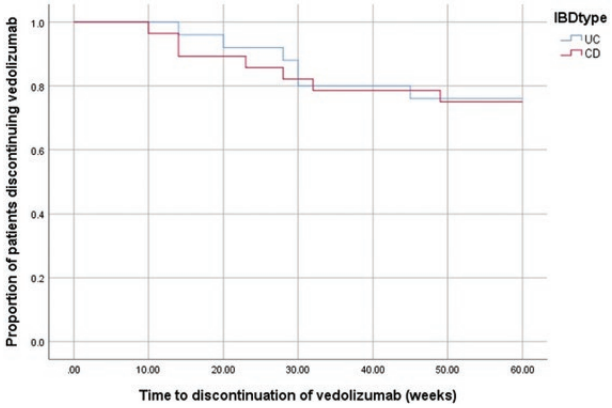

Figure 1. Kaplan–Meier survival curve of vedolizumab discontinuation.

Thirty-one adverse events occurred in 25/53 patients (47.2%); 5 (9.4%) were serious adverse events necessitating hospitalisation. Infections were the most common adverse event (37.7%, 20/53), with the majority being upper respiratory tract infections (24.5%, 13/53). Five patients (9.4%) developed gastrointestinal infections; 2 had *Clostridium difficile* colitis, 2 *Campylobacter jejuni* gastroenteritis, and 1 *Salmonella* gastroenteritis. Two patients (3.8%) experienced self-limiting infusion reactions. No malignancies or deaths occurred in our cohort.

Conclusions: The real-world experience with vedolizumab in Singapore supports its efficacy and safety in the treatment of IBD, especially in patients with UC.

P635

Carriage of the HLA-DQA1*05 allele is associated with a high risk of loss of response to infliximab in patients with inflammatory bowel disease

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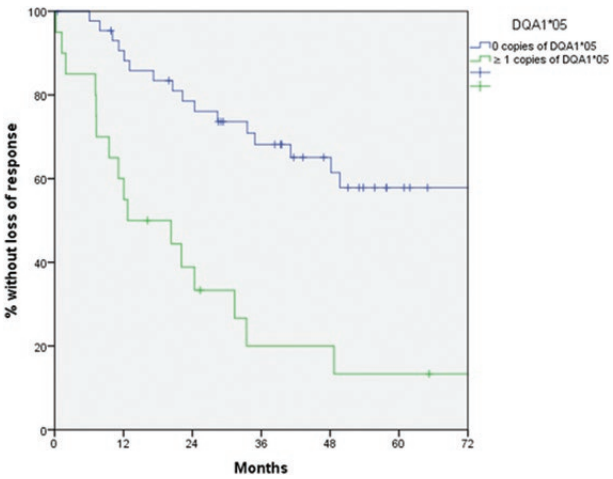
Background: Loss of response (LOR) to tumour necrosis factor antagonists occurs in up to 50% of patients with inflammatory bowel disease (IBD). Immunogenicity is a common cause of loss of response in patients due to the formation of antibodies directed against the drug. The ability to predict which patients are likely to lose response would allow therapies to be tailored to the patient's characteristics. In a recent study from the PANTS consortium, the HLA-DQA1*05 allele identified patients at increased risk of immunogenicity (Sazonovs A *et al*. JCC 2018; 12(S1): S009–010). The aim of our work was to know whether carriage of a HLA-DQA1*05 allele is associated with secondary loss of response to infliximab (IFX) in patients with IBD.

Methods: This is a retrospective cohort study from a prospectively maintained data base. Patients were included if they had achieved response to IFX. LOR was defined as recurrence or worsening of IBD-related symptoms that required a change or intensification in treatment, hospitalisation or surgery. Independent predictors of LOR were identified using univariate and multi-variable Cox proportional hazard regression.

Results: We included 64 patients (44 Crohn's disease, 20 ulcerative colitis) followed up to LOR (50%) or a mean of 56 months. Thirty-one per cent were carriers of an HLA-QA1*05 allele. On univariate analysis, body mass index (BMI) (HR 0.9, 95% CI 0.8–0.9, $p = 0.038$) and HLA-DQA1*05 carriage (HR 4, 95% IC 1.9–8.1, $p < 0.001$) were associated with LOR. On multi-variate analysis, after adjusting for immunomodulator use and BMI, only the carriage of an HLA-DQA1*05 allele was associated with LOR (HR 3.5, 95% CI 1.6–7.5, $p = 0.002$) (image 1).



Conclusions: HLA-DQA1*05 carriage is frequent in Spanish IBD population and it is associated with a marked increase in the risk of LOR to IFX. Testing for HLA-DQA1*05 could allow treatment to be tailored according to the risk of LOR.

P636

Impact of anti-TNF treatment on extra-intestinal manifestations in patients with inflammatory bowel disease: real-world data in Germany

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Background: Extra-intestinal manifestations (EIMs), common among patients with inflammatory bowel disease (IBD), can occur as an extension of immune responses from the gastrointestinal tract or as autoimmune diseases independent of IBD. Chronic inflammation is also linked to increased risk of cardiovascular (CV) problems. This study evaluated the real-world EIM rate for patients with IBD in Germany and the rate of EIM resolution after treatment with tumour necrosis factor inhibitors (TNFi), a drug class with systemic anti-inflammatory effect.
Methods: This retrospective study used anonymous healthcare claims data from the InGef database on individuals with statutory health insurance in Germany between 2011 and 2017. Adult patients with ≥2 diagnosis claims for Crohn's disease (CD) or ulcerative colitis (UC), ≥2 claims for a TNFi approved for IBD, and continuous enrolment for at least 12 months before and 15 months after the index treatment of the TNFi were identified. Prevalence rates for all EIMs were assessed for the 12-month baseline period prior to the index TNFi treatment. Subcategories of EIMs in musculoskeletal disorders (MSDs) and in CV events were also assessed. Among patients with any EIMs during baseline, rates of EIM resolution were assessed based on absence of EIM diagnoses over a 1-year period (month 3 to 15) after treatment with TNFi. The first 3 months of observation were not included in the analysis to allow time for treatment effect on EIMs.
Results: A total of 1658 IBD patients with TNFi were identified (CD, 67%; UC, 33%); 50% were female and mean age was 39 years. The majority of patients were treated with systemic corticosteroids (71%) and approximately half were on thiopurines (47%) or 5-aminosalicylic acid (54%) prior to the index TNFi. In the baseline period, over one-third patients (35%) had at least one type of EIM (CD: 34%; UC: 38%), 16% had ≥1 MSD (CD: 15%; UC: 17%) and 4% had ≥1 CV event (CD: 3%; UC: 7%). Among those with EIMs during baseline, resolution of at least one pre-existing EIM was found in 49% patients after TNFi treatment. Resolution rates were 42% for MSDs and 39% for CV events (table).

Table. Resolution of EIMs among patients with any EIM during baseline period (using 3-month buffer period and 12-month follow-up period).

Population at risk / EIM type	EIM resolution rate during 12-month follow-up window[a]		
IBD population with the specified EIM at baseline	*N*	*n*	*(%)*
Any EIM (resolution of ≥1 pre-existing EIM type)	581	285	(49.1%)
Musculoskeletal diseases[b]	259	110	(42.5%)
Cardiovascular events[c]	69	27	(39.1%)
CD population with the specified EIM at baseline	*N*	*n*	*(%)*
Any EIM (resolution of ≥1 pre-existing EIM type)	373	184	(49.3%)
Musculoskeletal diseases[b]	168	74	(44.0%)
Cardiovascular events[c]	33	13	(39.4%)
UC population with the specified EIM at baseline	*N*	*n*	*(%)*
Any EIM (resolution of ≥1 pre-existing EIM type)	208	101	(48.6%)
Musculoskeletal diseases[b]	91	36	(39.6%)
Cardiovascular events[c]	36	14	(38.9%)

CV: cardiovascular; EIM: extraintestinal manifestantion; IBD, irritable bowel disease; TNF: tumor necrosis factor.
[a]EIM resolution was assessed based on the presence/absence of diagnoses for the specified EIM type during the 12-month period starting 3 months after the index date and ending 15 months after the index date.
[b]EIMs in musculoskeletal diseases include diagnoses of arthropathy, peripheral arthritis, and ankylosing spondylitis.
[c]EIMs in cardiovascular events include diagnoses of acute myocardial infarction (AMI) / unstable angina pectoris, acute coronary syndrome, cardiac arrest, sudden cardiac death, cerebrovascular accident, venous thrombosis, arterial thromboembolism, pulmonary embolism, and procedure of surgical revascularization and percutaneous revascularization.

Conclusions: At least one-third of IBD patients experienced one or more EIM prior to a TNFi treatment. With the systemic anti-inflammatory effect, TNFi appear to be effective in resolving EIMs in nearly half of the affected patients, including those impacted by MSDs and CV events.

P637

MMP-2 and -8 degraded and citrullinated-vimentin (VICM) correlates to disease activity in inflammatory bowel diseases

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Background: Vimentin is a type III intermediate filament protein that stabilises cell architecture, but might be more active involved in intestinal inflammation during Crohn's disease (CD) and ulcerative colitis (UC). In lamina propria vimentin is found fibroblast and myofibroblasts, but are also produced by activated macrophages in inflammatory diseases. Protein fragments from vimentin turnover can be measured by competitive enzyme-linked immunosorbent assay (ELISA) targeting MMP-2 and -8 degraded and citrullinated-vimentin (VICM) and thereby maybe act as a serological biomarker of intestinal inflammation. The aim of this study was to evaluate how VICM correlates to clinical and endoscopic disease activity in CD and UC.
Methods: We included 63 CD patients, 107 UC patients and 20 healthy controls in a prospective biomarker evaluation study. Thirty-five per cent ($n = 24$) of CD patients and 49% ($n = 52$) of UC patients had active disease. We recorded Harvey–Bradshaw Index (HBI) or Simple Clinical Colitis Activity Index (SCCAI), and measured VICM, C-reactive protein (CRP), and faecal calprotectin (FC). Seventeen CD and 63 UC patients underwent sigmoidoscopy or colonoscopy

and were scored with Simple Endoscopic Score for Crohn's disease (SES-CD) or Endoscopic Mayo Score.

Results: VICM was significantly elevated in CD and UC patients compared with healthy controls ($p = 0.0001$). VICM correlated positively to SES-CD, SCCAI and Endoscopic Mayo Score (Figures 1B and 2A and B), and had a tendency to correlate to HBI (Figure 1A). VICM had a stronger correlation to the endoscopic scores than CRP (Figures 1B, D and 2B, D), but not as strong a correlation as FC (Figures 1A, E and 2A, E).

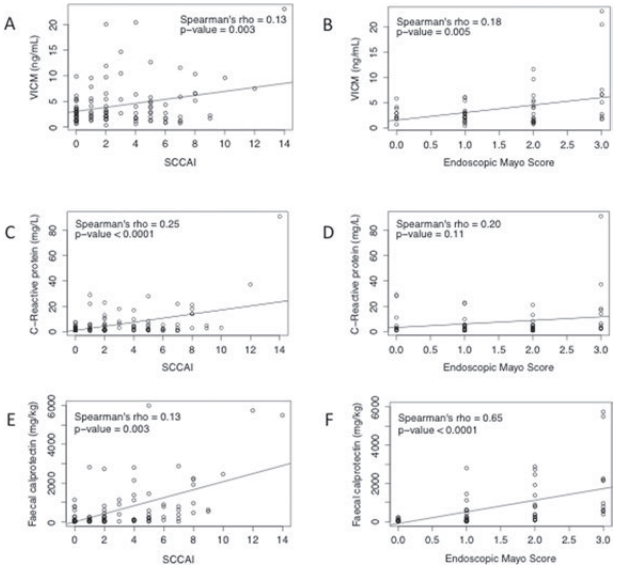

Figure 1. VICM, CRP, and f-calprotectin in relation to disease activity in CD patients.

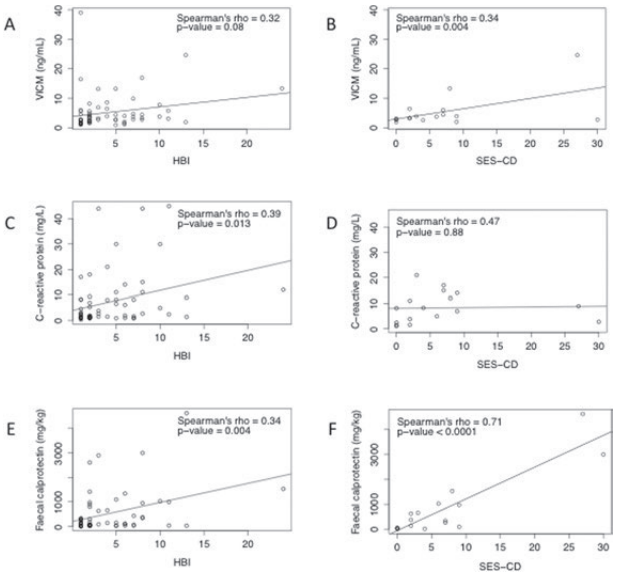

Figure 2. VICM, CRP, and f-calprotectin in relation to disease activity in UC patients.

Conclusions: VICM is significantly elevated in IBD patients in remission and IBD patients with active disease compared with healthy controls. Furthermore, VICM correlates significantly to endoscopic disease activity in CD and to clinical and endoscopic activity in UC. VICM has a higher correlation to the endoscopic scores compared with CRP. As VICM is produced locally in the inflamed gut and CRP is a systemic inflammation marker produced in the liver, VICM could be a more direct marker of the inflammation in the gut. Thus VICM might act as a serological biomarker of inflammation in the intestinal wall in IBD.

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BMS-986165, an oral selective tyrosine kinase 2 (TYK2) inhibitor, does not affect the pharmacokinetics of methotrexate in healthy subjects

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Background: Methotrexate (MTX), a substrate of organic anion transporter 1 and 3, is an immunosuppressive agent recommended for the treatment of steroid-dependent ulcerative colitis and active/relapsing Crohn's disease.[1,2] BMS-986165, an oral selective TYK2 inhibitor, has demonstrated efficacy and acceptable safety in patients with moderate to severe plaque psoriasis,[3] and is under investigation in moderate to severe Crohn's disease (LATTICE; NCT03599622), among other chronic autoimmune diseases. There is a potential for co-administration of BMS-986165 with MTX in many of these diseases. The objectives of this study were to evaluate the effects of BMS-986165 on the pharmacokinetics (PK; primary objective) and safety and tolerability (secondary objective) of MTX on co-administration.

Methods: This was a Phase 1, open-label, single-sequence study in healthy male volunteers. Subjects aged 18–50 years with a body mass index (BMI) of 18–32 kg/m^2 received a single oral (po) dose of MTX 7.5 mg on Day (D) 1 and D12 and BMS-986165 12 mg po from D8 to D14. Blood samples were collected after each treatment to determine the PK of MTX and BMS-986165. Safety evaluations (adverse events [AEs], physical and skin examinations, vital signs, electrocardiograms, laboratory tests) were performed during the course of the study.

Results: Overall, 10 subjects were treated (mean [standard deviation] age 33.6 [7.06] years, BMI 24.9 [2.31] kg/m^2), all of whom completed the study. Following co-administration of MTX + BMS-986165, MTX geometric mean maximum concentration (C_{max}) and total exposure (area under the curve extrapolated to infinity [AUC_{INF}]) increased by ~11% and 4%, respectively, compared with MTX alone (Table). The 90% confidence intervals (CIs) for the geometric least-square mean ratios for C_{max} and AUC_{INF} were contained within the no-effect boundary of 0.80–1.25. There were no serious AEs, deaths, or AEs leading to discontinuation. All treatment-emergent AEs were mild and resolved spontaneously.

Table. PK parameters for MTX and MTX + BMS-986165.

		Geometric LS means		Ratio test/reference 90% CI		
Treatment comparison (test vs reference)	PK parameter	Test	Reference*	Estimate	Lower	Upper
MTX + BMS-986165 vs MTX	C_{max} (ng/mL)	228	205	1.110	0.999	1.232
	AUC_{INF} (h*ng/mL)	785	756	1.038	0.966	1.114
	$AUC_{0\text{-}T}$ (h*ng/mL)	780	752	1.037	0.966	1.115

*Reference is MTX alone. $AUC_{0\text{-}T}$=area under plasma concentration-time curve; AUC_{INF}=area under the curve extrapolated to infinity; CI=confidence interval; C_{max}=maximum concentration; LS =least-square; MTX= methotrexate; PK=pharmacokinetic

Conclusions: BMS-986165 at steady state had no clinically meaningful effect on the PK of a single dose of MTX. MTX alone or in combination with BMS986165 was safe and well tolerated in this study.

Reference

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2. Gomollón F, et al. (2017) J Crohn's Colitis.
3. Papp K, et al. (2018) N Engl J Med.

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Is there a correlation between infliximab trough levels and the development of adverse events in patients with inflammatory bowel disease?

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Background: The measurement of infliximab trough levels (IFX-TLs) in patients with inflammatory bowel disease (IBD) has been suggested as a useful tool for the treatment optimisation. The association between the development of adverse events (AEs) of IFX and IFX-TLs has not been adequately studied so far. The aim of this study was to investigate the possible association of IFX-TLs with AEs in Greek patients with IBD under maintenance treatment with IFX.
Methods: Retrospective analysis of registered data of patients with at least one available measurement of IFX-TLs for the years 2016–2017 was applied. All AEs reported 4 months before and 4 months after measurement of IFX-TLs were recorded. The IFX-TLs of patients with or without AEs were compared.
Results: A total of 83 IBD patients [CD 61 (73.5%), UC 22 (26.5%), men 52 (63%), median age (IQR) 42 years (31–54), CD-L1 23 (38%), CD-L2 13 (21%), CD-L3 25 (41%), UC-E2 8 (36%), UC-E3 14 (64%)] were included. The median (IQR) time since the diagnosis was 9 (6–17) years whereas 48 patients (58%) were under immunosupressants (40 AZA and 8 MTX) and 6 (7%) under intensified dose of IFX. A total of 147 IFX-TLs were available with a median value of 4.69 (1.32–9.16) μg/ml and 99 (67.3%) AEs were reported of which 13 (13.1%) considered as severe requiring hospitalisation. Among the AEs 48 (48.5%) were related to infections, 27 (27.3%) to skin reactions and the other 24 (24.2%) to various causes (hypersensitivity reactions, cancers, less frequently neurological or musculoskeletal disorders, psychiatric reactions, general symptoms like fatigue or dizziness and abnormal laboratory tests). From 48 infections reported, 36 (75%) were referred to respiratory and 6 (12.5%) to urinary track. Median IFX-TLs of patients with AE (total) were 5.79 (1.36–10.25) μg/ml, higher than those without AE [3.40 (1.30–5.92)], but not statistically significant ($p = 0.071$). Patients also with infections had higher, but not statistically significant, IFX-TLs than patients without infections [5.99 (1.64–9.09) vs. 3.75 (1.28–9.33), $p = 0.16$]. There was also no difference of IFX-TLs according to the presence or absence of dermatologic reactions [5.98 (1.26–8.46) vs. 4.55 (1.34–9.25), $p = 0.9$]. Comparison of patients with IFX-TLs ≥15 μg/ml with those with those with IFX-TLs <15 μg/ml showed not significant difference in the prevalence of the total AEs (66.7% vs. 73.3%, $p = 0.77$) as well as in the by group analysis (all $p > 0.05$).
Conclusions: IFX-TLs are not significantly associated with the development of AEs in IBD patients under maintenance treatment with IFX. Further prospective investigation into larger populations is needed to make safe conclusions.

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Evaluation of dietetic services and the impact of diet on disease activity for patients with inflammatory bowel disease at Imperial College Healthcare NHS Trust

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Background: There are 4500 patients with inflammatory bowel disease (IBD) under review at Imperial College Healthcare NHS Trust (ICHNT). However, there are only 647 dietetic slots per year. This initial audit aimed to assess the dietetic services for IBD patients within ICHNT as well as determine patient views on the service they have received and identify dietary factors that exacerbate their symptoms.
Methods: The audit was carried out over a 10 week period in the IBD outpatient clinic. All patients had a confirmed diagnosis of IBD and were aged ≥18 years. Patients that consented to participate were given a questionnaire to complete. The questionnaire comprised of two components; (i) Patient opinion of the dietetic services both in general and within the ICHNT and (ii) identification of a link between food types and IBD symptoms.
Results: In total, 131 patients completed the questionnaire. Only 56 (43%) patients had received a dietetic consultation in relation to IBD. Of these patients, 46 (82%) had found dietetic input beneficial. Forty-four patients (78.5%) had seen a dietician within the Trust, with the remainder having accessed dietetic services privately or in the community. Of the patients who saw a Trust dietician, 34 (77%) found the consultation helpful. The majority of those receiving dietician appointments found the services at ICHNT adequate, good, or excellent. However, 7 (13%) felt the service was poor and 6 (11%) felt the service fell below average.
A total of 100 (76%) patients believed that specific foods directly exacerbate their IBD. Specific trigger foods that were identified included, tomatoes, red meat, fatty/fried foods, and onions. Symptoms precipitated by these foods included diarrhoea, bloating, constipation, and abdominal pain. A number of patients reported rectal bleeding after consumption of food including dairy products, alcohol and red meat.
Conclusions: The majority of those accessing dietetic services find dietary advice helpful. However, there are insufficient dietetic resources for IBD patients being seen at ICHNT. A number of specific food types were identified that patients feel contribute to a 'flare' of their IBD. Symptoms include increased bowel frequency, abdominal pain, and bloating. These are non-specific and could be related to co-existent irritable bowel syndrome or related to high FODMAP foods. Interestingly, there were a group of patients who reported rectal bleeding in relation to foods such as dairy products, alcohol and red meat—a finding which warrants further assessment. Increasing dietetic services for IBD patients at ICHNT would improve the care provided for this group and could help patients manage their symptoms more effectively.

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Ustekinumab efficiency as a higher-line therapy in association with serum levels in patients with Crohn's disease

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Background: Ustekinumab (UST) is an anti-IL-12/23 monoclonal antibody used for treatment of Crohn's disease (CD). We evaluated response to UST and its association with serum trough levels (TLs) in a cohort of patients from real clinical practice.
Methods: Data from consecutive CD patients who started UST between March 17 and October 18 were included. Disease activity was assessed retrospectively by Harvey–Bradshaw Index (HBI) at Week 0 and then every 8 weeks. HBI between 0–4 was considered as remission, 5–7 as mild, 8–15 as moderate, and ≥16 as severe disease activity. At Week 24, the patients with HBI decrease of ≥3 were considered as responders. C-reactive protein (CRP), faecal calprotectin (FC), and UST TLs were measured at every visit.
Results: Seventy-four patients (39% males, 61% females), mean age 36.9 years, were included. Mean disease duration was 14.5 years. In median, UST was administered as a third biologic agent. Concomitant immunosuppression (IS) was present in 43% of patients at Week 0 and 31% had systemic corticosteroids. At baseline, 7% of patients had severe disease activity, 22% had moderate, 29% mild clinical activity and 42% of patients had no disease activity. At Week 24 the proportions were 0%, 14% and 17%, and 69%, respectively. The HBI decreased from 6.4 ± 5.1 at week 0 to 4.4 ± 3.4 at Week 24 (p = 0.0430). Significantly more patients with concomitant IS at week 0 had no baseline clinical activity (63% vs. 28%; p = 0.0022); however, the proportion of patients with IS did not change until Week 24. In total, 40% of patients responded to therapy at Week 24. There was no change in mean CRP and FC between the two time points (CRP 13.2 ± 14.8 mg/l vs. 11.1 ± 13.0 mg/l, p = 0.2471; FC 1901 ± 1967 µg/g vs. 1818 ± 1972 µg/g, p = 0.5509). There was no predictive value of UST TLs at Week 8 or 16 for clinical or biochemical response at Week 24; however, patients in clinical remission at Week 24 had significantly higher UST TLs comparing to patients with clinical activity (5.9 ± 4.2 µg/ml vs. 2.7 ± 1.7 µg/ml; p = 0.0374). Patients with no or one previous biologic therapy tended to have higher TLs at Week 8 as well as lower HBI at all time points comparing to patients with two or more previous drugs, however, it did not affect the response rate. We observed multiple cases of eye redness, periorbital exanthema or other exanthema, and also increased hair loss. No patient discontinued the treatment until Week 24.
Conclusions: Despite no change in inflammatory markers, there was a clear clinical benefit of UST as a higher-line therapy for CD patients. UST TLs do not seem to predict short-term response and the usefulness of pharmacokinetic monitoring is yet to be elucidated. No adverse events requiring the treatment termination were observed.

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Anxiety and depression: beyond simple consequences of chronic inflammatory bowel diseases

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Background: Patients with inflammatory bowel disease show high level of stress, compared with general population or other categories of patients. The study's objectives are to determine the prevalence of anxiety and depression among patients with IBD in comparison to a statistically balanced control population, to study the prevalence differences depending on the type of disease and various demographic characters, to compare the levels of anxiety and depression in patients in remission with patients with active disease and control subjects respectively and to assess the correlation between psychological stress intensity and the disease duration and other various parameters of IBD disease activity.
Methods: This study enrolled 72 patients diagnosed with IBD in the Institute of Gastroenterology and Hepatology Iasi, Romania, between 1 January 2018 and 15th November 2018. The control group consisted of 35 healthy subjects and were recruited from the patients' families, hospital staff, and other volunteers. Anxiety and depression assessment was done using the Hospital Anxiety and Depression Scale (HADS). For each subject, there were recorded the education level as representing the highest level reached, the economic status estimated by the investigator through interview. The mean scores for the patients and the control group were calculated. Subsequently, the patient group was subdivided depending on the primary disease (UC or CD). The analysis was performed by dividing the values, stratifying the group of patients in remission or active phase and comparing with controls.
Results: The average anxiety score of the patients group was 9.78 ± 4.89, and in the control group 5.29 ± 3.72.(p < 0.01). Depression average score was 7.06 ± 4.14 for patients and 4.06 ± 2.79 for the control group (p < 0.01). There were 51 patients with UC (70.83%) and 21 with CD (29.17%). The mean anxiety score of UC patients was 10.06 ± 5.06, whereas for CD it was 9.1 ± 4.5(p = 0.45). Regarding depression, the average score was 6.73 ± 3.9 for UC, and 7.86 ± 4.62 for CD patients.(p = 0.29). Patients in the active phase had an average anxiety score of 11.11 ± 4.78, while those in remission of 7.56 ± 4.27(p = 0.002). Comparing anxiety scores of patients in remission, there were higher than those in the control group (mean=5.29 ± 3.62) (p = 0.027). Active phase IBD patients with depression had a mean score of 7.80 ± 4.27 compared with 5.81 ± 3.66 for those with IBD remission (p = 0.048).
Conclusions: Comparing the depression scores, we found that the active phase IBD (p < 0.01) and IBD remission (p = 0.036) had significantly higher values than the controls. Patients with CD had a good correlation between clinical IBD scores and anxiety (p < 0.01) and depression (p < 0.01).

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Effectiveness of enhanced recovery after surgery in IBD: a propensity score matched cohort study in a single Italian centre

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Background: Enhanced recovery after surgery (ERAS) provides many benefits for patients with colorectal cancer. However, its application to patients with Crohn's disease (CD) is still questioned because of lack of evidence. The aim of this propensity-matched study was to validate the results of ERAS protocol on CD patients.

Methods: A retrospective analysis of patients undergoing ileo-colic resection for primary or recurrent CD from 2007 to 2017 was carried out. Patients enrolled in ERAS protocol were compared with those undergoing standard care. Patients were propensity matched into two equal groups (ERAS vs. non-ERAS) according to stardard propensity score procedures. Propensity match was carried out considering the variables affecting length of stay. Patient demographic characteristics, length of hospital stay, bowel function, oral intake, and perioperative morbidity were analysed.
Results: In the study period, 23 (11%) out of 215 patients were selected for analysis as ERAS group. When unmatched groups were compared, significant differences were noted for gender, mean American Society of Anesthesiologists score, mean operative time. Median length of stay in ERAS and non-ERAS groups was 6 and 9 days (p = 0.002), respectively. Early bowel movement (within 3 days) in ERAS and non-ERAS groups was 14 (61%) and 3 (13%, p < 0.001), respectively. Variables used for propensity match are listed in Table 1.

Table 1. Variables associated to hospital length of stay >6 days.

Variable	*p*-value
Female gender	0.38
ASA score >2	0.01
Operation duration	0.0008
Cure OR	0.07 (0.02–0.18)

Patients who tolerated early solid oral intake (within 3 days) in ERAS and non-ERAS groups were 18 (78%) and none respectively (p < 0.001). However, after propensity match, no significant difference in postoperative outcomes were shown between the two groups, comparing ERAS and non-ERAS subgroups (Table 2).

Table 2. Patients characteristics after propensity match based on length of stay, with p values for comparisons.

	ERAS	Non-ERAS	Overall	*p*-value
Number of patients (*n*)	23	23	46	
ASA score I (%)	1 (4%)	1(4%)	2 (4%)	1.00
Laparoscopy	19	14	33	0.10
Early postoperative feeding (<4 days, %)	18 (78%)	0 (0%)	18 (39%)	**<0.001**
Early postoperative bowel movements (2–3 days, %)	14 (61%)	3 (13%)	17 (37%)	**<0.001**
Postoperative leakage (%)	1 (4%)	0 (0%)	1 (2%)	0.31
Postoperative complications Clavien-Dindo IIIb (%)	1 (4%)	1 (4%)	2 (4%)	1.00
90-days readmission (%)	0 (0%)	1 (4%)	1 (2%)	0.31

Conclusions: This propensity score matched study showed a significantly shorter hospital stay, earlier stool movement and return to free oral intake for patients with primary or relapse ileo-colic CD undergoing laparoscopic or open surgery, enrolled in ERAS protocol. It validates the ERAS protocol for a subgroup of complex pathology such CD and shows that optimised perioperative care combined with experienced surgical team may lead to further improvements in surgical outcomes for CD patients

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Mindfulness-based stress reduction in adult patients with active Crohn's disease: preliminary findings based on the subjective units of distress scale: an IIRN study

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Background: Crohn's disease patients suffer from a host of mental symptoms, particularly when the disease is active (Schwartz D et al. United European Gastroenterol J 2018; 6: Supplement 1). We postulated that psychological distress can be diminished by teaching Mindfulness-Based Stress Reduction (MBSR) to patients using an internet-based format.
Methods: Randomly selected adult patients with active Crohn's disease, attending for routine follow-up in a teaching hospital, were enlisted in a program where MBSR is taught by specially trained social workers in a series of 1-h sessions delivered once a week, using Skype™ and a standardised protocol. Home practice twice daily with feedback to an application was required. Disease activity (Harvey–Bradshaw Index) was monitored. The Subjective Units of Distress Scale (SUDS, Wolpe J, 1969) was administered before and after each teaching session. The SUDS scale range is 0–10; a higher score indicates more stress. Data analysis using the Wilcoxon signed-ranks test was conducted on SUDS scores of patients with five completed MBSR sessions each. The analysis included sessions 2 through 5 (session 1 was regarded as entry into the protocol). The SUDS scores are labelled as 'begin-score' (at beginning of each treatment session) and 'end-score' (at end of session). Data are given as median (range).
Results: The cohort comprised 13 patients, all with good compliance. Patients' characteristics were: age 29 (22–63) years, females 85%, non-smokers 92%, illness duration 3 (1–25) years, past surgery in 3 patients. All patients had active disease: The Harvey–Bradshaw Index was 8 (6–15). Seven patients were receiving long-term biological medication. The median SUDS begin-score was highest in session 2 and less in subsequent sessions (Table 1). SUDS end-scores were significantly reduced compared with begin-scores in all sessions. The end-score at session 5 was significantly lower than the begin-score at session 2 (p = .011).

Session	2	3	4	5
Begin score	6 (3–10)	4 (1–7)	3 (1–7)	5 (2–7)
End score	3 (1–7)	3 (1–6)	2 (0–5)	3 (1–6)
p	0.009	0.017	0.007	0.003

SUDS scores at beginning and end of sessions, median (range).

Conclusions: These preliminary findings, albeit in a small uncontrolled cohort, suggest that MBSR taught weekly, and accompanied by twice-daily home practice, reduces the level of subjective psychological distress in Crohn's disease patients. Teaching by Skype™ was effective (and could be a cost-saving measure) and daily report to an app ensured compliance. A randomised trial in a large cohort employing several psychological scales is in progress to determine the precise efficacy and long-term effect of MBSR in the armamentarium of therapies available to Crohn's disease patients.

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Pharmacokinetics and immunogenicity of Infliximab biosimilar in inflammatory bowel disease patients

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Background: Infliximab biosimilar (IFXbios) was the first monoclonal antibody approved by the European Medicines Agency (EMA) in 2013. Both reference IFX (IFXref) and IFXbios are approved for the treatment of eight immune-mediated inflammatory diseases including inflammatory bowel diseases (IBD). The aim of the present study was to compare real-life pharmacokinetics (PK) and the immunogenicity of IFXbios with IFXref in IBD patients.

Methods: This is a retrospective comparative study from a prospectively maintained data base. Adult patients with IBD who received IFX between January 2014 and February 2018 were included. The primary endpoints were IFX trough concentrations (Cmin) and AUC at steady state. Secondary endpoints included: (1) Clearance (CL), (2) volume of distribution (Vc), (3) elimination rate (K10), and (4) half-life (t1/2). Safety assessment included the proportion of patients with anti-IFX antibodies (ATI). PK parameters and AUC were estimated by implementing a previously published population PK model using the software NONMEM® ver 7.4. We measured Cmin IFX and ATI using a commercially available validated enzyme-linked immunosorbent assay (ELISA) kit (Promonitor®). All data were analysed using software R (R Core Team 2017).

Results: We included 73 patients (55 Crohn's disease, 18 ulcerative colitis). Fifty patients were on IFXref and 23 were on IFXbios. The majority (74%) received concomitant immunomodulator. Mean serum albumin concentration (SAC) was 4.38 g/dl (SD 0.42) and mean weigth was 69.53 kg (SD 15.39). The primary PK end points were shown to be similar among the two IFX formulations. IFXbios Cmin was 4.26 mg/l (SD 3.37), similar to IFXref Cmin (3.24 mg/l [SD 3.24]; p = 0.6668). There were no differences in AUC values between both IFXbios and IFXref. All secondary PK endpoints were also similar among the two treatment groups. The mean CL, Vc, K10, and t1/2 for IFXbios and IFXref were highly similar. PK characteristics of enrolled patients are in Table 1.

Table 1. PK parameters. Data are presented as mean (standard deviation). (1) p = 0.166, (2) p = 0.7401, (3) p = 0.2737, (4) p = 0.8498, (5) p = 0.9089.

PK parameter	IFXbios (n = 23)	IFXref (n = 50)
AUC (mg/l/h)[1]	28 938 (12 005)	25 409 (8965)
CL (ml/kg/day)[2]	5.42 (2.82)	5.46 (2.35)
Vc (ml/kg)[3]	51.23 (2.32)	52.06 (2.91)
K10 (h^{-1})[4]	0.00443 (0.00236)	0.00438 (0.00192)
$t_{1/2}$ (days)[5]	12.86 (4.95)	12.72 (4.51)

Finally, a similar proportion of patients (8% in the IFXbios group and 6% in the IFXref group) developed ATI.

Conclusions: Comparison between IFXbios and IFXref showed high similarity in the mean Cmin. The mean values of PK parameters (AUC, CL, Vc, Kel, and $t_{1/2}$) were comparable between treatment groups. The study also showed similar rate of ATI formation in patients on IFXbios and IFXref.

P646

Histological remission in patients with moderate-to-severe ulcerative colitis undergoing biological therapy: a single-centre experience

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Background: Histological remission (HR) is emerging as a new treatment target in patients with ulcerative colitis (UC). Biological drugs, as anti-tumour necrosis factor (TNF) agents and anti-integrins, represent the best choice for treating patients with moderate to severe disease. However, 'real-life' data about their efficacy in achieving this goal are limited. The aim of the study was to evaluate the efficacy of biological drugs to achieve histological remission in UC patients.

Methods: We enrolled in a retrospective observational study adult patients with moderate-to-severe UC referring between 2014 and 2018 to IBD Unit (Negrar Hospital), both naïve and experienced to a previous Anti-TNF. We performed endoscopic (by Mayo Endoscopic Subscore, MES) and histological (Nancy Histological Index, NHI, a recent validated score) at baseline (before starting biological therapy) and at Week 48 (control time). Histological remission was defined as NHI < 2. The worst colonic segment was used for the assessment of disease activity. Fisher exact test was used for the statistical analysis (a p-value of <0.05 was considered statistically significant).

Results: Sixty-one patients were included. At baseline median MES was 2.6 (2–3), median NHI was 3.5 (2–4). Twenty-eight patients were treated with Infliximab (IFX), 10 with Adalimumab (ADA), 20 with Golimumab (GOL), 3 with Vedolizumab (VDZ), all according to conventional regimen. At Week 48, 26.2% (16/61) of patients achieved histological remission; the subgroup analysis showed that 21.4% (6/28) of patients treated with IFX, 60% (6/10) of patients treated with ADA and 20% (4/20) of patients treated with GOL achieved histological remission. All 3 patients treated with VDZ still showed histologically active disease at control time (NHI ≥ 2). There were no significant

differences among drugs (p = 0.082). 42.6% (26/61) of patients achieved endoscopic remission (MES 0 or 1). All patients achieving histological remission were also in endoscopic remission; of these, 62.5% (10/16) had a MES=0. Median MES and NHI significantly improved at Week 48 (1.8 and 2.7, respectively; p < 0.001). There were no differences between naïve and experienced patients (p = 0.703).
Conclusions: All anti-TNF agents are able to achieve histological remission in patients with moderate-to-severe UC. For considerations about VDZ more data are required.

P647

A pilot study: The importance of cognitive flexibility and flexibility in coping with stress for the quality of life in inflammatory bowel disease patients during biological therapy

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Background: There are studies demonstrating the relationship between psychological factors and efficiency of treatment in the course of the inflammatory bowel disease (IBD). The biological treatment is an alternative therapy for IBD patients in whom conventional therapy failed. They often experience ups and downs, which makes it increasingly important to provide this group with appropriate psychological counselling. It is possible by, for example, getting to know their psychological resources and checking, whether their level is related to the quality of life. Such resources include cognitive flexibility and flexibility in coping with stress, which allow assessing the ability to cope with a change in life and adapt to new conditions.
Methods: The study group consisted of 33 adults (n = 33), 14 women and 19 men, who were diagnosed with CD (18) or UC (15). All persons were in the course of the biological treatment and were taking the third dosage of the drug the minimum. The average age equalled 35.3 years (SD = 13). The average duration of the disease was 8.5 years (SD = 6.9). The following research methods were used: the Flexibility in Coping with Stress Questionnaire—FCSQ-14 (Basińska et al.), the Cognitive Flexibility Inventory, CFI, (Dennis, Vander Wal, Polish adapt. by Piórowski et al.), the Quality of Life SF-36v2 Questionnaire—the Polish version; the Satisfaction with Life Scale SWLS (Diener, Emmons, Larson, Griffin, Polish adapt. by Juczyński) and the author's own questionnaire to collect the demographic data.
Results: A strong positive correlation (p < 0.01) was observed between cognitive flexibility and a lower sense of limitation imposed by physical or emotional problems in everyday functioning (r = 0.46; r = 0.49)., as well as between cognitive flexibility and the sense of satisfaction with life (r = 0.47). The mental component of the quality of life correlated positively with cognitive flexibility p < 0.05; r = 0.38). In turn, the sense of satisfaction with life correlated (p < 0.05) with the following FCSQ scales: changeability and repertoire (r = 0.39; r = 0.39) and additionally with the cognitive flexibility component alternatives (r = 0.44). The study did not prove that the disease diagnosis (UC or CD) differed the level of cognitive flexibility or flexibility in coping with stress. Older respondents achieved lower results in that scale of the cognitive flexibility (p < 0.01; r = –0.46).
Conclusions: Psychological factors, as cognitive flexibility and flexibility in coping with stress, can be considered to be resources which help to cope with challenges posed by the inflammatory bowel disease. Therefore, it is so significant to increase their level by applying psychotherapeutic methods tailored to the age and the needs of a patient.

P648

Anti-TNF-α therapy, use of corticosteroids, and colectomy among paediatric and adolescent patients with ulcerative colitis: a nationwide study

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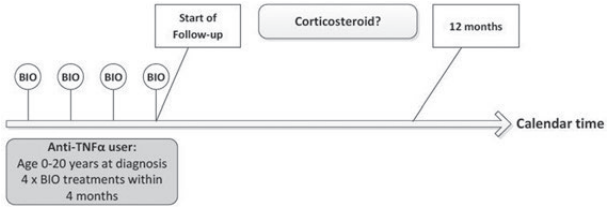
Background: The long-term beneficial effects of anti-TNF-α therapy are debatable referring to the need for corticosteroids and changes in colectomy rates among paediatric and adolescent patients with ulcerative colitis (UC). We aimed to investigate whether anti-TNF-α treatment reduced the use of corticosteroids and to examine colectomy rates in the era of anti-TNF-α therapy compared with a historical cohort.
Methods: The study population included an unselected nation-wide cohort of children and adolescents (0–20 years of age) diagnosed with UC through 1977–2016. The data were retrieved from the Danish National Patient Registry. We identified anti-TNF-α use as patients who had at least four anti-TNF-α treatments within a period of 4 months to examine a subsequent need of corticosteroid prescriptions (Figure 1). To examine the change of colectomies we calculated the cumulative risk 5 years following the diagnosis and used an adjusted Cox regression model in the comparison of colectomies between a historical cohort (1977–2003) and a cohort representing the era of anti-TNFα (2004–2016).

Figure 1. Anti-TNF-α use: individual patient timeline illustration.



Results: We identified totally 4449 patients with UC in the study period. We identified 334 children and adolescents treated with anti-TNF-α. A total of 20.7% (69 patients) was prescribed corticosteroids in a 3-month period calculated from the fourth anti-TNF-α treatment. The proportion of steroid dependent users declined after 6 and 12 months

to 6.6% and 0.6%, respectively (Figure 2). The 5-year cumulative proportion of colectomy in the historical cohort was 9.12% (95% confidence interval [CI]: 8.01–10.37) and 7.76% (95% CI: 6.70–8.98) in the era of anti-TNF-α treatment (Figure 3). The adjusted hazard ratio was 0.84 (95% CI: 0.68–1.03) for colectomy within a 5-year period in the era of anti-TNF-α compared with the historical cohort.

Figure 2. Corticosteroid prescriptions among anti-TNF-α users with 3-, 6-, 9- and 12-month follow-up

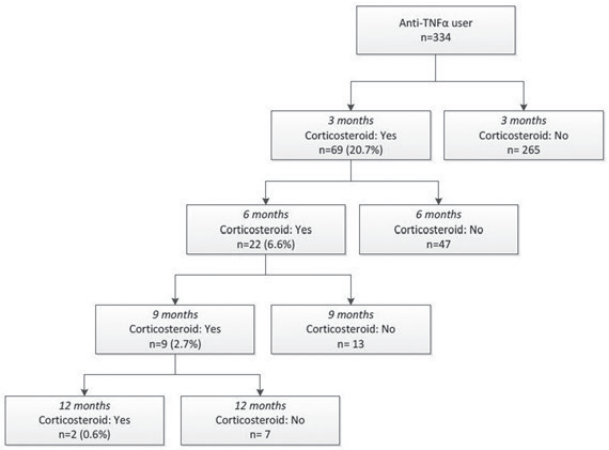
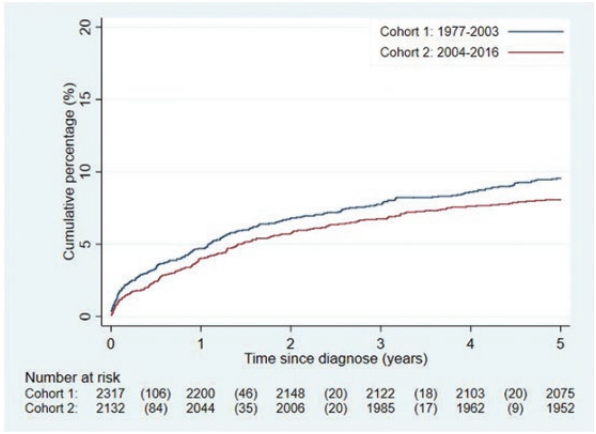


Figure 3. Cumulative percentage for colectomy, a 5-year follow-up



Conclusions: The concomitant use of corticosteroid prescriptions was virtually terminated after 12 months among patients treated with anti-TNF-α. Within a period of 5 years from the time of diagnosis, the adjusted hazard ratio for colectomy in the era of anti-TNF-α treatment was reduced, but not significantly compared with a historical cohort.

P649

Anti-TNF agent drug survival in patients with IBD: real-world comparisons of individual anti-TNF agents based on the Swedish National Quality Registry for IBD (SWIBREG)

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Background: Studies comparing drug survival in different anti-tumour necrosis factor (TNF) agents in IBD patients are scarce, especially for second-line anti-TNF agents. We aimed to (A) assess drug survival and predictors of response and adverse drug reactions to first-line anti-TNF treatment and (B) examine drug survival for individual anti-TNF agents when used as second-line anti-TNF.

Methods: Well-characterised patients with IBD (*n* = 955) starting their first anti-TNF treatment between 2006 and 2016 (Table 1), were identified from the Swedish National Quality Registry for IBD (SWIBREG). Drug survival was examined, stratified by reason for discontinuation, that is, lack/loss of clinical effectiveness or adverse drug reactions. Multi-variable Cox regression models were used to identify predictors of drug survival. Drug survival for the second anti-TNF was assessed by type of first anti-TNF agent.

Results: Risk factors at baseline for shorter drug survival, in patients with Crohn's disease, were use of infliximab as first-line anti-TNF (compared with adalimumab, adjusted HR = 1.95, 95% CI: 1.19–3.18) (Figure 1A) and colonic disease (L2) (compared with ileal disease (L1) and ileocolonic disease (L3), adjusted HR = 2.16, 95% CI: 1.25–3.74). Consistently, Crohn's disease patients who switched from adalimumab to infliximab had shorter drug survival, compared with those who switched from infliximab to adalimumab (Figure 1B). A normalisation of CRP level at 3 months was associated with decreased risk of short drug survival in both Crohn's disease (adjusted HR = 0.40, 95% CI: 0.19–0.81) and ulcerative colitis (adjusted HR = 0.40, 95% CI: 0.19–0.86). In Crohn's disease, but not in ulcerative colitis, immunomodulators were associated with a lower risk of short drug survival due to adverse drug reactions (adjusted HR = 0.50, 95% CI: 0.31–0.82).

	Crohn's disease, *n* = 570	Ulcerative colitis, *n* = 385
Male sex, no (%)	298 (52)	222 (58)
Median age at baseline (IQR)	35 (24–48)	33 (24–46)
Median disease duration in years (IQR)	6 (1–16)	4 (0–10)
L1 Ileal (± L4) CD, *n* (%)	103 (18)	
L2 Colonic (± L4) CD, *n* (%)	169 (30)	
L3 Ileocolonic (± L4) CD, *n* (%)	289 (51)	
L4 Upper gastrointestinal tract, *n* (%)	6 (1)	
Concomitant immunomodulators, *n* (%)	278 (49)	176 (46)

Baseline data on age, year, CD behaviour, UC extent, previous IBD surgery, CRP concentration, and smoking habits are not shown

Demographics and clinical characteristics at baseline for the 955 IBD patients treated with anti-TNF.

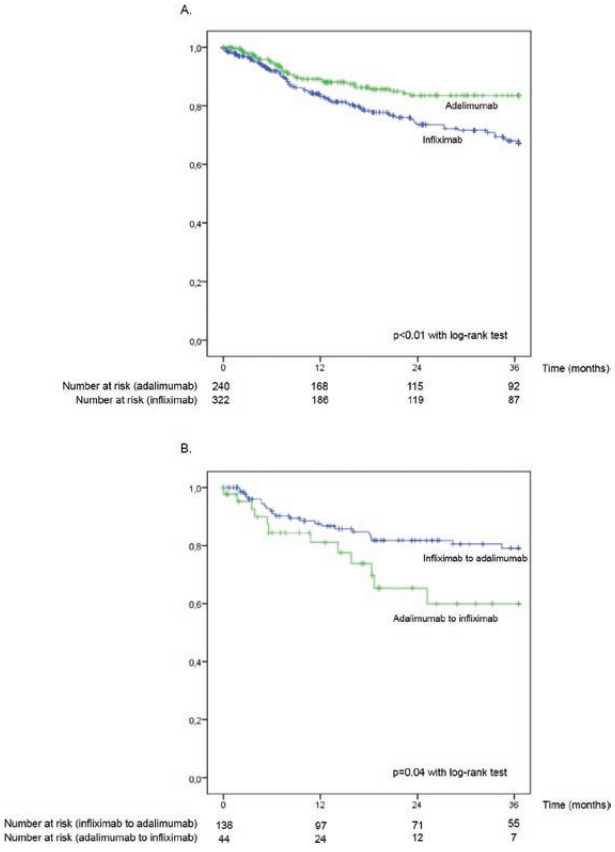

Figure 1. (A) Cumulative probability of remaining on the first anti-TNF treatment (Crohn's disease). (B) Cumulative probability of remaining on the second anti-TNF treatment (Crohn's disease). Reason for discontinuation was lack/loss of response.

Conclusions: Drug survival duration was longer for adalimumab compared with infliximab both when used as first anti-TNF agent and when used as second-line treatment. The consistent pattern indicates that these differences are not only explained by channelling bias (differential prescribing behaviour).

P650

Mechanisms of Infliximab failure: the predictive role of MMP3

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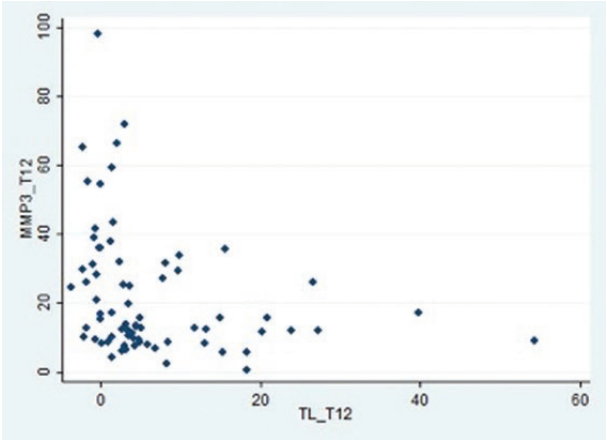
Background: Recently, further pathways of degradation of anti-TNF therapies have been hypothesised such as the presence of activated metalloproteinases (MMPs), particularly MMP3, which seem to cleave the IgG1 and neutralise the drug activity. However, no data to have been published evaluating whether levels of MMP3 can be associated to anti-TNF failure in patients with inflammatory bowel disease (IBD) in a longitudinal study.

Methods: Retrospectively, we included 73 IBD patients (37 UC, 36 CD) responder (R 37) and non-responder (NR 36) to infliximab therapy after 52 weeks of treatment and who had started biologic therapy because of moderate-to-severe clinical activity at baseline (T0). Patients underwent MMP3 dosage at baseline, post induction (TPI), and at 12 months (T12). In addition, trough level (TL) and anti-drug antibody (ATI) values were also determined at t12. For comparison, MMP3 levels were determined in 28 healthy subjects as controls. Demographic and clinical features were recorded, including BMI, HBI/Mayo score, endoscopy score, CRP, faecal calprotectin, and albumin. We used medians with inter-quartile for continuous data and percentages for discrete data. Chi-square test and Mann–Whitney *U* test were used to compare categorical and continuous values, respectively. We also performed Spearman and an ROC analysis. A *p*-value of <0.05 was considered significant.

Results: Serum levels of MMP3 between R and NR were not statistically significant at T0 (R = 17.92 ng/ml, NR = 21.98 ng/ml, p = 0.80), while they were statistically significant at TPI (R = 8.68, NR = 25.7, $p < 0.001$) and at T12 (R = 11.63, NR = 29.72, $p < 0.001$). Instead, calprotectin concentrations were not significant at T0 (R = 967 µg/g, NR = 1362, $p = 0.09$) and at TPI (R = 415, NR = 743, $p = 0.17$), and became significant only at T12 (R = 102, NR = 458, $p < 0.001$) (Figure 1). Serum albumin and patients' BMI were not significant at T0, TPI, and T12 (p = ns). Finally, among NR patients with low TL, those with high ATI and those without ATI had the same MMP3 levels (32.01 vs. 24.56, $p = 0.1$). We found a statistically significant negative correlation (Spearman 0.3, $p < 0.001$) between MMP3 level and TL at T12 in all population (Figure 1). Through an ROC curve analysis, we identified the MMP3 value to discriminate healthy subjects from IBD active patients evaluated at T0 (11.63, Sens. 76.6%, Spec. 85.19%).

Conclusions: High MMP3 levels at post-induction predict loss of response over the next 12 months. Patients NR to Infliximab therapy, both with high ATI and low ATI, have high MMP3 levels; higher MMP3 levels correspond to lower TL.



Spearman correlation

P651

Disease severity and intensity of therapy predicts serious adverse events in paediatric ulcerative colitis: the DEVELOP experience

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Background: DEVELOP is a multi-centre (USA, Canada, European Union), prospective, observational registry of the long-term safety and clinical status of 6070 paediatric patients with inflammatory bowel disease (IBD including 1678 ulcerative colitis [UC] patients) treated with anti-tumour necrosis factor biologics (aTNF) and/or other medical therapies as part of physician dictated clinical care. AIM: To identify covariates that were significant predictors to time to first serious adverse event (SAE) in patients with UC. A SAE is defined as any undesirable experience that results in hospitalisation, requires medical intervention or is otherwise life-threatening.
Methods: Physicians participating in the registry prescribe IBD treatments based on their usual clinical practice and standards of care. Patients are categorised into cohorts according to their IBD medication exposure. The cohorts represent prevalent or incident exposure, including patients receiving therapy prior to enrolment and patients receiving therapy during registry follow-up. Enrolment was targeted such that about 50% of the initial population had been exposed to originator infliximab. Hazard ratio (HR) for SAE was calculated by stepwise Cox regression modelling.
Results: Time to first SAE are shown in Table 1. This includes 1121 UC patients who were exposed to aTNFs as the only biologic and/or non-biologics and had at least 1 post-baseline follow-up visit, complete baseline covariate data, and complete disease severity data (partial Mayo score) at event or censoring. The covariates that were significantly associated with a shorter duration of time to first SAE in UC patients included combination therapy with aTNF/immunomodulators (IMM) and corticosteroids (CS) or combination therapy with aTNF and CS. Monotherapy with CS, disease activity (hazard ratio [HR] 2.657) and recent hospitalisation were also significantly associated. Conversely, combination therapy with aTF and IMM or monotherapy with aTNF or IMM alone were not associated with significantly increased risk of time to first SAE.
Conclusions: In terms of HR, disease severity was the strongest predictor of time to first SAE. Combination therapy with aTNF and CS and also triple therapy with aTNF, CS and IMM were predictors as was monotherapy with CS. On the other hand, monotherapy with aTNF or with IMM were not found to be significant predictors.

	Adjusted Hazard Ratio	95% Confidence Interval	p-value
Partial Mayo Score (Moderate to Severe vs. Inactive)	2.657	1.905-3.707	<.0001
Anti-TNF and Immunomodulator and Corticosteroids	2.073	1.223-3.512	0.0067
Partial Mayo Score (Mild vs. Inactive)	1.975	1.477-2.640	<.0001
Anti-TNF and Corticosteroids	1.924	1.240-2.985	0.0035
Corticosteroids Only	1.897	1.169-3.078	0.0095
Hospitalization in the Year Prior to Enrollment (Yes vs. No)	1.787	1.417-2.254	<.0001
Immunomodulator and Corticosteroids	1.549	0.915-2.623	0.1033
Anti-TNF Only	1.311	0.944-1.821	0.1066
Anti-TNF and Immunomodulator	1.267	0.880-1.823	0.2030
Immunomodulator Only	0.933	0.656-1.327	0.6990

Analysis performed using a stepwise selection procedure.
Time dependent: Variable status updated at every visit until event or censoring occurred.
Data from patients who were exposed to anti-TNF's as the only biologics or who had not been exposed to any biologics were included in the analysis.
Partial Mayo: 0-2 inactive disease, 3-4 mild disease, >=5 moderate to severe disease.

P652

Compare risk factors associated with infectious complication in Crohn's disease with and without preoperative infliximab

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Background: Infliximab therapy plays important roles in Crohn's disease (CD). The relationship between infliximab and infectious complications are still unclear. Our aim was to clarify this relationship and to compare the risk factors to predict infectious complications in CD with and without preoperative infliximab.
Methods: 390 CD patients undergoing surgery from June 2014 to June 2018 were eligible. Postoperative complications were compared in patients with and without preoperative infliximab. Univariate and multi-variate analyses were performed to identify risk factors for infectious complications. Receiver-operating characteristic curves were performed to examine the cut-off value of predictors in infectious complications.
Results: 85 CD patients received infliximab within 8 weeks of surgery. 129 patients had postoperative complications, with 35 receiving infliximab. No significant difference of postoperative complications was found in CD patients with and without infliximab (p = 0.073). However, CD patients receiving preoperative infliximab suffered more infectious complications (p = 0.010). Preoperative infliximab was confirmed to be an independent risk factor in infectious complications (p = 0.042). Multi-variate analysis suggested that erythrocyte sedimentation rate was an independent risk factor associated with infectious complications in patients receiving preoperative infliximab (p = 0.022), and C-reactive protein was an independent risk factor in patients not receiving preoperative infliximab (p = 0.019).

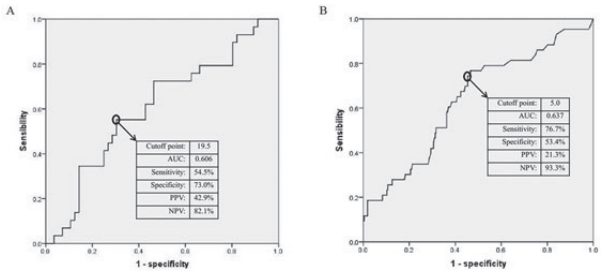

Figure01.A: ROC curve showing ESR-levels before surgery predictive of postoperative infectious complications in CD patients with IFX. B: ROC curve showing CRP levels before surgery predictive of postoperative infectious complications in CD patients w

Conclusions: Preoperative use of infliximab ≤ 8 weeks was independently associated with infectious complications in CD. Preoperative erythrocyte sedimentation rate and C-reactive protein could predict infectious complications in CD with and without infliximab. Different risk factors associated with postoperative infectious complications in CD exposed and unexposed to infliximab should be noticed.

P653

Ligation of the intersphincteric fistula tract vs. endorectal advancement flap for high perianal fistulas in Crohn's disease: a retrospective cohort study

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Background: The ligation of the intersphincteric fistula tract (LIFT) and advancement flap (AF) procedures are well-established,

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sphincter preserving procedures, for closure of high perianal fistulas. As surgical closure is not commonly offered in patients with Crohn's fistulas, long-term data are limited. The aim of this study was to compare outcomes after both procedures in Crohn's patients.

Methods: In this retrospective cohort study, all consecutive Crohn's patients ≥18 years treated with LIFT or AF between 2007 and February 2018 were included. Primary outcome was clinical healing defined as closure of external fistula opening without discharge. Secondary outcomes included radiological healing evaluated by MRI, recurrence, newly developed postoperative incontinence, prospective Vaizey Incontinence Score and global subjective change in continence (improved, unchanged or deteriorated). A clinical minimally important difference (MID) for improvement in the Vaizey Incontinence Score was determined using a clinical anchor-based method to assess the clinical relevance of changes in this score.

Results: Forty procedures in 37 patients (35.1% male, median age 33.9, LIFT: 19, AF: 21) were included. A non-significant trend was seen towards higher clinical healing percentages after LIFT compared with AF (89.5% vs. 60.0%; p = 0.065). The overall radiological healing and recurrence rates were not significantly different between LIFT and AF (52.6% vs. 47.6%; p = 0.752, 21.1% vs. 19.0%; P>0.999, respectively). In AF a trend was seen towards higher clinical healing percentages after anti-TNF/immunomodulator use (75.0% vs. 37.5%; p = 0.104).

Newly developed postoperative incontinence was not significantly different (LIFT: 15.8% vs. AF: 21.4%; P>0.999). Interestingly, 22.2% had improved continence postoperatively (LIFT: 31.6% vs. AF: 11.8%; p = 0.236), and the global change question demonstrated improved continence in 47.4% (LIFT: 52.9% vs. AF: 42.9%; p = 0.612). The mean total Vaizey score prior to surgery, was 6.8 (SD 4.8) and after surgery this decreased to 5.3 (SD 5.0) (p = 0.067). The MID was calculated to be 2.92 and five patients with a deteriorated continence, all after AF (23.8%), reported a difference of more than 2.92 points and were therefore clinically relevant.

Conclusions: In Crohn's high-perianal fistulas the clinical and radiological healing, recurrence and incontinence rates are not significantly different between LIFT and AF. However, clinical healing rates seem higher after LIFT, and incontinence rates seem lower. Furthermore, the global change question demonstrated that the majority of patients actually benefitted from surgical intervention with respect to continence.

P654

Monitoring of drug concentrations to predict remission under ustekinumab induction therapy in Crohn's disease patients

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Background: Ustekinumab, targeting the p40 subunit of interleukin-12 and -23 has been approved for the treatment of moderate to severe Crohn's disease (CD). Predictors of response to this therapy are lacking. We investigated prospectively the usefulness of monitoring faecal calprotectin, serum CRP and ustekinumab concentrations to predict the response to ustekinumab induction therapy in active CD.

Methods: All consecutive anti-TNF refractory and active CD patients received an initial i.v. ustekinumab infusion followed by s.c. injections every 8 weeks. Clinical remission, defined as a Harvey–Bradshaw index ≤ 4, was assessed at Week 16. Blood and stool samples were collected at weeks 0, 4, 8, and 16 for measurements of serum CRP, ustekinumab concentrations and faecal calprotectin.

Results: Fifty-one patients were included. At Week 16, 32 out of 51 patients (63%) achieved a steroid-free clinical remission. Faecal calprotectin concentrations dropped gradually and significantly over the time between weeks 0 and 16, only in responder patients to ustekinumab induction (p = 0.006) and not in primary non-responders (p = 0.36). At Week 8, serum ustekinumab trough levels were significantly higher in responders compared with those in non-responders and was a reliable marker to predict response to induction therapy assessed at week 16 (AUROC = 0.75; sensitivity = 87%; specificity = 66%) with a best cut-off point of 2.0 µg/ml.

Conclusions: Ustekinumab induction therapy was effective in two-third of refractory CD patients. Monitoring of serum ustekinumab trough levels at Week 8 is useful to identify responders from non-responders to induction therapy and may contribute to the clinician's decision-making to adapt further the therapeutic strategies.

P655

Microencapsulated Sodium Butyrate significantly modifies the microbiota in patients with inflammatory bowel disease mimicking prebiotic activity and proving effects on the treatment of the disease

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Background: Inflammatory bowel disease (IBD) is characterised by severe inflammation of the small bowel and/or the colon leading to recurrent diarrhoea and abdominal pain. Butyrate represents one of the final product of saccharolytic fermentation of complex and non-digestible polysaccharides by anaerobic bacteria and has shown anti-inflammatory and regenerative properties, providing symptomatic relief when orally supplemented in patients suffering from a various range of colonic diseases.[1] We investigate the effect of a microencapsulated form of sodium Butyrate (MSB, ButyroseR, SILA, Noale, Italy) on the faecal microbiota of patients with IBD

Methods: In this prospective-randomised-placebo-controlled study, 49 IBD patients, 19 CD and 30 UC with mild-to-moderate clinical activity were enrolled (Figure 1)

Figure 1.

	IBD All Population	Treatment group	Placebo group	p-value
Male, n, %	36, 73.46	15, 71.4	21, 75	1
Median Age, years	51 (19-73)	51(19-69)	50(25-73)	0.41
Median BMI	24.12(16.04-30.02)	23.84	24.21	0.83
Type of disease, n, %	CD, 19, 38.77	7	12	0.7
Montreal Classification UC n, %				
E1	2, 6.6	1	1	
E2	13, 43.3	6	7	0.99
E3	15, 50	7	8	
CD Behaviour n, %				
B1	16, 84.2	4	12	
B2	3, 15.7	3	-	0.02
B3	0	-	-	
Location n, %				
L1	5, 26.3	3	2	0.12
L2	5, 26.3	-	5	
L3	9, 47.3	4	5	
Endoscopic score				
Mayo score, n, %				
0	14, 46.6	7	7	0.37
1	8, 26.6	4	4	
2	5, 16.6	3	2	
3	3, 10	-	3	
SES-CD, n, %				
0-2	9, 47.36	3	6	0.91
3-6	7, 36.8	3	4	
7-15	3, 15.7	1	2	
>15	0	-	-	
Previussurgery n, %	7, 31.5	6	1	0.03
Smokers CD, UC	3, 2	2	3	1
Therapy:				
Biologics n, %	20, 40.8	8	12	0.74
5-ASA n, %	45, 91.8	20	25	0.82
Probiotics(EDN) n, %	4, 8.1	2	2	1
Steroids n, %	7, 14	1	6	0.21
Immunosupptressant n, %	6, 12.2	3	3	1
PPI	7, 14	1	6	0.21

Patients with extensive surgery were excluded. After stratification by clinical assessment, colonoscopy, and faecal calprotectin (FC) levels, patients were randomised to oral administration of MSB (1800 mg/die) or placebo for 2 months, in addition to conventional therapy. Clinical activity was defined according to HBI in case of Crohn's disease (CD) and Mayo score in case of ulcerative colitis (UC). Before (T0) and after (T1) butyrate-treatment, stool samples were collected for faecal microbiota assessment analysis by 16S ribosomal RNA Illumina MiSeq sequencing. Patients completed the quality of life questionnaire in IBD (IBDQ) on T = 0 and T = 1.

Results: MSB induced similar changes in the microbiota of IBD patients by increasing the bacteria able to produce short-chain fatty acids (SFCA). However, an increased abundance of butyrogenic colonic bacteria (including genera *Butyricicoccus* and *Subdoligranulum*) were observed in CD patients, whereas in UC patients we observed a major increase of Lachnospiraceae (sPLS-DA analysis). Clinically, when only patients with calprotectin levels above 250 μg/g[1] for CD and 150 μg/g[2] for UC were considered, a 30% decrease of calprotectin levels were observed in 67% of CD patients treated with MSB vs. 33.3% in those treated with placebo. Subjective improvement in QoL based on IBDQ was significantly observed either in the treatment (p = 0.0046) and in placebo (p = 0.039) group. However, a greater effect was observed among the UC patients.

Conclusions: MSB supplementation showed a mimicking prebiotic effect increasing the production of endogenous and physiological SCFAs with a marked improvement of QoL and reduction of the level of inflammatory markers

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P656

Malnutrition rates are highest in pre-surgical Crohn's disease when compared with active CD, CD in remission and UC in remission

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Background: Malnutrition occurs in 20–85% of patients with inflammatory bowel disease (IBD) depending on the nutrition assessment criteria and disease activity. Patients with Crohn's disease (CD) and malnutrition awaiting surgery are at increased risk of post-operative complications compared with patients without malnutrition. This study aimed to assess whether there were any differences in nutrition status between pre-surgical CD, active CD, CD in remission and ulcerative colitis (UC) in remission.

Methods: Patients with pre-surgical CD, active CD, CD in remission and UC in remission were recruited from a UK hospital IBD unit. Anthropometric measurements were weight, height, body mass index (BMI), waist circumference (WC), mid-upper arm circumference (MAC), triceps skinfold (TSF) and mid-arm muscle circumference (MAMC). Bioelectrical impedance analysis (BIA) determined fat mass (FM) and fat-free mass (FFM). Muscle strength was assessed using hand-grip strength (HGS). Malnutrition was categorised as ≤5th percentile of the age- and gender-specific population reference range for MAC, MAMC and TSF and < 85% of the age- and gender-specific population reference range for HGS. Comparisons between groups were made using one-way ANOVA for continuous data and chi-squared for categorical data with significance set at $p < 0.05$. For significant results, post hoc analysis identified which groups differed.

Results: A total of 121 patients with IBD were assessed. Malnutrition was identified in 21 (17%) patients using MAC, 6 (5%) patients using TSF, 39 (32%) patients using MAMC and 55 (46%) patients using HGS. No differences between groups were identified for weight, height, WC, FM, FFM, TSF and MAMC. Differences between groups were found for BMI, MAC and HGS (Table 1). Post hoc analysis showed where the differences between groups were: BMI (pre-surgical CD vs. CD in remission, p = 0.04), MAC (pre-surgical CD vs. CD in remission, p = 0.003; presurgical vs. UC in remission, p = 0.033) and HGS (presurgical CD vs. CD in remission, p = 0.014; presurgical vs. UC in remission, $p < 0.001$).

	Pre-surgical CD n=30	Active CD n=30	CD in remission n=31	UC in remission n=30	p-value
Age (years; mean ± SD)	38.80 ± 11.69	33.17 ± 10.22	35.48 ± 12.38	38.07 ± 10.62	0.202
Male (n)	19	19	17	18	0.892
Weight (kg; mean ± SD)	67.05 ± 14.90	73.15 ± 16.97	76.69 ± 18.34	76.83 ± 14.81	0.074
Height (m; mean ± SD)	1.71 ± 0.09	1.76 ± 0.10	1.72 ± 0.11	1.74 ± 0.88	0.234
BMI (kg/m²; mean ± SD)	22.79 ± 3.88	23.75 ± 5.49	26.07 ± 6.01	25.22 ± 3.18	**0.040**
WC (cm; mean ± SD)	84.71 ± 13.91	83.58 ± 17.88	88.08 ± 14.58	89.41 ± 12.61	0.383
FM (%)	22.34 ± 9.62	20.06 ± 9.62	24.06 ± 13.47	23.62 ± 6.68	0.423
FFM (%)	77.66 ± 9.62	79.93 ± 9.62	75.94 ± 13.47	76.38 ± 6.67	0.424
MAC (% malnourished)	36.7%	20.0%	3.2%	10%	**0.004**
TSF (% malnourished)	6.7%	10.0%	3.2%	0%	0.652
MAMC (% malnourished)	46.7%	33.3%	25.8%	23.3%	0.208
HGS (% malnourished)	73.3%	46.7%	38.7%	23.3%	**0.001**

Table 1. Comparison of nutrition status across IBD groups (mean ± SD for continuous data or % for categorical data).

Conclusions: Across IBD phenotypes and disease activity groups, nutrition status is most depleted in pre-surgical CD patients. Nevertheless, clinically significant rates of malnutrition also occur during active disease and in remission. These data may help healthcare services prioritise dietetic provision to IBD patients, specifically for pre-surgical CD patients.

P657

Backwash ileitis not influences the risk of the pouchitis, but can increase the risk of the pouch dysplasia

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Background: Backwash ileitis (BI) is the term given to endoscopic and/or histological inflammation that extends from the caecum continuously into the terminal ileum in a ulcerative colitis (UC) patient with extensive colitis. The opinion about the role of the BI in patients after restorative proctocolectomy, as a risk factor for pouchitis development is very controversial. Most author's present the results showing no influence of the BI on the pouchitis occurrence, both acute and chronic. The data about correlation between BI and pouch dysplasia and neoplasia are incidental and not clear.
Methods: The study group consisted of 276 patients with ulcerative colitis after restorative proctocolectomy performed between the years 1984 and 2009. Within this group there were 143 women and 133 men with a mean age of 33.4 ± 12.1 years. The clinical data from screening assessments made in 2014–2018 was analysed. The flexible or rigid endoscopy was done in all patients. Dysplasia and neoplasia were recognised on the basis of standard pathological examinations of the pouch mucosa. Backwash ileitis (BI). To recognise the backwash ileitis the full large bowel resected during proctocolectomy was analysed as a standard histological protocol.
Results: Pouchitis was observed in 66 patients, while backwash ileitis was presented in 30 patients, co-occurrence of pouchitis and backwash ileitis was described in 10 patients. Pouch dysplasia was found in 8 cases, pouch malignancy in 1 patient. Backwash ileitis positively correlated with the occurrence of each kind of dysplasia ($p = 0.000001$). However, the presence of pouchitis did not correlate with appearance of backwash ileitis in whole group ($p = 0.2$).
Conclusions: Occurrence of backwash ileitis do not correlate with the pouchitis frequency in operated patients, but in backwash ileitis patients severity of pouchitis (measured in PDAI score) is higher than in non-backwash ileitis group. In this group of patients (BI + pouchitis) the risk of dysplasia in pouch mucosa as higher and follow-up with endoscopies and biopsies is necessary.

P658

Efficacy and safety of thalidomide in adults with refractory Crohn's disease to maintain clinical remission: a retrospective cohort study

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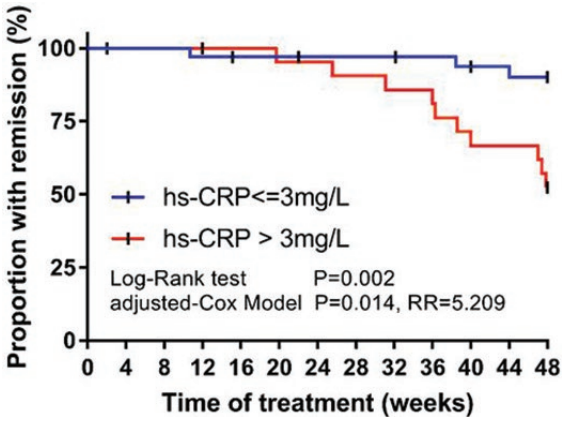
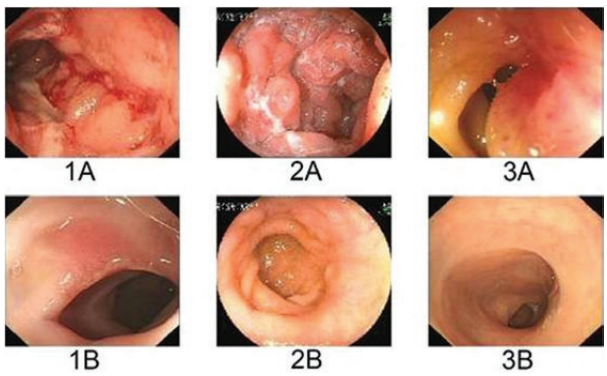
Background: Thalidomide is effective in inducing clinical remission in children and adolescents with refractory Crohn's disease (CD). However, the efficacy and safety of thalidomide in adult patients with refractory CD to maintain clinical remission remain unclear.
Methods: Seventy-nine consecutive adult CD patients in remission, who were refractory or intolerant to thiopurines and dependent on steroid before, were retrospectively enrolled. Thalidomide (50–100 mg/day) was administrated to maintain clinical remission. Patients who were induced by other immunosuppressants before would continue the concomitant therapy in low dose. Primary outcome was the time of clinical relapse that defined as the Harvey–Bradshaw Index (HBI) scores >4. Mucosal healing after thalidomide treatment was defined as simplified endoscopic activity scores for CD (SES-CD) = 0.
Results: By Week 48, the clinical remission rate was 70.89% out of all the 79 patients. Normalisation of high-sensitivity C-reactive protein levels (hs-CRP) at baseline (adjusted relative risk, 5.209; 95% CI, 1.402–19.349; $p = 0.014$) predicted the efficacy of remission maintenance (Figure 1). Forty-four patients consented to undergo colonoscopy at the time before and after thalidomide treatment. The mucosal healing rates after thalidomide treatment was 14.63% (Figure 2). Adverse events occurred in 54 (68.35%) patients, but only 8 (10.13%) patients had to discontinue therapy. None of the side effect was irreversible.



Proportion with remission in patients that stratified by the normalisation of hsCRP levels at baseline. *p*-value and RR were calculated for comparison between two groups in Log-Rank test and Cox proportional hazard model, which were adjusted for disease duration and disease behavior.



Colonoscopies of patients who got mucosal healing after thalidomide therapy. 1A, 2A, and 3A were three patients' colonoscopies before treatment. 1B, 2B, and 3B were the patients' colonoscopies after thalidomide treatment, respectively.
Conclusions: Low-dose thalidomide was efficacious in maintaining clinical remission in 48 weeks and achieving mucosal healing in adult patients with refractory CD. The patients with normal hs-CRP

levels at baseline may have a longer duration of clinical remission maintenance. The side effects of thalidomide were mild, tolerable, and reversible. Therefore, thalidomide may be an alternative candidate for adult refractory CD patients.

P659

Efficacy of switching from infliximab to golimumab in ulcerative colitis patients on deep remission

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Background: Increasing number of patients with ulcerative colitis (UC) patients on infliximab (IFX) scheduled maintenance therapy constitute a burden to many infusion units. Elective and effective switching to subcutaneous golimumab (GLM) may at least partially relieve this burden. We aimed to assess prospectively the long-term impact of elective switching of UC patients in deep remission from IFX to GLM.
Methods: Open-label, prospective, single-centre study. Eligible were UC patients in deep remission defined as clinical [normal patient-reported outcomes for UC (UC-PROs)], biomarker [normal serum C Reactive Protein (CRP) and faecal calprotectin (FC)] and endoscopic remission (endoscopic Mayo sub-score ≤1) on infliximab scheduled monotherapy for ≥2 years. FC cut-off values for endoscopic Mayo sub-score ≤1 were ≤ 150 μg/g faecal tissue. Patients consenting to participate were switched to GLM (dosing according to the recommended regimen) and followed in the outpatient IBD clinic at 6-month intervals. In addition, unscheduled visits were arranged if needed. At each visit, patients underwent clinical evaluation, CRP measurement and filled questionnaires (short IBD quality of life, work productivity and activity impairment, disability, satisfaction with therapy). In addition, at 1 year a blind expert endoscopist performed colonoscopy with biopsies to assess for endoscopic and histological remission, while FC was once again measured.
Results: This is an ongoing trial. From October 2015 to October 2017 14 patients have been recruited. We here report the clinical, biomarker, IBDQ and endoscopic results of an interim analysis on 13 patients who completed at least 1 year of scheduled GLM therapy. One patient became pregnant and did not undergo the 1 year follow-up evaluation. Patient demographic, clinical data and results are shown in Table 1. At the annual follow-up UC-PROs, serum CRP and FC remained normal. All patients were in endoscopic remission. No unscheduled visits were needed and no side effects from GLM administration were reported.

	Baseline	1-year follow-up	*p*
Males/females (*n*)	11/3	11/2	
Age (years), median (range)	42.8 (20–66)	42.9 (20–66)	
Disease extent (E2/E3) (*n*)	8/6	7/6	
Disease duration (months), median (range)	32.8 (24–68)		
Time of IFX administration, (months), mean (SD)	29.2(5.9)		
Serum CRP mg/dl, median (range)	0.20 (0.08–0.21) (normal < 0.60)	0.20 (0.20–0.40) (normal < 0.60)	NS
Faecal calprotectin μg/g faecal tissue, median (range)	80 (41–144)	60 (35–130)	NS
Mayo endoscopic sub-score, mean (SD)	0.38 (0.50)	0.41 (0.51)	NS
IBDQ score, mean (SD)	69.15 (0.98)	69.38 (0.76)	NS

Demographics, clinical data, biomarkers and endoscopy at inclusion and at 1-year follow-up.
Conclusions: Elective switching from IFX to GLM in UC patients in deep remission appears to be efficacious and well tolerated.

P660

Stability of serum concentrations of infliximab and adalimumab across pregnancy in IBD

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Background: Infliximab (IFX) and adalimumab (ADA) are IgG1 anti-tumour necrosis factor (TNF) monoclonal antibodies, which are transferred across the placenta in the second and third trimesters of pregnancy. There remains a paucity of data relating to maternal serum levels in pregnancy. A small study by Seow et al.observed that IFX levels increased during pregnancy while ADA levels remained stable.[1] However, the sample size and number of intra-partum samples was limited.
Methods: Female patients with IBD on ADA or IFX, and either pregnant or planning pregnancy were enrolled. Serum trough ADA and IFX were measured in each trimester and at delivery by ELISA (Q-INFLIXI and Q-ADA, Matriks Biotek, Turkey or Promonitor, Grifols, Spain).
Results: 12 patients on IFX and 4 patients on ADA with at least 2 intra-partum measurements were included. The median number of levels per patient was 3 (range 2–5). Patient characteristics are shown in Table 1.

Median (IQR) or n (%)	Infliximab (n=12)	Adalimumab (n=4)
Age at beginning of pregnancy (y)	33.5 (29.9-36.5)	32.0 (25.7-37.2)
Disease -CD -UC -IBDU	 10 (83.3%) 1 (8.3%) 1 (8.3%)	 4 (100%)
Duration of IBD (y)	10.5 (6.2-17.5)	11.2 (3.4-18.3)
Duration of anti-TNF therapy (y)	4.0 (1.0-6.3)	2.8 (0.1-7.5)
Concomitant immunomodulator	8 (66.7%)	3 (75%)

Table 1. Patient characteristics

Infliximab cohort (*n* = 12): Median and individual trough IFX levels were stable (Figure 1). IFX was administered 6–8 weekly at doses of 5 mg/kg (*n* = 10) or 10 mg/kg (*n* = 2). The last dose was given at a median 30 weeks gestation. All patients were in clinical remission at the time of drug levels with normal faecal calprotectin (FCP) (< 250 μg/g).

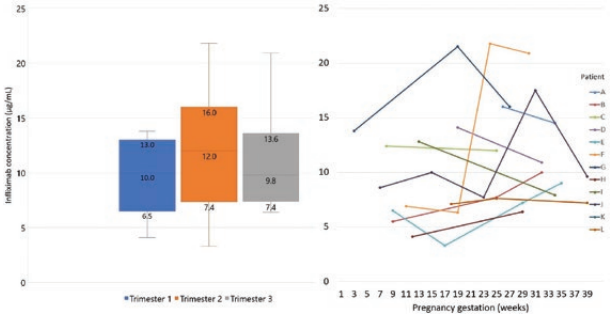

Figure 1. Maternal infliximab levels in pregnancy—median and individual trough concentrations.

Adalimumab cohort (*n* = 4): intra-partum and delivery ADA concentrations appeared stable (Figure 2). Three of the patients were on ADA 40 mg fortnightly and continued the drug throughout

pregnancy; Patient A, on weekly ADA, elected to cease the drug at 30 weeks gestation. Patient B was switched to adalimumab in her second trimester 12 weeks before her earliest ADA level in pregnancy. Patient C had an elevated FCP in first trimester which then normalised, while the other three patients had normal FCP in pregnancy. Patient D was in her third trimester at the latest blood draw.

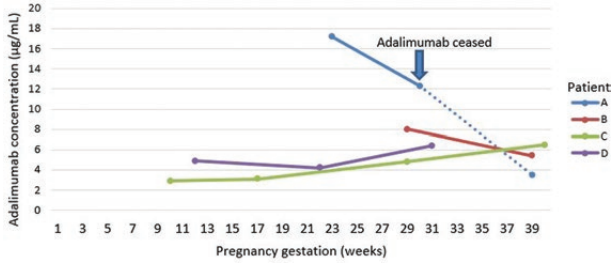

Figure 2. Maternal adalimumab levels in pregnancy.

Conclusions: In patients on stable dosing of IFX or ADA and in remission during pregnancy, maternal drug levels remain stable. Further data are required to clarify the pharmacokinetics of anti-TNF in pregnancy before recommendations can be made about dosing intervals.

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P661

Early histological improvement demonstrated with oral ozanimod in patients with moderately to severely active Crohn's disease in the STEPSTONE trial

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Background: Ozanimod, an oral immunomodulator that selectively targets $S1P_1$ and $S1P_5$, has demonstrated efficacy and safety in ulcerative colitis (UC) (Sandborn *NEJM* 2016) and is being evaluated in active Crohn's disease (CD).[1] The aim of the STEPSTONE study was to examine histological, endoscopic, and clinical outcomes, and safety of ozanimod in adults with CD.

Methods: STEPSTONE was an open-label uncontrolled phase 2 multi-centre trial of ozanimod for 12 weeks, followed by an extension period. Patients with active CD (Crohn's disease Activity Index [CDAI] score 220–450, total simple endoscopic score for CD [SES-CD] ≥6 (or in isolated ileum disease SES-CD ≥4) received ozanimod 1 mg daily. Ileo-colonic endoscopic biopsies (perpendicular to the mucosal surface at the edge of the largest ulcer or in the most severely affected area in segments without ulcers) were obtained from the terminal ileum and 4 colonic segments at baseline and Weeks 12 and 52 for assessment of histological change. A post hoc analysis of histology data through Week 12 are reported here, based on an 02-October-2017 interim data cut. The Robarts Histopathology Index (RHI) is a validated, reproducible, and responsive index that incorporates four histological descriptors (severity of chronic inflammatory infiltrate, the number of lamina propria neutrophils, the number of neutrophils in the epithelium, and the severity of erosions or ulceration), each of which is objectively graded from 0 to 3 (Mosli *Gut* 2015).[2]

Results: Sixty-nine patients were enrolled. At baseline, mean age was 38 years, mean SES-CD was 13, mean CDAI score was 321, and mean RHI was 16.3. Mean CD duration was 10 years, with 54% of patients having had prior exposure to biologic therapy (ie, anti-TNF-α, vedolizumab). Table 1 presents the mean change in RHI for paired segments from baseline to Week 12 in the overall study population and in subgroups of patients with or without prior exposure to biologic therapy and by segment.

Study Group	N (ITT N=69)	Mean (Standard Deviation)
Overall Population	52	-4.5 (9.48)
Biologic Exposure		
Prior Biologic Exposure	30	-4.0 (8.59)
Biologic Naive	22	-5.1 (10.75)
Segment		
Rectum	48	-1.7 (3.27)
Left Colon	45	-1.6 (3.41)
Transverse Colon	47	-0.1 (2.56)
Right Colon	42	-0.3 (3.69)
Ileum	41	-1.5 (3.26)

Note: Preliminary data

Change from baseline in robarts histopathology index (RHI) score at Week 12 – observed cases, intent-to-treat population

Through 12 weeks, most non-serious and serious adverse events appeared to be related to underlying moderate to severe CD. No new safety signals were identified.

Conclusions: Results of the STEPSTONE trial demonstrated early histological improvements among patients with moderately to severely active CD who were treated for 12 weeks with ozanimod. These improvements were seen in the patients with and without prior biologic exposure and across all segments.

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P662

Remission to vedolizumab is not higher in TNF-naïve compared with TNF-pre-treated patients with Crohn's disease

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Background: Vedolizumab (VDZ) a humanised monoclonal antibody against α4β7 integrin is used in Crohn's disease (CD) and ulcerative colitis (UC). It is still unclear whether biologic-naive patients will respond better to VDZ than TNF-pre-treated patients in a real life setting. Our study aimed to determine the efficacy of VDZ among TNF-pre-treated compared with TNF-naive patients.

Methods: In total, 265 patients of the Swiss IBD cohort study were analysed, 17 patients were excluded due to incomplete data. Of the remaining 248 patients 130 suffered from CD and 118 patients from UC. Remission was defined as calprotectin < 200 mg/kg in faecal samples and/or mucosal healing determined by endoscopy.

Endpoints were determined between month 4 and 8 and between month 12 and 16 after VDZ induction.
Results: In total, 112 patients (45%) (43% CD and 48% UC) achieved remission between month 4 and 8 and 130 patients (52%) at month 12 and 16. In patients with UC, significantly more TNF-naïve patients (60%) achieved remission compared with TNF-pre-treated patients (33%) (p = 0.01, OR 0.24, CI 0.09–0.65). In patients with CD however, we observed no significant difference between TNF-pre-treated and TNF-naive patients. Almost a third of all patients discontinued VDZ treatment (29.8%), the most frequent reason was non-response to VDZ (20%), followed by adverse events (6%) and exacerbation of extraintestinal manifestations (3%).
Conclusions: A significant proportion of patients TNF-naïve and TNF-pre-treated patients achieved remission. Previous anti-TNF failure was associated with a lower efficacy of VDZ in UC patients between month 4 and 8, whereas remission rates in anti-TNF–naïve vs. experienced CD patients were similar.

P663

The effect of vitamin D deficiency, and its correction, on healthcare utilisation among patients with inflammatory bowel disease (IBD)

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Background: Vitamin D (25(OH)D) deficiency is frequent in patients with inflammatory bowel disease (IBD). Observational studies have associated this with an increased risk of flaring disease, although under-sized supplementation studies have not shown improved clinical outcomes. Here, we undertake a case–control study to compare healthcare utilisation in patients with sustained vitamin D deficiency to those whose 25(OH)D levels have been corrected.
Methods: An electronic medical record (EMR) search query was used to identify all patients at a single medical centre with a diagnosis code for IBD and two recorded 25(OH)D levels (at T0 and T1) within an 18-month time window. The EMR of this cohort was searched for all clinic, emergency room (ER), and hospital visits in the 24 months after T0. Patients were grouped by 25(OH)D levels to three groups; 'low' (< 20 ng/ml), 'high' (>30 ng/ml), and 'restored' (T0 < 20 ng/ml, T1 >30 ng/ml). A point was assigned for each IBD-related healthcare visit to determine healthcare utilisation. Logistic regression modelling was used to find propensity scores between 'low' and 'restored' groups and to estimate a treatment effect of vitamin D correction on healthcare utilisation, when controlled for confounding variables.
Results: Data on 332 patients were analysed; mean age 58 years, 65% female, and 83% white. Ulcerative colitis (UC) and Crohn's disease (CD) were distributed 44% and 56%. The 'low' cohort consisted of 31 patients (M = 14 ng/ml), the 'high' cohort had 105 patients (M = 48 ng/ml) and the 'restored' included 51 patients (M = 41 ng/ml after correction). Outcomes from the rest of the cohort (those who had insufficient change in 25(OH)D or had decreased levels) were not analysed for the purpose of this study. Mean number of IBD-related clinic visits was 3.33, and 15% had more than one IBD-related ED visit or hospitalisations over 24 months. 'Low' vitamin D status was not associated with an increased risk of IBD-related clinic, ER, or hospital visits, when compared with 'high' vitamin D status patients. Patients who converted from 'low' to 'high' vitamin D status ('restored') increased their mean 25(OH)D from 15 ng/ml to 41 ng/ml. There was no statistical difference in any outcome between matched controls ('low') and cases ('restored') over 24 months follow-up. Power for these analyses was confirmed to be >0.8 for dichotomous outcomes based on this sample size and proportions.
Conclusions: Persistently 'high' (>30 ng/ml) vitamin D levels, or restoration of levels from < 20 ng/ml to >30 ng/ml, did not reduce IBD-related healthcare utilisation over 24 months in this observational study of more than 300 patients. A higher goal for levels may be necessary to determine whether there is an effect of vitamin D replacement on IBD outcomes.

P664

SB5 and reference adalimumab show cross-immunogenicity in patients with inflammatory bowel disease or rheumatoid arthritis

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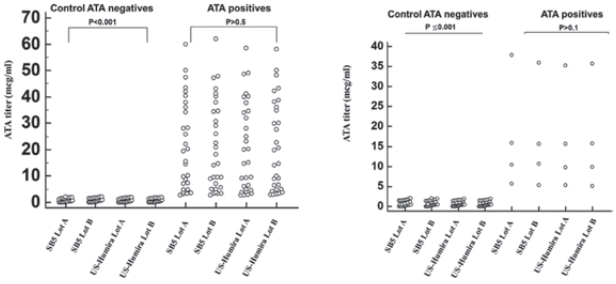
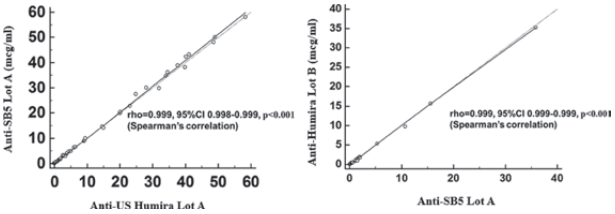
Background: SB5 has been approved by the European Commission as a biosimilar of reference adalimumab. The study was aimed at analysing immunogenicity similarity including functional binding of TNFs between SB5 and its reference product in IBD and in RA. Further analysis was carried out to test cross-reactivity of anti-infliximab antibodies with SB5.
Methods: Sera from IBD or RA patients treated with adalimumab with or without measurable antibodies-to-adalimumab (ATA) were tested for their cross-reactivity to SB5 or reference adalimumab. Functional inhibition of TNF binding was measured by graded concentrations of SB5 and reference adalimumab. Finally, sera with antibodies to infliximab (ATI) and ATA from IBD patients treated with reference infliximab and adalimumab were examined for cross-reactivity with SB5. Sera were tested by ELISA with the cut-off level of 2.3µg/ml-equivalent for antibody detection. Comparison of mean concentrations was tested by paired t-test (if normality was accepted) and Wilcoxon test (if normality was rejected), and a correlation was tested using Spearman correlation test.
Results: There was no difference between the ATA concentration measured against SB5 or reference adalimumab lots in ATA+ IBD (30 sera) or RA sera (4 sera). Even though background signal generated in ATA- sera was higher in SB5 lot compared with two reference adalimumab lots ($P \leq 0.001$), the absolute difference was minimal to < 0.1 µg/ml (Figure 1a and b).

Figure 1. (a) Comparative ATA titers towards reference adalimumab reference adalimumab and SB5 lots among ATA-positive and negative sera in IBD patients ATA, antibody-to-adalimumab; IBD, inflammatory bowel disease; RA, rheumatoid arthritis. (b) Comparative ATA titers towards reference adalimumab and SB5 lots among ATA-positive and negative sera in RA patients.



Moreover, there was a strong correlation between titres of ATA to SB5 and reference adalimumab lots from reference adalimumab-sensitised IBD sera or SB5-sensitised RA sera (Figure 2a and b).

Figure 2. (a) Correlation between ATA concentrations from reference adalimumab-sensitised IBD patients using the designated SB5 or reference adalimumab lots as the antigen for serum immune-reactivity. ATA, antibody-to-adalimumab; IBD, inflammatory- bowel disease; RA, rheumatoid arthritis. (b) Correlation between ATA concentrations from SB5-sensitised PA patients using the designated SB5 or reference adalimumab lots as the antigen for serum immune-reactivity.



In addition, ATA from reference adalimumab-sensitised IBD patients had similar functional inhibition on TNF binding capacity between SB5 and reference adalimumab. Finally, ATI from reference infliximab-sensitised IBD sera did not cross-react with SB5.

Conclusions: SB5 and reference adalimumab show cross-immunogenicity in that ATA similarly identify reference adalimumab and SB5 in IBD and RA patients. On the other hand, anti-infliximab antibodies do not cross-react with SB5, further supporting that SB5 and reference adalimumab share immunogenic profile but not with infliximab.

Disclaimer: The study was conducted at Sheba Medical Center, Tel-Aviv, Israel

P665

1-Year clinical and endoscopic follow-up of vedolizumab therapy in refractory PIBD patients

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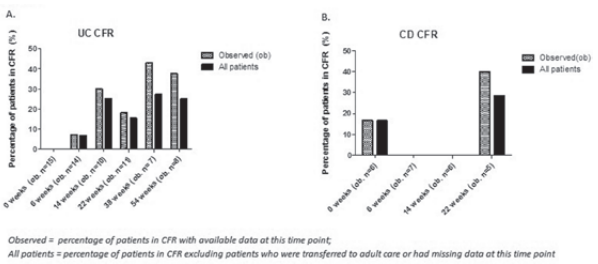
Background: In adult IBD patients vedolizumab has proven to be effective but prospective studies in paediatric IBD (PIBD) patients have not been performed. Available retrospective studies in PIBD are promising regarding corticosteroid-free remission (CFR) rates, especially in refractory ulcerative colitis (UC) patients. Vedolizumab is therefore to be considered in refractory PIBD patients failing anti-TNF. Data on endoscopic findings and long-term follow-up are especially scarce. We investigated the long-term clinical and endoscopic follow-up in PIBD patients.

Methods: For this retrospective per protocol study PIBD patients receiving vedolizumab from 2015–2018 in a tertiary centre were included. Most patients received 300 mg at week 0, 2, 6 and every 8 weeks thereafter, and had oral prednisolone as bridging therapy. At each infusion visit clinical disease activity scores, routine laboratory parameters and serum samples were collected. Endoscopy was performed after at least 3 infusions.

Results: In total, 22 PIBD patients (12 UC, 7 CD and 3 IBDU) with a median age of 15.3 years (IQR 12.3–17.1) received vedolizumab after previous anti-TNF failure (73% pharmacodynamic, 13% immunogenic, 4% pharmacokinetic failure). Median follow-up after start of vedolizumab was 60 weeks (IQR 18–75). 1-year follow-up data were available in 17 patients. Five patients were transferred to adult care within 1 year after starting vedolizumab treatment. Vedolizumab was discontinued in 42% (5/12) of UC/IBDU patients compared with 80% (4/5) of CD patients (77 and 23 weeks of median therapy duration, respectively). Corticosteroid-free remission (CFR) rates, defined as no use of corticosteroids and a PUCAI < 10 or PCDAI < 12.5, were 25% in UC/IBDU and 0% in CD at 14 weeks. After 54 weeks 25% of the UC/IBDU patients were in CFR.

Figure 1.



Observed = percentage of patients in CFR with available data at this time point;
All patients = percentage of patients in CFR excluding patients who were transferred to adult care or had missing data at this time point

Endoscopy was performed in 12 patients (11 UC/IBDU, 1 CD) after a median follow-up of 23 weeks (IQR 19–29), which showed mucosal healing (Mayo score 0) in 36% of UC/IBDU patients (n = 4) but active disease in the one CD patient. At last follow-up 37% (8/22) of patients needed a surgical resection (2 in CD and 6 colectomies in UC/IBDU) after a median therapy duration of 38 weeks (IQR 23–60). Analysis of trough levels is currently ongoing.

Conclusions: In this group of refractory PIBD patients 25% of UC and none of the CD patients had CFR at 14 weeks. After 54 weeks 25% of UC patients was in CFR. Mucosal healing was shown in 36% of UC/IBDU patients. Future studies including vedolizumab trough levels and subsequent optimal dosing in PIBD are essential.

P666

Safety of combination biologic and immunosuppressive therapy post-orthotopic liver transplantation in patients with inflammatory bowel disease: a systematic review

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Background: inflammatory bowel disease (IBD) patients post orthotopic liver transplantation (OLT) often have ongoing mucosal inflammation necessitating biologic agents for therapy. The safety of combined biologic and immunosuppressive therapy post-OLT in this population is unclear. The aim of this study was to systematically review the evidence for safety of combination biologic and immunosuppressive therapy in patients with Primary sclerosing cholangitis (PSC)/other liver diseases and concomitant IBD after OLT.

Methods: EMBASE, Medline, Cochrane CENTRAL, clinialtrials.gov, and the International Clinical Trials Registry Platform were searched without language restriction using keywords identifying

OLT and IBD up to 1 March 2018. All studies evaluating the safety of combined biologic and anti-rejection therapy were included. All eligible studies were reviewed for safety outcomes, including infections, cancers, death, and colectomy rate. Meta-analysis was not performed due to the low quality of evidence available.
Results: A total of 2713 citations were identified: 2315 articles were screened after removal of duplicates (*n* = 399) and we identified 20 articles (12 case series and 8 case reports) that were eligible for inclusion. From these studies, a total of 109 IBD patients were treated with combination biologic and immunosuppressive therapy. PSC was the primary indication for OLT in 87 patients (79.8%) with 67 (61.5%) having ulcerative colitis. TNF antagonists were used in 91 patients (83.5%) while 17 patients (15.5%) received vedolizumab, and a single patient received ustekinumab. The most commonly used anti-rejection therapies were tacrolimus, prednisone, azathioprine and mycophenolate mofetil. A total of 22 (20.2%) patients experienced an infectious complication (cholangitis (*n* = 3), clostridium difficile (*n* = 3), CMV colitis and viremia (*n* = 1), Post-op infections (*n* = 5), cryptosporidiosis (*n* = 2), bacterial pneumonia (*n* = 1), oral candidiasis (*n* = 1), oesophageal candidiasis (*n* = 1), campylobacter (*n* = 1), infectious diarrhoea (*n* = 1), enterococcus faecalis bacteraemia (*n* = 1), molluscum contagiosum (*n* = 1), wound infections (*n* = 1)). All infections were reported in patients on anti-TNF therapy. Malignancy was reported in 6 patients (5.5%). Four patients had colorectal cancer, one patient had cholangiocarcinoma and one patient had cervical cancer. There were two deaths (CRC and recurrent PSC with cholangitis).
Conclusions: Post-OLT IBD patients receiving anti-TNF therapy are at an increased risk of enteric and postoperative infectious complications. Enteric infections should be actively screened for in patients experiencing worsening IBD symptoms.

P667

Thiopurine withdrawal during sustained clinical remission in inflammatory bowel disease: relapse and recapture rates in 72 patients, a report from a district general hospital

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Background: Long-term treatment with thiopurines is associated with an increased risk of opportunistic infection, lymphoma and other malignancies. Treatment withdrawal should be considered in patients who are in deep remission.
Aim: To establish the percentage of patients that relapse after withdrawal of azathioprine and time from withdrawal to relapse and recapture rate.
Methods: We searched our IBD database for patients where azathioprine (AZA) was withdrawn following a deep remission (defined as faecal calprotectin (FCP) < 200 mg/kg and/ endoscopic remission defined as no ulceration or quiescent inflammation). We reviewed the length of time on AZA, the relapse rates following withdrawal and recapture rate following re-starting.
Results: 72 patients were identified (36 Crohn's disease (CD); 36 ulcerative colitis (UC). Mean age at stopping = 61.5 years (range 21–84). 36 (50%) male; Median duration of thiopurine use prior to withdrawal = 6.5 years (range 1.0–14.8). Fifty-two (72%) had FCP measured; mean = 37 (5–161). Endoscopic remission was confirmed in 36 (50%). In 3 (18.8%) FCP was normal with mild inflammation endoscopically. A total of 28 (38.8%) patients relapsed; 17 UC (60.7%) 11 CD (39.3%), mean time until relapse =16 months (range 7 days–79 months). Relapse was confirmed endoscopically in 22 (78.6%) and by FCP in 6 (21.4%). Mean FCP 940 (range 459–2329); 20 (68.9%) re-started AZA with concomitant prednisolone. Of these 14 (70%) entered clinical remission. Six patients (50% UC) failed to enter remission with AZA. Three patients required admission (10.3%). A clinical decision was made to start 2 (6.9%) on methotrexate because of better risk profile in older age. Seven (24.1%) re-started mesalazine monotherapy. 1 (3.1%) opted for colectomy (immunosuppression was not re-started due to a diagnosis of malignant melanoma). And 1 had vedolizumab due to a diagnosis of sarcoma. In total 16 patients (57.1%) entered and maintained remission (length of follow-up = mean 29.7 months (range 2–120) without requiring surgery or biologics.
Conclusions: Our data demonstrate that 38.8% of patients stopping thiopurine will relapse and 79.4% of these patients will relapse within 3 years. Reassuringly, 71.5% achieved remission on re-starting AZA/methotrexate/ mesalazine. Interestingly, 3 of our patients were identified to be in remission with FCP but had mild inflammation on endoscopy. These three patients subsequently relapsed. This raises the possibility of the need for diagnosis of remission endoscopically rather than using FCP alone. These data should aid discussion regarding the safety of withdrawing thiopurine in patients in a long-term remission.

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Ustekinumab induction effectiveness in Crohn's disease in a real-life cohort

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Background: Ustekinumab (UST), a humanised monoclonal antibody targeting the IL-12/23 shared p40 subunit, was approved in Spain in 2017 for treatment of moderate-to-severe Crohn's disease (CD). The aim of this study was to analyse the patients' characteristics starting UST in a real-life cohort and the induction effectiveness.
Methods: A retrospective observational study including patients initiating UST between August 2017 and September 2018 was conducted in a single tertiary centre. We recorded demographic and descriptive variables, activity indexes Crohn's Disease Activity Index (CDAI) and Harvey–Bradshaw (HB), inflammatory markers, and the reason to start UST. Induction effectiveness was analysed in patients who had reached Week 16. Response was defined as a reduction 100 points in CDAI and remission if CDAI was 150. A response/remission Physician's Global Assessment (PGA) was also done. A stratified analysis based on the reason for starting UST was performed.
Results: We included 41 patients (36.6% women) with median disease duration until start of UST of 10.6 years (0–36). Most patients did not receive concomitant steroids (78%) or immunomodulatory drugs (73.2%). UST was the second biologic in 31.7%, the third in 46.3%, the fourth in 19.5% and the fifth in 2.4%. Previously, 100% had anti-TNF agents and 17.1% had Vedolizumab. The reason to start UST was primary failure in 12.2%, secondary failure 68.3% and intolerance/allergy to previous anti-TNF agents 19.5%. Baseline CDAI was 195 (18–351), HB 8 (1–13), C-reactive protein 9.5 (0.5–92.7 mg/l) and faecal calprotectin 403 (52- >3000 mg/kg). A total of 28 patients completed induction (Week 16). Response rates were 73.1%/71.4% and remission rates 65.4%/57.1% according to the CDAI criteria

and PGA, respectively. All patients (6) starting UST due to intolerance/allergy responded (83.3% remission); of those with previous primary failure (3), 66.7% achieved remission and 33.3% failed; and of those with previous loss of response to anti-TNF agents (19), 63.2% responded (47.4% in remission). UST was used as second biologic (7) with 71.4% remission, as third biologic (14) with 71.4% response (57.1% remission) and as fourth biologic (5) with 80% remission.
Conclusions: In this real-life cohort, two thirds of patients responded to UST after the induction, with different response rates according to treatment indication: 80% remission in patients who started UST due to prior intolerance/allergy, 60% of patients with previous primary failure and 60% of those with previous loss of response. We consider it convenient to present stratified results according to UST indication.

P669

Transmural healing is associated with higher infliximab trough levels in Crohn's disease

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Background: Transmural healing (TH) leads to improved long- term outcomes in Crohn's disease. TH can be easily assessed with intestinal ultrasound (IUS). Infliximab trough levels (ITL) are associated with the likelihood of clinical response, clinical remission, mucosal healing and fistula healing in both CD and UC. However, it is unclear whether high ITL is associated with TH .
Methods: This was a retrospective chart review. CD patients treated with IFX that had available ITL during maintenance (fourth infusion and beyond) and available concurrent IUS results (within 3 months from each other) were included in the study. TH was defined as terminal ileum thickness of ≤3 mm without increased blood flow. ITL levels were measured using an in-house sandwich ELISA and compared between patients with TH and patients with non-equivocal transmural disease, defined as terminal ileum thickness >5 mm.
Results: Thirty-three CD patients (51% male, mean duration of disease-7.5 years, 91% anti-TNF-naïve) were included in the study .All patients had IUS results following the fourth (Week 14) infusion. TH was demonstrated in 15/33 (45%) of the patients; median ITL levels in patients with TH were significantly higher in comparison to patients with terminal ileum thickness > 5 mm (5.39, IQR 25–75% 2.5–8.9 μg/ml vs. 0.75, IQR 0.012–1 μg/ml, $p = 0.011$). In patients with undetectable IFX level (<1 μg/ml), median terminal ileum thickness was significantly higher than in patients with detectable ITL (4.5, IQR 3–6 mm vs. 3.2, 2.2– 4.1 mm, $p = 0.034$).
Conclusions: In CD patients treated with IFX, IUS-determined transmural healing is associated with higher trough Infliximab levels. As transmural healing may be associated with long-term clinical remission, it could serve as a potential target for guiding anti-TNF therapy. Our data merits validation in a larger prospective cohort.

P670

Therapeutic efficacy and economic impact of half sulfasalazine therapy for refractory ulcerative colitis

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Background: Numerous novel biologics are emerging for refractory ulcerative colitis (UC), but rising medical costs are a serious problem. Sulfasalazine (SASP) is an inexpensive drug. Although the effectiveness of 5-aminosalicylic acid (5-ASA) and SASP for UC is equivalent, SASP sometimes appears effective for refractory UC in daily clinical practice. SASP has dose-dependent side effects and there is a considerable amount of cases of high-dose intolerance of SASP. To solve this problem, we have provided 'half SASP therapy' for patients with UC, where 5-ASA and SASP are administered in combination with half of a high dose. This study aimed to investigate the short- and long-term efficacy, safety, and economic effect of half SASP therapy in refractory UC.
Methods: We performed a retrospective, observational study in two-IBD specialised facilities. We reviewed the outcome of patients with refractory UC who were treated with half SASP therapy from 2011 to 2018. Clinical remission and response were evaluated on the basis of the partial Mayo score. The cumulative rates of immunomodulator-, biologic- and colectomy-free survival rates were calculated using the Kaplan–Meier method. For evaluation of safety, any adverse event (AE) that occurred after administration of SASP was considered. Medication costs before and after treatment were also evaluated.
Results: A total of 211 patients were enrolled. Among these, 52% had chronic active colitis with high-dose oral 5-ASA treatment and concomitant topical treatments, 48% were steroid refractory/dependent cases, and the median partial Mayo score was 5.0 (0–8). At Weeks 8, 26, and 52 after half SASP therapy, 26%, 35%, and 39% of the patients achieved clinical remission, respectively. Among 173 patients who continued therapy after a median follow-up of 3.0 years (0.3–7.3 years), immunomodulator-free survival rates at 1 and 5 years were 93% and 81%, respectively. The biologic-free survival rates were 95% and 84%, and colectomy-free survival rates were 99% and 91%, respectively. The AE rate was 37%, 17% of patients had to discontinue SASP, and five required hospitalisation for allergies. No other severe AEs or mortality occurred. The average medication cost before half SASP was 398 USD per month. At 52 weeks after treatment, medication costs were as follows: 52-week responder, 139 USD; discontinuation of SASP due to AEs, 401 USD; and 52-week non-responder, 953 USD per month.
Conclusions: The incidence of AEs in half SASP therapy for refractory UC was high and 17% of patients needed to discontinue treatment, but there were no serious AEs. In patients who could continue therapy, the response rate was 60%, there was a good long-term prognosis, and medical costs were reduced.

P671

Experiences of using vedolizumab in the treatment of inflammatory bowel disease in the East Midlands: a retrospective observational study

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Background: Randomised controlled trials have demonstrated efficacy of vedolizumab in ulcerative colitis (UC) and Crohn's disease (CD). Its use is increasing and data in the real-world setting is needed to inform future practice.
Methods: A multi-centre retrospective observational study was conducted with patients initiated on vedolizumab across 7 UK hospitals between 1/11/14–30/11/16. The Health Research Authority approved the protocol (19/HRA/0008). Clinical disease activity was assessed at baseline, Week 14, 30 and 52 using the Harvey–Bradshaw Index (HBI) and partial Mayo Score (pMS). Clinical remission was defined as HBI ≤ 4 or pMS < 2 with a combined stool frequency and rectal bleeding subscore of ≤1. Clinical response was defined as ≥2 point decrease from baseline in pMS and ≥3 point decrease from baseline in HBI. The primary aim of this study was to describe corticosteroid-free and clinical remission after vedolizumab initiation. Secondary outcomes included effect on disease activity scores, biochemical markers (C-reactive protein (CRP) and faecal calprotectin (FCP), concomitant drug use, mucosal healing, surgical intervention, hospital admissions and adverse effects.
Results: 192 patients were included in the final analysis: 99 CD, 88 UC and 5 IBD unclassified (grouped with CD in this analysis). Forty-five per cent of UC and 10% of CD patients were anti-TNF naïve. Immunomodulator and corticosteroid use at baseline for UC and CD was 41%, 49%, 27% and 27%, respectively. The median age at exposure was 44 (range 18–79) years; 49% male and median BMI was 25.7 (range 15.3–44.6). Median exposure to vedolizumab was 38.4 (IQR 23.6–58.9) for UC and 31.0 (IQR 21.6–52.5) weeks for CD. Corticosteroid-free remission rates for UC and CD were 46% and 45%, while clinical remission rates were 52% and 44%, respectively. Clinical response rate for UC was 49% and CD was 53%. The median time to corticosteroid-free remission for UC and CD was 17.6 (IQR 8.7–29.6) and 15.7 (IQR 6.0–21.7) weeks and clinical remission was 15.1 (IQR 7.4–24.9) and 10.1 (IQR 3.1–21.0) weeks, respectively. Time to clinical response for UC was 9.4 (IQR 5.3–16.4) and CD was 9.5 (IQR 6.1–18.2) weeks. Median disease activity scores decreased from baseline to 14 weeks: pMS 5 (IQR 0–9) vs. 3 (IQR 0–9), HBI 7(IQR 0–15) vs. 5 (IQR 1–14). CRP and FCP normalisation occurred by 52 weeks in CD and 14 weeks in UC. The overall rate of IBD-related hospital admissions per patient per year was 1.3 (0–18). Adverse events were reported in 6% of patients.
Conclusions: Results in our vedolizumab patient population, predominately anti-TNF experienced, mirror other published real-world data and demonstrate very good clinical effectiveness and comparable safety profile. Takeda UK Ltd. sponsored this study.

P672

Drug therapy and monitoring for inflammatory bowel diseases: preliminary data from a multi-centre investigation in Asia

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Background: There is a growing population of patients with inflammatory bowel diseases (IBD) in Asia in recent years. The present investigation intended to obtain a better understanding of the current situation on drug therapy and monitoring for IBD from physicians' viewpoints in Asian areas.
Methods: A questionnaire investigation about drug therapy and monitoring for IBD was conducted in Asia before the sixth Annual Meeting of Asian Organization for Crohn's and Colitis (AOCC). Questionnaires were sent to AOCC members to fill out via email between March and May 2018.
Results: One hundred and sixty-nine physicians of 132 medical centres from Mainland China, Hong Kong, Taiwan, Japan, South Korea, India, Malaysia, Singapore and Thailand responded to the survey, in which 74 centres from all parts of Mainland China except Tibet participated. The average number of consultant gastroenterologists with specialist IBD experience of the investigated centres was 4.8 in Taiwan, which was the most among the surveyed regions. Mainland China had the largest average number of 2.5 of IBD specialist nurses in their centres. 5-aminosalicylic acid (5-ASA)/sulfasalazine (SASP) (99.41%) was the most preferred first-line choice for mild–moderate ulcerative colitis (UC), then followed by steroids (34.9%) and azathioprine (8.9%). Steroids (84.7%) were widely applied for severe UC, followed by infliximab (29.8%), 5-ASA/SASP (20.3%), azathioprine (14.9%) and ciclosporin A (11.9%). The first-line medication for Crohn's disease (CD) markedly varied among the responders as steroids (69.1%) were the most preferred in Mainland China, Japan and South Korea, followed by infliximab (52.3%), azathioprine (46.5%), 5-ASA/SASP (42.5%) and adalimumab (11.4%). Step-up strategy for mild–moderate UC was adopted by a large majority of physicians (96.4%) while it was only favoured by 36.1% physicians for severe UC. For CD, top-down treatment was adopted by 51.5% physicians while 39.1% chose step-up. For therapeutic drug monitoring, only 19.4%, 37.1%, 41.2%, 25.9% and 17.7% of the centres were able to test blood concentration of 6-mercaptopurine, FK506, ciclosporin A, infliximab and antibody to infliximab, respectively. The frequency for monitoring adverse events of IBD medication varied from 1 week to 6 months according to responders' answers.
Conclusions: The quantity of medical personnel with specialist IBD experience, the availability of IBD drugs and the preferences for drug choice vary from region to region in Asia. Therapeutic drug monitoring is insufficient in most investigated areas, which suggests little optimism in quality of drug therapy. Asian version of recommended indicators for drug therapy and monitoring is encouraged to be established for further improvement of IBD management.

P673

Achievement of tight control based on serum C-reactive protein and albumin correlated with better outcomes in Japanese Crohn's disease patients treated with biologics

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Background: Tight control management based on the clinical symptoms together with biomarkers has been proven to be more effective than conventional clinical management for Crohn's disease in the CALM study. However, there are insufficient data on what are indicators to be used for tight control management. Optimal biomarkers and their optimal standards that can be used conveniently in daily clinical practice are desired. We aimed to clarify whether tight control management based on serum biomarkers (C-reactive protein or albumin) results in better outcome, and to identify their optimal standards for tight control management in Japanese Crohn's disease patients treated with biologics.
Methods: We reviewed the treatment courses of 245 patients with Crohn's disease who were naïve to biologics and treated with anti-TNF agents (185 with Infliximab and 60 with adalimumab). Tight control was set at CRP < 0.3, CRP < 0.5, Alb ≥ 4.0 or Alb ≥ 3.8. The association between the achievement of tight control at Week 8 or 24 and major adverse outcomes (hospitalisation, surgery and discontinuation due to treatment failure) were analysed using the Log-rank test. To identify factors affecting major adverse outcomes, we also performed multi-variate analyses using a Cox proportional hazards model with clinical characteristics and serum biomarkers as covariates.
Results: In 223 patients followed for more than 8 weeks, the rate of major adverse outcomes was significantly higher in patients with CRP ≥ 0.3, CRP ≥ 0.5, Alb < 4.0 or Alb < 3.8 at Week 8. In a multi-variate analysis, the fistulising type, CRP ≥ 0.5 and Alb < 3.8 were identified as independent risk factors for major adverse outcomes with hazard ratios of 2.2, 2.0 and 2.1, respectively. In 204 patients followed for more than 24 weeks, the rate of major adverse outcomes was significantly higher in patients with CRP ≥ 0.3, CRP ≥ 0.5, Alb < 4.0 or Alb < 3.8 at Week 24. In a multi-variate analysis, the fistulising type, CRP ≥ 0.5 and Alb < 3.8 were identified as independent risk factors for major adverse outcomes with hazard ratios of 2.3, 1.9 and 2.2, respectively.
Conclusions: Tight control management may lead to avoidance of hospitalisation, surgery or discontinuation of anti-TNF agents in Japanese Crohn's disease patients. Among serum biomarkers that can be used conveniently in daily clinical practice, CRP < 0.5 and Alb ≥ 3.8 were the best candidates for tight control management. We should achieve tight control until Week 24 with optimisation of anti-TNF agents or addition of immunomodulators.

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Blood thiopurine level, anti-TNF drug level and body composition parameters in inflammatory bowel diseases patients: a cross-sectional study in a Hungarian IBD centre

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Background: Clinical data suggest a synergistic effect between thiopurine and anti-tumour necrosis factor (anti-TNF) therapy in IBD. However, azathioprine (AZA) metabolites and biological drug trough levels have not been investigated simultaneously. Furthermore, the effect of body composition on 6-thioguanine nucleotide (TGN) level has never been studied. The aim of the study was to evaluate potential correlation between AZA active metabolite 6-TGN levels and anti-TNF drug (infliximab [IFX] and adalimumab [ADA]) serum trough levels and body composition parameters.
Methods: This was a cross-sectional study involving 98 IBD patients. Patients on maintenance AZA (n = 30) and on IFX+AZA or ADA+AZA combinations (n = 34, 14 ADA, 20 IFX) and activity indices based on pair-matched controls on IFX or ADA monotherapy (n = 34, 14 ADA, 20 IFX) were prospectively enrolled. Thiopurine metabolite blood level was measured with high-performance liquid chromatography (HPLC) and body composition analysis was performed with bioelectrical impedance analysis.
Results: Therapeutic concentration of 6-TGN was detected in 50 patients (78%). Mean concentration was 425; the range was 248–797 pmol/8 × 10^8 RBC. Antibody formation proved to be significantly lower in patients receiving combined IFX+AZA therapy compared with IFX monotherapy (p = 0.0001). There was no difference in antibody formation between ADA+AZA vs. ADA monotherapy patients. ADA trough levels were significantly higher in patients with ADA+AZA combined vs. ADA monotherapy. In contrast, no difference was found between IFX trough level in patients receiving combined IFX+AZA vs. IFX monotherapy. The level of 6-TGN correlated with body weight-based AZA doses (p = 0.017), however no correlation was found with body surface area-based AZA doses (p = 0.081). Further correlation was shown regarding to body composition parameters such as total body water (r = –0.33, p = 0.011), intra-, and extracellular water (r = –0.325 and –0.334, p = 0.008 and p = 0.008, respectively), skeletal muscle mass (r = –0.326, p = 0.01). No correlation was found with body fat mass (r = –0.091, p = 0.487).
Conclusions: Most of the patients had therapeutic 6-TGN level with body-weight based administration without previous measurement. This is due to our findings that 6-TGN level correlated with body weight-based AZA doses total body water, intra-, extracellular water and skeletal muscle mass. Our data suggest the possible synergistic effect of thiopurine and anti-TNF combination therapy based on the decreased antibody formation among IFX-treated patients and increased anti-TNF drug level regardless of antibody formation in ADA-treated patients. However the small number of the patients requires further investigations.

P675

The relationship between gender, severity of disease, treatment type, and employment outcome in patients with inflammatory bowel disease in Israel

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Background: Since individuals with IBD typically experience symptoms during their prime years of employment, it raises the question about IBD impact on employment status. Most studies concentrated on absenteeism from work with varying results in different populations. However, absenteeism reflects only one dimension of the ability to work and does not expose the problem of inability to hold a full-time job. We aimed to evaluate the influence of IBD on unemployment and working hours in Israel. Secondary aims were to investigate the correlation between working hours and the type of medical treatment and the impact of severity of disease.
Methods: Demographic data, employment status, number of weekly working hours and disease parameters. The data were compared with that of the general Israeli population extracted from the website of the Central Bureau of Statistics.
Results: 242 IBD patients were interviewed. Patients median age was 37.04(IQR 30.23–44.68) years, 88 (36.4%) were men and 154 (63.6%)women. Diagnosis of CD was established in 167 (69%) patients and UC in 65(26.9%). There was no significant reduction in employment rates or working hours among the IBD patients comparing to the general population. Immunosuppressive or biologic treatment did not influence employment status. The unemployed patients had higher disease severity (median 7.33, IQR 5–10.66) compared with employed patients (median 6, IQR 3.66–7.66; $p = 0.003$).
Conclusions: Although IBD patients in Israel do not have higher unemployment, those with severe disease have lower proportion of employment.

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The impact to disease activity, iron and vitamin D deficiency on fatigue in IBD patients

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Background: Individuals with inflammatory bowel disease (IBD) and are at risk for a variety deficiencies because of decreased nutrient intake or absorption and/or increased losses. Iron and vitamin D deficiency are common in IBD patients, particularly during periods of prolonged disease activity. They are associated with adverse clinical outcomes and a reduced quality of life.
Methods: The aim of the current study is to evaluate the correlation between serum 25(OH)D concentrations and serum iron concentrations, in patients with ulcerative colitis (UC) or Crohn's disease (CD), and their effect on the quality of life, more specifically on fatigue. In 79 consecutive patients with confirmed IBD diagnosis, 51 with CD and 28 with UC, who attended the gastroenterology clinic during a 1-year period 25(OH)D, serum iron concentrations were measured. In all of the patients the prevalence of fatigue was assessed though the IBDQ and SF36 questionnaires for evaluation of the quality of life. For the quantitative determination of total 25-hydroxyvitamin D [25(OH) vitamin D] levels we used a commercial paramagnetic particle chemiluminescent immunoassay. Serum 25(OH)D ≤ 10 50 nmol/l was considered a VitD deficiency and 50 ≤25(OH)D < 75 nmol/l a VitD insufficiency.
Results: There is a poor correlation between fatigue and the 25(OH) D concentrations, $r = 0.204$ $p < 0.05$. In IBD patients with Vitamin D deficiency SF 36-Energy/Fatigue (SF 36 E/F) is 48.43, which is significantly lower than SF 36 E/F in patients with normal Vitamin D-65.63 concentrations, $p < 0.05$. There is a poor correlation between the measured concentrations of serum iron and the prevalence of fatigue $r = 0.218$ $p < 0.05$, in low serum iron concentrations SF36 E/F – 46.69, and in normal serum iron concentrations – 53.12. There is a significant difference between fatigue levels in different IBD activity $p < 0.001$, as follows: in remission SF36 E/F is 59.12; in mild activity SF36 E/F is 55.71; in moderate activity SF36 E/F is 42.08; in severe activity SF36 E/F is 30.68. We established a moderate direct correlation between fatigue and IBD activity $r = 0.402$ $p < 0.001$. In IBDQ levels >170, SF 36 E/F is 67.82, whereas in IBDQ < 170 SF 36 E/F is 41.94 $p < 0.001$. There is a strong direct correlation between the total IBDQ score and SF 36 E/F $r = 0.695$ $p < 0.001$. It can be said that 46.90% of the measured quality of life via IBDQ depends on the level of fatigue.
Conclusions: The low levels of serum iron and Vitamin D have no effect on fatigue in IBD patients, unlike the activity of the disease, with which we have established a strong direct correlation.

P677

Effect of late faecal loss of infliximab on treatment response of inflammatory bowel disease

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Background: Anti TNF drugs are being used commonly in treatment of severe or non-responding cases of inflammatory bowel disease. Hence there are still some patients who are non-responder to these drugs or they lose their response throughout the course of treatment. Recently it has been proposed that loss of these drugs to the colonic lumen through the inflamed bowel may be responsible for the lack of response in the first 2 weeks of therapy. We evaluate the association of serum and faecal level of Anti TNF in patient treatment response.
Methods: In this cohort study 28 patient were included during June 2016 to June 2017 at Imam Khomeini Hospital. Serum and faecal infliximab level were measured by enzyme-linked immunosorbent assay. The severity of Crohn's disease was assessed by Crohn's disease activity index (CDAI) and UC severity was determined by Montréal classification at initiation of therapy and then on Day 14 and Week 24 of therapy.
Results: There was significant difference between serum infliximab level on Day 14 and 96 in crohn's disease (p value: 0.03). But was not seen in ulcerative colitis patients (p value: 0.7).The mean serum infliximab level on Day 96 was 2.3 µg/ml and 5.2 µg/ml in non-responder and responder groups, respectively, and showed significant difference in both ulcerative colitis and Crohn's disease patients. The mean faecal infliximab level on Day 14 and 96 was 11 µg/ml and 5 µg/ml, respectively, and showed no significant difference between responder and non-responder groups. There was an insignificant

indirect relationship between serum and faecal infliximab level in UC patients (R = 0.401, p = 0.175) whereas this relationship was directly insignificant in crohn disease (R = –0.411, p = 0.239). There was a significant direct relationship between faecal infliximab level and CRP on Day 96 (R = 0.839, p = 0.002).

Conclusions: We showed that faecal infliximab level other than the first days of treatment does not affect the treatment response. Although it was shown that increased faecal infliximab on first days of treatment is related to loss of response in UC patients, our study did not find significant relation in faecal infliximab with response to treatment on Week 24 in both crohn's and UC patients, but our results were matched with previous studies to show the relation of response with serum infliximab level. Decreased level CRP was related to increased level of faecal infliximab just in crohn's patients. Our study revealed that late faecal ant TNF concentration will not affect the treatment response and may not be a good predictor of response. Further studies will be needed to evaluate this relationship.

P678

Treatment of moderate to severe UC patients with new 5ASA tablets

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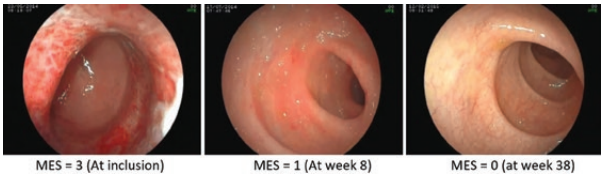
Background: In previous mesalazine trials, patients with mild-to-moderate UC disease were investigated. Mesalazine is not thought to be efficacious for severe patients. For the first time, we present the efficacy results of mesalazine in moderate to severe patients.

Methods: In the largest mesalazine induction trial, 737 patients (mean MAYO 7.7 at screening) completed an 8-week induction period with 3.2 g/day of mesalazine. 675 patients entered an open-label extension for a total of 38 weeks (including induction period). They were separated in 3 groups: remitters, responders and non-responders to 8 weeks of 3.2 g/day. They received, respectively, 1.6 g/day, 3.2 g/day, or 4.8 g/day, respectively, of mesalazine (a new 1600 mg tablet). For each patient, the site endoscopic scoring was reviewed by a central reader.

Results: During screening, of 675 patients who entered the OLE, 73.2% and 26.8% had an MES of 2 and 3, respectively. None of the patients had an MES of 0 or 1. 53.8% of the moderate to severe patients were in endoscopic remission after 38 weeks of treatment with 1600 mg mesalazine. Of 494 patients with moderate endoscopic activity, 57.7% were in endoscopic remission (MES ≤ 1) and 28.34% in total endoscopic remission (MES = 0) after 38 weeks. Of 181 patients with severe endoscopic activity, 43.1% achieved endoscopic remission (MES ≤ 1) and 14.9% total endoscopic remission (MES = 0) after 38 weeks. Picture 1 shows the endoscopic result of such a case. 64.2% and 14.5% of all patients in OLE had a moderate or severe partial mayo score, respectively.



Picture 1: Patient 34804001.

51% and 50% of moderate and severe patients, respectively, achieved clinical remission with a PMS score ≤ 1 at Week 38 of the study. 88.9% and 83.7% of moderate and severe patients, respectively, were in clinical remission or had only mild clinical activity at Week 38 of the study. TEAE were similar between the 1.6 g/day, 3.2 g/day and 4.8 g/day treatment groups (29.2%, 26.6% and 19.1%, respectively).

Conclusions: The new 1600 mg mesalazine tablet was effective in achieving endoscopic remission (MES≤1) in both moderate and severe UC. Our results show that corticosteroids, immunomodulator and biologics can be avoided in moderate and some severe UC patients by dose escalation or prolongation of high-dose mesalazine therapy.

P679

Development of a novel auto-injector of subcutaneous CT-P13 infliximab: Phase I randomised, open-label, single-dose trial to compare the pharmacokinetics and safety to pre-filled syringe in healthy subjects

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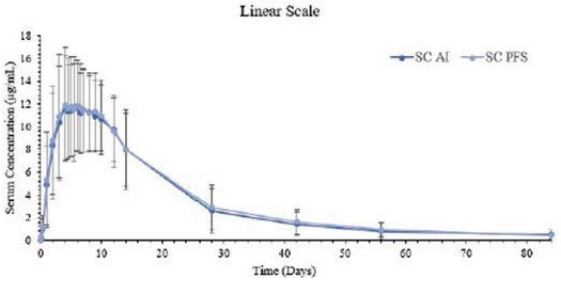
Background: Comparable efficacy and safety were suggested between new subcutaneous (SC) and intravenous formulation of CT-P13 both in patients with rheumatoid arthritis[1] and Crohn's disease.[2] As auto-injectors (AI) offer several advantages over pre-filled syringe (PFS) including simplified self-administration and reduced patient distress, CT-P13 SC AI is also being developed along with the CT-P13 SC PFS. This report is to demonstrate comparable pharmacokinetic (PK) and overall safety of CT-P13 SC administered by AI vs. PFS in healthy subjects.

Methods: Healthy subjects were enrolled and randomly assigned in a 1:1 ratio into one of the 2 arms (SC AI arm or SC PFS arm). In each arm, all subjects received a single dose of CT-P13 SC (120 mg) via AI or PFS on day 0, followed by 12 weeks during PK and safety were assessed. The primary endpoints were to demonstrate the bioequivalence of CT-P13 administration by AI vs. PFS defined by the confinement of the 90% CI of the geometric least squares means ratios of the primary PK parameters ($AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and C_{max}) within the equivalence margin of 0.80 to 1.25.

Results: A total of 218 subjects (109 subjects in each arm) were randomised, and 215 subjects received study drug on day 0. In the PFS Group 3 subjects received no dose. Bioequivalence was established (Table 1). Overall, mean (±SD) serum concentration of CT-P13 following a single SC dose using AI or PFS showed similar trend throughout the study period (Figure 1). Safety results for CT-P13 SC AI were also comparable to those for SC PFS (Table 2). There were two cases of road accidents reported as serious adverse events and both were considered as unrelated to the study drug by the investigator. The proportion of subjects experienced injection site reaction was lower in SC AI compared with SC PFS, and the mean of injection site pain was also found to be lower than PFS. (6.7 and 9.0 scores for SC AI and SC PFS, 0 means no pain, 100 means extreme pain.) Generally, the proportion of subjects with positive anti-drug antibody results was similar between the CT-P13 SC AI and CT-P13 SC PFS arms during the study.

PK Parameter (unit)	Geometric Least Squares Means		Ratio (90% CI)
	Test (SC AI)	Reference (SC PFS)	
$AUC_{0\text{-}inf}$ (hr*µg/mL)	5184.9 (n=84[1])	5406.5 (n=84[1])	0.96 (0.87, 1.06)
$AUC_{0\text{-}last}$ (hr*µg/mL)	3736.3 (n=109)	3855.2 (n=106)	0.97 (0.87, 1.09)
C_{max} (µg/mL)	11.22 (n=109)	11.42 (n=106)	0.98 (0.91, 1.07)

1. The value of $AUC_{0\text{-}inf}$ was excluded from the statistical analysis summary, if it did not meet one or more of the criteria: at least three PK concentration data points (excluding C_{max}), R-square greater than or equal to 0.8 or $\%AUC_{extrap}$ less than 20%.



Demographics				
		SC AI (N=109)	SC PFS (N=109)	Overall (N=218)
Age (years)	Median (range)	35.0 (18-55)	36.0 (18-55)	35.0 (18-55)
Gender, n(%)	Male	96 (88.1)	95 (87.2)	191 (87.6)
	Female	13 (11.9)	14 (12.8)	27 (12.4)
Body weight (kg)	Mean (SD)	78.11 (10.166)	77.19 (10.828)	77.65 (10.489)
Body Mass Index (kg/m²)	Mean (SD)	26.08 (2.628)	25.62 (2.581)	25.85 (2.609)
Summary of Safety and Immunogenicity Results, n(%)				
		SC AI (N=109)	SC PFS (N=106)	Overall (N=215)
Adverse events		55 (50.5)	54 (50.9)	109 (50.7)
Serious adverse events		2 (1.8)	0	2 (0.9)
Adverse events leading to discontinuation		0	0	0
Administration-related reaction		3 (2.8)	3 (2.8)	6 (2.8)
Injection site reaction		5 (4.6)	9 (8.5)	14 (6.5)
Infection		9 (8.3)	7 (6.6)	16 (7.4)
Infection prompting treatment		5 (4.6)	3 (2.8)	8 (3.7)
Ever ADA positive*		99/103 (96.1)	97/102 (95.1)	196/205 (95.6)
Ever NAb positive*		91/103 (88.3)	89/97 (91.8)	180/200 (90.0)

Abbreviation: ADA, anti-drug antibody; NAb, neutralizing antibody; SD, standard deviation.
*Proportion of subjects who reported at least one ADA/NAb positive after study drug administration in subjects who did not report any ADA/NAb positive before study drug administration and had at least one ADA/Nab result after study drug administration was calculated. Unscheduled visit results were excluded from analyses.

Conclusions: Equivalence of PK was demonstrated and comparable safety profiles were observed between healthy subjects treated with CT-P13 SC AI or PFS.

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Long-term efficacy of ustekinumab with and without concomitant immunosuppressants for Crohn's disease: results from IM-UNITI long-term extension through 2 years

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Background: Ustekinumab (UST) is a fully human immunoglobulin G1 kappa mAB to human IL 12/23p40 approved for the treatment of moderate to severe active Crohn's disease (CD). The continuing IM-UNITI long-term extension (LTE) evaluates the efficacy and safety of subcutaneous (SC) UST through approximately 5 years of treatment. Results through maintenance Week 44 previously demonstrated no apparent benefit of concomitant immunosuppressant (IMM) use on efficacy, drug levels or immunogenicity of UST.[1] Results through 2 years are reported herein.

Methods: 1281 patients entered the maintenance study, including 397 UST induction responders in the primary population (randomised to placebo (PBO) SC; *n* = 133, UST 90 mg SC q12w (q12w); *n* = 132, or UST 90 mg SC q8w (q8w); *n* = 132). A one-time dose adjustment to UST 90 mg SC q8w occurred in randomised patients who met loss of response (LOR) criteria between Weeks 8 and 32. All patients completing Week 44 were eligible to enter the LTE continuing the treatment they were on at Week 44. This analysis included the 82 patients on UST q8w from the primary population who did not meet LOR criteria for dose adjustment and entered the LTE. Clinical remission at each study visit, serum UST concentrations from maintenance Weeks 44 to 92, and immunogenicity were assessed in patients taking vs. not taking concomitant IMMs.

Results: Baseline use of concomitant IMMs in the randomised UST q8w LTE population was 35.4% (29/82). Patients who were not on IMMs at baseline (64.6%, 53/82), all remained off IMMs through Week 92. Rates of remission in the q8w group were not higher among patients with baseline IMM use and were similar through Week 92 (Table 1). Furthermore, concomitant use of immunomodulators did not appear to have any notable or consistent effect on serum UST concentrations or antidrug- antibody formation at any time point examined (Table 1).

	Continuous UST 90 mg q8w with IMM N=29	Continuous UST 90 mg q8w without IMM N=53	p-value
Clinical Remission[a], n (%)			
Week 44	24/29 (82.76%)	45/53 (84.91%)	0.80
Week 56	23/29 (79.31%)	44/53 (83.02%)	0.69
Week 68	23/29 (79.31%)	42/53 (75.25%)	0.99
Week 80	22/29 (75.86%)	46/53 (86.79%)	0.21
Week 92	21/29 (72.41%)	40/53 (75.47%)	0.76
Median Serum Concentration, µg/mL [IQR), [N]			
Week 44	5.32 (4.06, 7.26), [29]	6.44 (4.32, 9.14), [53]	N/A
Week 56[b]	2.06 (1.33, 3.29), [26]	2.51 (1.60, 3.48), [51]	N/A
Week 68	5.81 (5.09, 8.73), [21]	6.49 (4.24, 8.36), [39]	N/A
Week 80[b]	2.38(1.30, 3.99), [24]	2.33 (1.22, 3.60), [47]	N/A
Week 92	6.94 (4.62, 7.55), [18]	6.19 (4.23, 8.86), [27]	N/A
Incidence of antidrug antibodies at any timepoint between Weeks 0 and 96	1/29 (3.4%)	2/53 (3.8%)	N/A

IQR: Interquartile range; N/A: Not Applicable
[a] Patients who had insufficient data at the designated analysis time point are considered not to be in clinical remission or response; [b] Trough value

Table 1. Clinical remission and serum concentration through Week 92 based on IMM use at induction baseline: randomised patients who entered LTE in IM-UNITI.

Conclusions: Data through 2 years of UST treatment (90 mg q8w maintenance) in the IM-UNITI LTE study suggest that concurrent use of immunomodulators does not increase remission efficacy. Further supporting the notion that concomitant use of IMM with UST is not necessary, no effect on serum UST concentrations or antidrug antibodies was seen across all time points, in contrast to findings with other biologic agents.

Reference

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Ustekinumab therapy induced clinically meaningful improvement and remission as measured by the Inflammatory Bowel Disease Questionnaire: Results from the phase 3 UNIFI induction and maintenance studies

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Background: The UNIFI studies evaluated the safety and efficacy of ustekinumab (UST) intravenous (IV) induction and subcutaneous (SC) maintenance in patients with moderately to severely active ulcerative colitis (UC). Here, we present patient-reported outcomes from the Inflammatory Bowel Disease Questionnaire (IBDQ).

Methods: In the induction study, eligible patients were randomised to a single IV dose of placebo (PBO, n = 319), UST 130 mg (n = 320), or UST ~6 mg/kg (n = 322). Patients who were in clinical response 8 weeks after receiving UST induction were eligible for the maintenance study and were randomised to SC PBO (n = 175), UST 90 mg q12w (n = 172), or UST 90 mg q8w (n = 176). The IBDQ is a 32-item questionnaire with 4 dimensions: bowel symptoms, systemic symptoms, emotional function, and social function. The total score ranges from 32 to 224, higher scores indicate better quality of life, a score ≥170 indicates remission, and a change ≥16 or >20 points was defined as clinically meaningful.

Results: Mean total IBDQ scores at induction baseline ranged from 126.0 to 127.4 and were comparable across treatment groups (Table 1).

Outcome	Placebo IV	Ustekinumab IV 130 mg	Ustekinumab IV ~6 mg/kg[a]
Primary efficacy analysis set, n	319	320	322
Induction baseline score, mean (standard deviation)	127.4 (34.45)	126.0 (33.14)	127.0 (33.27)
Change from baseline to Week 8, mean (standard deviation)	16.1 (31.39)	33.4 (32.53)	35.0 (31.86)
p-value		<0.001	<0.001
Patients with improvement from baseline to Week 8, n (%)			
Achieved ≥16-point improvement	141 (44.2%)	213 (66.6%)	221 (68.6%)
p-value		<0.001	<0.001
Achieved >20-point improvement	118 (37.0%)	196 (61.3%)	200 (62.1%)
p-value		<0.001	<0.001
Achieved IBDQ remission (≥170)	101 (31.7%)	141 (44.2%)	150 (46.6%)
p-value		<0.001	<0.001

[a]Weight range-based ustekinumab doses approximating 6 mg/kg: 260 mg (weight ≤ 55 kg), 390 mg (weight > 55 kg and ≤ 85 kg), 520 mg (weight > 85 kg).

Table 1. Total Inflammatory Bowel Disease Questionnaire (IBDQ) scores through Week 8 in patients who received IV induction treatment with ustekinumab or placebo.

Eight weeks after IV induction, patients receiving UST reported significantly greater improvement in mean IBDQ scores, and greater proportions of patients achieved clinically meaningful improvements from baseline and IBDQ remission compared with PBO (p < 0.001 for all comparisons of UST vs. PBO). Through 44 weeks of the maintenance study, mean IBDQ scores worsened in the PBO group, were maintained in the UST q12w group, and improved in the UST q8w group (Table 2, p < 0.001).

IBDQ Outcome	Placebo SC[a]	Ustekinumab SC 90 mg q12w	Ustekinumab SC 90 mg q8w
Primary efficacy analysis set, n	175	172	176
Maintenance baseline score, mean (standard deviation [SD])	174.3 (29.15)	175.4 (29.75)	174.1 (26.76)
Change from maintenance baseline to Week 44, mean (SD)	-15.1 (35.43)	-3.0 (32.89)	3.9 (31.54)
p-value		<0.001	<0.001
Improvement from induction baseline to Week 44, n (%)			
Achieved ≥16-point improvement	83 (47.4%)	118 (68.6%)	129 (73.3%)
p-value		<0.001	<0.001
Achieved >20-point improvement	75 (42.9%)	114 (66.3%)	123 (69.9%)
p-value		<0.001	<0.001
Maintained improvement through Week 44,[b] n (%)			
Maintained ≥16-point improvement	70 (51.9%)	102 (66.7%)	112 (74.2%)
p-value		0.008	<0.001
Maintained >20-point improvement	64 (49.6%)	95 (66.0%)	102 (71.3%)
p-value		0.004	<0.001
Remission at Week 44, n (%)			
Remission: ≥170 points	72 (41.1%)	97 (56.4%)	111 (63.1%)
p-value		0.004	<0.001
Remission through Week 44,[c] n (%)			
Maintained remission: ≥170 points	53 (49.5%)	75 (68.8%)	68 (66.0%)
p-value		0.002	0.019

[a]Patients who responded to ustekinumab IV induction dosing and were randomly assigned to placebo SC upon entry into the maintenance study.
[b]Includes patients who maintained improvement from induction baseline at both maintenance Weeks 20 and 44 among patients with that level of improvement at maintenance baseline.
[c]Includes patients who maintained remission from maintenance baseline at both maintenance Weeks 20 and 44 among patients in remission at maintenance baseline.

Table 2: Total Inflammatory Bowel Disease Questionnaire (IBDQ) scores through Week 44 in patients who received SC maintenance treatment with ustekinumab or placebo

Significantly greater percentages of patients in the UST groups achieved or maintained clinically meaningful improvement (p < 0.01) or IBDQ remission (p < 0.02) through Week 44 compared with PBO. Patients receiving UST induction showed greater improvement in each of four domain scores of the IBDQ at Week 8 compared with PBO, and the improvements were sustained through 44 weeks of maintenance.

Conclusions: Patients reported significantly greater improvements in IBDQ scores with UST IV induction compared with PBO. In patients who responded to UST IV induction, significantly greater proportions of patients who received UST SC maintenance sustained the improvements achieved during induction through Week 44, including remission, compared with PBO.

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GO-CARE: a prospective multi-centre observational study of golimumab effectiveness and quality of life in a real life UC patient population in Italy.

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Background: The ultimate treatment target in UC must be the restoration of patient (PT) quality of life (QoL).[1] Aim of the study is to identify predictors of improvement QoL measured by Inflammatory Bowel Disease Questionnaire (IBDQ) after 8 and 56 weeks of treatment with Golimumab (GLM) and to investigate other effectiveness outcomes in a real life setting

Methods: Responders to GLM induction therapy (by PMS) were enrolled 8 weeks after the start of GLM (wk8) and clinical-demographic data, present at start of GLM (baseline), were collected retrospectively. Predictors of IBDQ increase considered were: age, gender, weight, height, BMI, smoking status, comorbidities, disease duration/localisation, concurrent/previous therapy, CS dependence, FMS, PMS, endoscopic score, CRP and ESR. An interim analysis was conducted to evaluate (primary endpoint) predictors of IBDQ increase (≥16 points), achieved at wk8 and wk56 compared with baseline. Mean change in IBDQ at wk8, 32 and 56, clinical response (PMS decrease ≥2 points or ≥30% and decrease ≥1 point in rectal bleeding) and clinical remission (PMS ≤2 with no sub-score >1) at wk8, 32 and 56 [also per FMS] were also assessed (secondary endpoints).

Results: 110 patients were enrolled. At baseline: mean age was 43years(69 males), mean disease duration was 9.5years,77.3% of patients were steroid-dependent, 48.2% had pancolitis and 46.4% left-sided colitis. 80.9% of patients had moderate disease activity (median PMS 6) and 72.7% had a moderate endoscopic score (Mayo = 2), 20%, 12.7% and 77.3% of patients were treated with Corticosteroids, AZA, oral 5-ASA, mean IBDQ was 137. 27.3% of patients were anti-TNF experienced. By univariate analysis oral 5-ASA and higher disease activity (by PMS and FMS) were identified as predictors of QoL improvement at wk8 and wk32 respectively. From baseline(N = 110) to wk8 (n = 110), 32 (n = 67) and 56 (n = 44): a significant increase of mean IBDQ($p < 0.05$) (137, 170, 172, 178) and a significant reduction of median PMS($p < 0.0001$) (6, 1, 0, 0) were observed. Median FMS significantly decreased from baseline (N = 110) to wk56 (N = 44) ($p < 0.001$). Twenty-six and 12pts discontinued treatment before wk32 and wk56 respectively. At wk32: 59/93(63%) and 58/93(62%) were in sustained clinical response and remission. At wk56: sustained clinical response was observed in 44/82(53.3%) and 30/82(36.5%) and remission in 38/82(46.3%) and 23/82(28.0%) by PMS and FMS, respectively.

Conclusions: This interim analysis of GO-CARE study identified the concomitant therapy with oral 5-ASA and higher disease activity as predictors of significant improvement of QoL. The analysis confirms the effectiveness of GLM in a real life setting with sustained response and remission, and improvement of QoL.

Reference

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Higher serum golimumab concentrations are significantly associated with combined clinical-biochemical remission during maintenance therapy: results from the GO-LEVEL study

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Background: The exposure–response relationship associated with the use of golimumab for UC has been previously demonstrated in the PURSUIT trials. A significant association between serum golimumab concentrations (SGC) and favourable outcomes were observed during both induction and maintenance therapy.

Methods: GO-LEVEL was an open-label, phase IV study (NCT03124121) which included a prospective cohort commencing induction therapy as well as a cross-sectional cohort of patients receiving maintenance treatment (defined as a minimum of 18 weeks from initiation). Here we report the results of the maintenance study. Patients receiving maintenance therapy were recruited either at the point of flare, or during stable remission. Clinical disease activity was evaluated using SCCAI and PRO2, biochemical activity using faecal calprotectin (FC) and CRP and QoL using the IBD-Control questionnaire. Clinical remission was defined as SCCAI < 3. Combined clinical-biochemical remission was defined as SCCAI < 3 as well as FC < 250 μg/g. SGC and anti-golimumab antibodies (AGA), measured using a drug-sensitive ELISA (LISA-TRACKER, Theradiag). Samples were collected within 7 days of the subsequent administration. Fishers Exact or Mann–Whitney U were used to compare groups and ROC analysis to identify therapeutic threshold.

Results: In total, 49 patients on maintenance treatment were recruited; 31 in clinical remission and 18 at the point of flare. There was no significant difference in median SGC between the two groups (2.7 vs. 2.1 μg/ml, respectively, p = 0.27). Of the 46 patients with FC data available, 24 were in combined remission, 22 were not. The median SGC of those in combined remission was significantly higher than those who were not (3.0 vs. 2.0 μg/ml, respectively, p = 0.031). Univariate analysis comparing groups can be seen in Table 1. No AGA were detected.

Characteristic	Combined clinical-biochemical remission (n=24)	Not in combined clinical-biochemical remission (n=22)	*p*
Gender, male:female	18:6	9:13	**0.035**
Median age, years	33	36	0.75
Concomitant immunomodulator	18 (75%)	17 (77%)	>0.99
Prior anti-TNF experience, exposed:naïve	0 (0%)	2 (9%)	0.22
Maintenance dose, 50mg:100mg	12:12	10:12	0.78
Median body mass index	23.5	25.0	0.37
Disease activity			
Median SCCAI	0	5	**<0.0001**
Median PRO2	0	2.5	**<0.0001**
Median Calprotectin (ug/g)	17	419	**<0.0001**
Median CRP (mg/L)	1	1	0.17
Median Albumin (g/L)	47	46	**0.042**
Quality of life			
Median IBD-Control-8	16	6	**<0.0001**
Median IBD-Control-Visual Analogue Scale	92	49	**<0.0001**
Golimumab Measurement			
Median Serum Golimumab Concentration (ug/ml)	3.0	2.0	**0.031**

Univariate analysis of comparing characteristics, disease activity evaluations, quality of life and golimumab levels of patients in combined clinical-biochemical remission with those who were not.

ROC curve analysis demonstrates 2.1 μg/ml as the optimal therapeutic threshold for combined remission (sens 0.75, spec 0.59, AUC 0.69).

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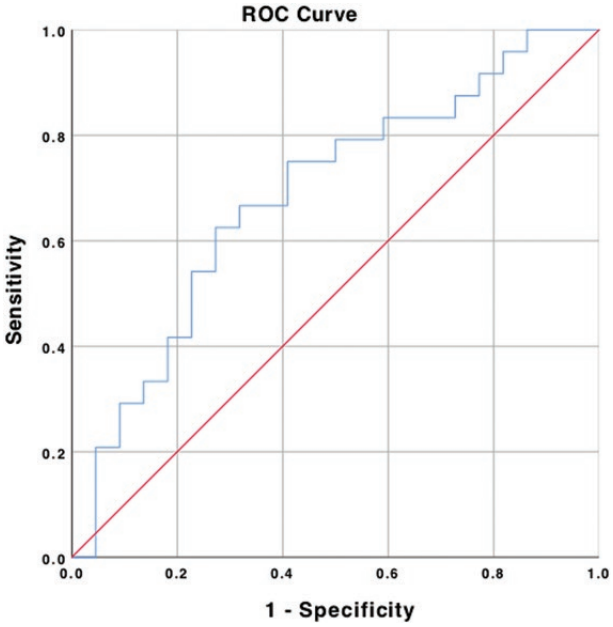

ROC curve analysis of optimal SGC thresholds associated with combined clinical-biochemical remission.

Conclusions: The GO-LEVEL maintenance cohort offers further evidence of the exposure–response relationship with golimumab, particularly when using a combined definition of remission that includes an objective marker of disease activity (FC). Clinicians may consider using therapeutic drug monitoring to optimise golimumab dosing aiming to achieve our suggested therapeutic threshold of 2.1 µg/ml.

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Vaccination strategies for IBD patients

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Background: Several vaccinations are strongly recommended patients with inflammatory bowel disease (IBD), especially in those on immunosuppressive therapy or in elderly IBD patients. Unfortunately, adherence to vaccination programmes is poor. The aim of the present study was to test different strategies with regard to adherence.

Methods: we identified among our outpatients with IBD those with indication for vaccination for seasonal influenza and pneumococcus vaccination, that is, patients on immunomodulator or biotecnologic therapies, patients aged ≥65 years, and those with both indications. At start, in autumn 2016, all these patients were verbally informed during their outpatient visits, on the opportunity to follow recommendation for influenza vaccination. In the following year, autumn 2017, all patients were invited to adhere to vaccination by letter addressed to their primary care physician. At the end of the vaccination campaign (January 2018), all patients were interviewed (during visits or by telephone interview) to assess adherence to vaccination; in case of negative reply, the reasons for non-vaccination were investigated. Finally, a third strategy was employed for vaccination against pneumonia (Prevenar®). In this setting, the patients were informed and directly vaccinated in our outpatient unit in collaboration with the Vaccination Centre of our hospital.

Results: Among the 1432 patients followed in our centre, indication for vaccination programmes were given in 341 patients on immunosuppressive therapy, in 100 elderly patients, and 60 patients with both indications. Adherence to verbal invitation for influenza vaccination was very low reaching only 19.6%, whereas written recommendation directed to primary care physicians did increase vaccination coverage reaching 51.7%. Reasons for non-vaccinating were safety concerns in 65.5%, scepticism about efficacy in 22.3%, forgetfulness in 11.2%, and in 1% vaccination was discouraged by their primary care physicians. Finally, the direct proactive strategy vaccinating patients directly in our Unit yielded an 89.67% adherence to pneumococcus vaccination.

Conclusions: Vaccination programmes based on patients' collaboration or collaboration by their primary care physicians yielded poor adhesion not exceeding 51.7% %. A proactive approach, providing directly the vaccination during outpatients visits reached a considerable success rate and should be offered in IBD centres. Training programmes for primary care physicians may be useful to increase territory-based adherence to vaccination programmes.

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Improvement in patient-reported Inflammatory Bowel Disease Questionnaire outcomes, and relationship with disease activity, in tofacitinib-treated patients with ulcerative colitis: Data from the OCTAVE clinical trials

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Background: Tofacitinib is an oral, small-molecule JAK inhibitor approved in several countries for the treatment of ulcerative colitis (UC). We assessed relationships between patient (pt)-reported Inflammatory Bowel Disease Questionnaire (IBDQ) outcomes and Mayo score (a widely used measure of clinical activity) in tofacitinib UC induction and maintenance studies.

Methods: We analysed patients from two randomised, placebo-controlled, 8-week tofacitinib induction studies (OCTAVE Induction 1 and 2, NCT01465763 and NCT01458951) and a 52-week, randomised, placebo-controlled maintenance study (OCTAVE Sustain, NCT01458574). We evaluated IBDQ remission (total score ≥190) and response (≥30-point increase from baseline) at Week 8 (induction) and Weeks 24 and 52 (maintenance). These criteria are more stringent vs. previously reported IBDQ remission (total score ≥170) and response (≥16-point increase from baseline) thresholds. We evaluated relationships between IBDQ total scores and total Mayo scores at baseline and Week 8 (induction) and Weeks 24 and 52 (maintenance) using Spearman correlation.

Results: In OCTAVE Induction 1 and 2, mean baseline IBDQ total score of each treatment ranged from 117.5 to 124.9. Statistically significant effects of treatment with tofacitinib 10 mg twice daily (BID) vs. placebo were observed at Week 8 for IBDQ remission ($p < 0.05$) and response ($p < 0.0001$) (Table 1). In OCTAVE Sustain, mean baseline IBDQ total score of each treatment ranged from 181.3 to 182.3. There were statistically significant maintenance treatment effects with 5 and 10 mg BID vs. placebo for IBDQ remission and response at Weeks 24 and 52 (all $p < 0.0001$; Table 2). Spearman correlation coefficients between IBDQ total score and total Mayo score in OCTAVE Induction 1 and 2 at Week 8 were –0.67 and –0.59, respectively. In OCTAVE Sustain, correlation coefficients were –0.57 at Week 24 and –0.40 at Week 52.

Conclusions: For patients with moderate to severe UC, induction and maintenance therapy with tofacitinib resulted in statistically significant improvements in patient-reported quality of life vs. placebo, as measured using comparatively stringent IBDQ criteria. Moderate correlations between IBDQ and Mayo scores were observed from Week 8 in OCTAVE Induction to Week 52 in OCTAVE Sustain.

	OCTAVE Induction 1			OCTAVE Induction 2		
	Placebo (N=122)	Tofacitinib 10 mg BID (N=476)	Difference (95% CI)	Placebo (N=112)	Tofacitinib 10 mg BID (N=429)	Difference (95% CI)
IBDQ total score ≥190, n (%)	25 (20.5)	156 (32.8)	12.3 (4.0, 20.6)*	20 (17.9)	129 (30.1)	12.2 (3.9, 20.5)*
≥30-point increase from baseline in IBDQ total score, n (%)	42 (34.4)	281 (59.0)	24.6 (15.1, 34.1)***	45 (40.2)	262 (61.1)	20.9 (10.7, 31.1)***
Correlation between IBDQ total score and total Mayo score, Spearman correlation coefficient						
Baseline	-0.26 (N1=593)			-0.29 (N1=538)		
Week 8	-0.67 (N1=564)			-0.59 (N1=495)		

IBDQ binary endpoint data are for the full analysis set with non-responder imputation. Spearman correlation coefficient data are for the full analysis set, based on central read endoscopy.
*p<0.05; ***p<0.0001 vs placebo; treatment effect for the IBDQ efficacy endpoints was assessed using Cochran-Mantel-Haenszel chi-square test stratified by prior treatment with tumor necrosis factor inhibitors, baseline corticosteroid use, and geographic region; 95% CI based on the normal approximation for the difference in binomial proportions
BID, twice daily; CI; confidence interval; IBDQ, Inflammatory Bowel Disease Questionnaire;
N, number of patients in treatment group; N1, number of patients with non-missing IBDQ and total Mayo score; n, number of patients with response in specified category

	OCTAVE Sustain				
	Placebo (N=198)	Tofacitinib 5 mg BID (N=198)	Difference (95% CI)	Tofacitinib 10 mg BID (N=197)	Difference (95% CI)
IBDQ total score ≥190, n (%)					
Week 24	37 (18.7)	94 (47.5)	28.8 (20.0, 37.6)***	94 (47.7)	29.0 (20.2, 37.9)***
Week 52	26 (13.1)	76 (38.4)	25.3 (17.0, 33.5)***	87 (44.2)	31.0 (22.7, 39.4)***
≥30-point increase from induction baseline in IBDQ total score, n (%)					
Week 24	61 (30.8)	115 (58.1)	27.3 (17.9, 36.7)***	132 (67.0)	36.2 (27.0, 45.4)***
Week 52	38 (19.2)	98 (49.5)	30.3 (21.4, 39.2)***	110 (55.8)	36.6 (27.8, 45.5)***
Correlation between IBDQ total score and total Mayo score, Spearman correlation coefficient					
Week 24	-0.57 (N1=391)				
Week 52	-0.40 (N1=291)				

IBDQ binary endpoint data are for the full analysis set with non-responder imputation. Spearman correlation coefficient data are for the full analysis set, based on central read endoscopy.
***p<0.0001 vs placebo; treatment effect for the IBDQ efficacy endpoints were assessed using Cochran-Mantel-Haenszel chi-square test stratified by treatment assignment in the induction study and remission status at baseline of OCTAVE Sustain; 95% CI based on the normal approximation for the difference in binomial proportions
BID, twice daily; CI; confidence interval; IBDQ, Inflammatory Bowel Disease Questionnaire;
N, number of patients in treatment group; N1, number of patients with non-missing IBDQ and total Mayo score; n, number of patients with response in specified category

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Neither high infliximab maintenance doses nor high trough levels trigger skin side effects of the drug: a prospective cross-sectional study

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Background: Skin lesions induced by infliximab are an important side effect and lead to drug discontinuation in many cases. It is not known whether these lesions occur more often with high-dose treatment or high drug concentrations that are needed to induce and maintain remission of IBD in some patients. We thus investigated whether high-dose infliximab treatment or high trough levels increase the incidence of skin lesions.

Methods: This was a prospective observational cross-sectional study of all patients with IBD on infliximab maintenance treatment at a tertiary referral centre. Every patient's skin was examined by an experienced gastroenterologist and those with skin lesions were referred to a dermatologist for further evaluation. Furthermore, infliximab trough levels were measured and the dose of infliximab recorded in all patients. High-dose infliximab was defined as a maintenance dose of ≥10 mg/kg q 8 weeks and high trough levels as ≥7 µg/ml.

Results: In total, we included 171 patients (103 CD, 63 UC, 5 IBD-unclassified). Skin lesions were observed in 40/171 (23%) patients (8 psoriatic, 7 psoriasiform eczema, 11 eczema, 4 xerosis, 10 others). Among patients on high-dose infliximab the incidence of skin lesions was not higher than in those with lower dose (9/53 [17%] vs. 31/118 [26%], $p = 0.184$). Similar was observed for patients with high vs. low trough levels (22/102 [22%] vs. 18/69 [26%], $p = 0.493$). Moreover, the median dose of administered infliximab was not different in patients with skin lesions compared with those without them (7.45 mg/kg q 8 weeks [IQR (interquartile range): 5.71–9.91] vs. 7.85 mg/kg q 8 weeks [IQR: 5.88-10.98], $p = 0.741$); the same was observed for median trough levels (7.46 µg/ml [IQR: 4.44–9.69] vs. 8.60 µg/ml [IQR: 5.48-12.00], $p = 0.389$). Finally, no differences were observed for specific skin lesions (Figures 1&2).

Median maintenance dose of infliximab by specific skin lesion

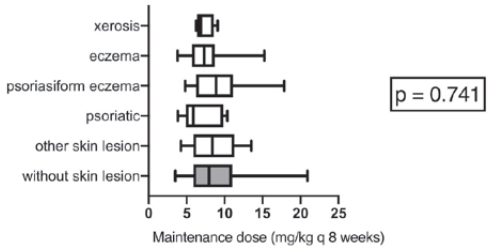

Figure 1.

Median infliximab trough level by specific skin lesion

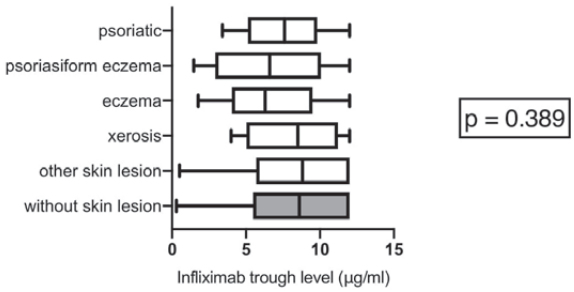

Figure 2.

Conclusions: In this prospective study, high-dose infliximab treatment or high infliximab trough levels were not associated with the occurrence of drug-induced skin lesions. This is a clinically important observation that enables the use of high-dose infliximab maintenance and targeting high trough levels when needed.

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Clinical remission demonstrated with oral ozanimod in the overall population and across multiple subgroups of patients with moderately to severely active ulcerative colitis in the TOUCHSTONE trial

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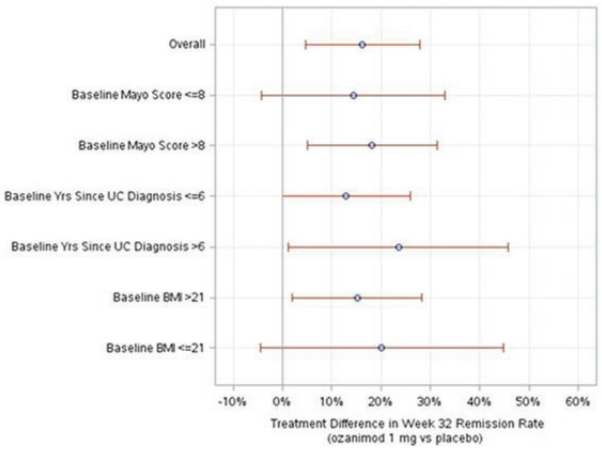
Background: Ozanimod is an oral immunomodulator that selectively targets $S1P_1$ and $S1P_5$. TOUCHSTONE, a randomised, double-blind, placebo-controlled phase 2 trial that evaluated patients with moderately to severely active ulcerative colitis (UC) showed significantly higher rates of clinical remission, clinical response, and endoscopic mucosal healing (Mayo endoscopic subscale score of 0/1) at Weeks 8 and 32 in patients assigned to ozanimod 1 mg compared with those who received placebo (Sandborn et al., *NEJM*, 2016).[1] Clinical remission at Week 32 also was assessed across subgroups of interest.
Methods: Patients were randomised 1:1:1 and received ozanimod 1 mg, ozanimod 0.5 mg, or placebo. Mayo score, based on stool frequency, rectal bleeding, mucosal appearance at endoscopy, and physician rating of disease activity was calculated at baseline, end of induction (Week 8), and end of maintenance (Week 32). Clinical remission was defined as total Mayo score ≤2, with no subscore >1. A post hoc sub-group analysis evaluated clinical remission rates at Week 32 according to baseline Mayo score, years since UC diagnosis, and body mass index (BMI).
Results: A total of 197 patients were randomised to ozanimod 1 mg (n = 67), 0.5 mg (n = 65), or placebo (n = 65), with 103 (52.3%) entering a maintenance period based on response criteria and 91 (88.3%) completing the study. Differences in the proportion of patients in clinical remission with ozanimod 1 mg vs. placebo by subgroup illustrate that the treatment effect favoured ozanimod 1 mg in every subgroup analysed (see Figure 1).



Forest plot of clinical remission at Week 32 in the overall population and by subgroup (ITT population, non-responder imputation) – RPC1063 1 mg vs. placebo.
The 95% confidence intervals for the treatment difference between ozanimod 1 mg and placebo exclude 0 for the overall population and subgroups of baseline Mayo score >8, years since UC diagnosis >6, and BMI >21.
Conclusions: In the TOUCHSTONE trial, ozanimod therapy was consistently more efficacious than placebo for induction of clinical remission across a wide range of patient subtypes including those with relatively long disease duration and high disease activity.

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P688

Ustekinumab in resistant Crohn's disease: 1-year UK IBD tertiary referral centre 'real-world' experience

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Background: Ustekinumab (UST) binds to the p40 subunit of IL12 and IL23 to prevent IL12RB1 cell-surface receptor activation thus inhibiting downstream inflammatory signalling and cytokine production. In the UK, it is approved for moderately to severely active Crohn's disease (CD). We assessed the efficacy and safety of UST in a 'real-world' cohort of refractory CD patients treated at a single UK centre over the course of 1 year.
Methods: We retrospectively collected data from the electronic records of CD patients treated with UST at a single UK IBD tertiary referral centre. Patient demographics and adverse events were recorded. Clinical response to UST was evaluated at baseline and follow-up using Harvey–Bradshaw Index (HBI) scores, C reactive protein (CRP), and faecal calprotectin (FC). Paired Student's T-tests were used to determine statistical significance.
Results: 46 patients with CD (mean age at UST commencement 36 years; range 18–73 years; M:F ratio 1:1.2) with mean CD duration at UST commencement of 9 years (range 1–20 years) were treated with UST. CD location was ileal in 10 patients (22%), colonic in 11 patients (24%) and ileo-colonic in 25 patients (54%). 1 patient (2%) also had upper gastrointestinal CD involvement. CD behaviour was penetrating in 8 patients (17%), stricturing in 18 patients (39%) and non-penetrating, non-stricturing in 20 patients (44%). All patients had failed at least one anti-TNF agent. 19 patients (41%) had failed two anti-TNF agents and 16 patients (35%) had failed two anti-TNF agents and vedolizumab. Fourteen patients (30%) received concomitant immunomodulator therapy and 14 patients (30%) received bridging steroids. Data were available for 38 patients at 3 months and 17 patients at 12 months of UST treatment. Mean HBI significantly improved by both month 3 (9 vs. 4; $p < 0.001$) and 1 year (8 vs. 3; $p < 0.001$). Mean FC also significantly improved by both month 3 (1532 vs. 583; $p < 0.001$) and 1 year (1252 vs. 324; $p = 0.0016$). There was no statistically significant change in mean CRP by month 3 (16 vs. 9; ns) or 1 year (11 vs. 8; ns). Three/38 (8%) patients discontinued due to primary non-response and 2/38 (5%) patients discontinued due to secondary loss of response. A transitional cell carcinoma recurrence was detected in 1 patient while on treatment. A further patient developed a facial palsy.

Conclusions: UST appears clinically effective and safe in this cohort of treatment-refractory CD patients after 1 year of therapy. Future work to combine 'real-world' data and to assess longer term outcomes will help us to better understand when and how to use UST in the management of CD.

P689

The effect of nutritional therapy on bone mineral density and bone metabolism in paediatric Crohn's disease

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Background: Childhood is a critical time for accrual of bone density, which peaks at age 18–20 years. Both the inflammatory burden of CD and corticosteroid therapy have a negative effect on bone density, hence exclusive enteral nutrition (EEN) is the preferred treatment option to induce remission. We aimed to explore the effect of nutritional therapy on bone health in paediatric CD.

Methods: This was a planned sub-study of a randomised controlled trial of children with mild-to-moderate CD who were randomised to receive either 6 weeks of EEN followed by 6 weeks of 25% PEN with free diet or 6 weeks of 50% partial enteral nutrition (PEN) with a Crohn's disease exclusion diet (CDED) followed by 6 weeks of 25% PEN+CDED. For the aim of this ancillary study, we measured bone mineral density (BMD) by DXA scan at baseline and Week 24 (total body less head adjusted for age and height). In addition, bone formation was measured at baseline, Week 12 and Week 24, by the serum biomarker C-Propeptide of Type I Procollagen (CICP) and bone resorption was measured by serum Type I Collagen N-Telopeptide (NTX).

Results: Repeated BMD was completed for 23 children and showed BMD < -1 SD in 17 (74%) and BMD < –2 in 7 (30%) at baseline. DXA results did not improve at Week 24 (BMD -1.52 ± 0.72 at baseline vs. –1.65 ± 0.81 at Week 24; $p = 0.36$). The change was also not significant in analysis of the individual treatment arms. In the subset of patients who achieved remission at Week 12, DXA scores did not worsen but did not improve either (median change of –0.01, IQR 0.17--0.26); compared with patients not in remission, the difference was not significant. Serial biomarkers were available for 29 children. Median CICP improved from 130 ng/ml (IQR 3–1 189-106)) at baseline to 223 (258-143)) at Week 12 and 189 (227–145) at Week 24 ($p = 0.016$ for both). Median NTX remained unchanged, from 36 nmol bone collagen equivalents/l (IQR 58–30) at baseline to 50 (66–28) at Week 12 ($p = 0.45$) and 37 (66–24) at Week 24 ($p = 0.37$). Analysis of individual treatment arms was not possible for the bone biomarkers due to small sample size.

Conclusions: BMD did not improve in children with active CD treated with nutrition. However, CICP, a much more responsive and sensitive marker of bone formation increased significantly, raising the possibility that bone improvement is slow and should be further examined in longer-term studies.

P690

Comparative efficacy of vedolizumab and adalimumab as second-line therapy in ulcerative colitis patients previously treated with infliximab

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Background: Adalimumab (ADA) and Vedolizumab (VDZ) have shown efficacy in moderate to severe ulcerative colitis (UC) patients who failed Infliximab (IFX). Though, a comparative efficacy evaluation of ADA and VDZ in this clinical setting is currently missing.

Aim: to compare the efficacy of ADA and VDZ in patients affected by UC who failed the first-line therapy with IFX.

Methods: Clinical records of UC patients from 8 Italian IBD referral centres, who failed IFX given for active luminal disease and candidate to receive a second-line biologic with either ADA or VDZ were retrospectively reviewed. Clinical variables, including reason for IFX discontinuation, clinical activity and therapy duration were recorded. The proportion of patients still on therapy at Week 52 was evaluated as primary endpoint. The failure-free survival was analysed by univariate and multi-variate analysis. Secondary endpoints included therapy discontinuation at Week 8, 24 and 52, discontinuation-free survival and safety.

Results: Of 161 UC patients (15 [9%] primary, 87 [52%] secondary failures to IFX and 63 [39%] IFX intolerants), 64 (40%) received ADA and 97 (60%) VDZ as second-line therapy. At Week 52, 37.5% and 28.9% of patients on ADA and VDZ, respectively, showed therapeutic failure ($p = 0.302$). However, the failure rate was significantly higher in the ADA- when compared with VDZ group among IFX secondary failures (48.0% ADA vs. 22.4% VDZ, $p = 0.035$). The therapy discontinuation-free survival was significantly higher in the group of IFX secondary failures who received VDZ when compared with ADA at both the univariate ($p = 0.007$) and multi-variate survival analysis (OR 2.6; 95% CI 1.11–5.98; $p = 0.028$). No differences in the failure and biologic discontinuation-free survival was observed in the IFX primary failure and intolerant subgroups.

Conclusions: VDZ might be the therapy of choice in those UC patients who showed secondary failure to IFX.

P691

Trends in diagnostic prevalence and treatment patterns of adult ulcerative colitis patients in the USA, 2007–2017

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Background: There has been much variation between epidemiological studies that report the prevalence of ulcerative colitis (UC). This study aimed to analyse the diagnostic annual prevalence rates and treatment patterns of UC patients in the USA (U.S) adult insured population from 2007 to 2017.

Methods: Trends in UC prevalence were calculated for the 11-year period covering January 1, 2007 to December 31, 2017. Adult (18+ years old) UC patients were included in this retrospective analysis of medical and pharmacy claims data from the IBM Marketscan Commercial, Medicaid and Medicare-Supplemental Claims database. Prevalence was determined as having ≥1 UC diagnostic codes (ICD-9: 556.x; ICD-10:K51.x) within the calendar year. Patients with a Crohn's disease diagnosis (ICD9: 555.x; ICD-10: K50.x) were excluded. Prevalence rates in the database were determined and age- and gender-adjusted rates were projected to the U.S. population in 2017. Trends in treatment patterns were also analysed.

Results: The UC adult prevalence increased from 0.25% to 0.39% from 2007 to 2017. The mean age between 2007 and 2017 ranged from 41.75–49.31 years. Consistently throughout the years, approximately half of the UC patients were male. Rates of use of biologics and corticosteroids increased, while rates of 5-ASA and opioids decreased. Immunomodulators remained stable (Figure 1).

Variable	N=58,367
Gender	
Male	27,368 (46.9%)
Female	30,999 (53.1%)
Mean Age (SD)	50.20 (15.20)
18-24 years old	3,702 (6.3%)
25-34 years old	6,431 (11.0%)
35-44 years old	9,589 (16.4%)
45-54 years old	14,270 (24.4%)
55-64 years old	16,097 (27.6%)
65+ years old	8,278 (14.2%)
Insurance	
Commercial	49,884 (85.5%)
Medicare	8,483 (14.5%)
Geographic Region	
Northeast	13,210 (22.6%)
North Central	13,528 (23.2%)
South	24,062 (41.2%)
West	7,442 (12.8%)
Unknown	125 (0.2%)
Comorbid Conditions	
Type 1 Diabetes	802 (1.4%)
Type 2 Diabetes	7,573 (13.0%)
Psoriasis	1,103 (1.9%)
Ankylosing Spondylitis	352 (0.6%)
Psoriatic Arthritis	295 (0.5%)
Uveitis	263 (0.5%)
Anthropathy	305 (0.5%)
Medications	
Biologics	7,320 (12.5%)
Immunomodulators	6,053 (10.4%)
5-ASA	29,171 (50.0%)
Corticosteroids	18,151 (31.1%)
Opioids	22,342 (38.3%)

Table 1. Characteristics of Adult Patients with ulcerative colitis (2017)

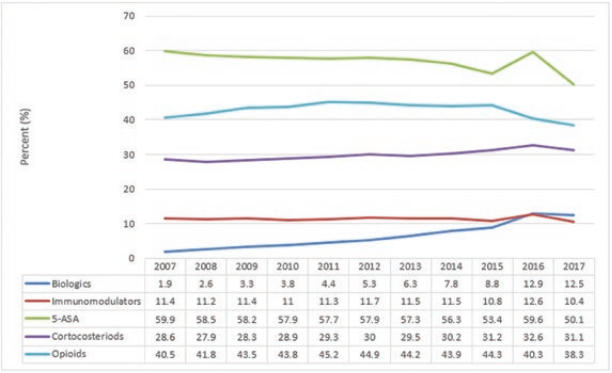

Figure 1. Trends in Treatment Patterns among Adult UC Patients, 2007–2017.

Conclusions: The prevalence of UC diagnosis codes increased between 2007 and 2017, and is projected to affect approximately 1 million US adults in 2017.

P692

Positive histological margins is a risk factor of recurrence after ileocaecal resection in Crohn's disease

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Background: Surgical resection is not curative in Crohn's disease (CD) and recurrence after surgery is a common situation. The identification of patients at high risk of recurrence remains disappointing in clinical practice. The impact of residual microscopic disease on margins on the risk of recurrence after ileocaecal resection is still subject to debate.

Methods: All patients who underwent ileocaecal resection between January 1982 and December 2016 were prospectively identified. Demographic data, clinical, surgical and histological variables were retrospectively collected. Positive histological margin was defined by the presence of acute inflammatory lesions on margins: erosion, ulceration, chorion infiltration by neutrophils poly- nuclears, cryptic abscesses or cryptitis.

Results: 125 patients were included, with a median follow-up of 8 years (Interquartile Range (IQR), 4.3–15.2). Half (49.6%, n = 62) were women, and the median age at surgery was 33 years (24–42). Fifty-six (44.8%) had positive inflammatory margins. Five years after surgery,, respectively, 29 (51%) and 23 (34%) patients with positive and negative margins had clinical recurrence (p = 0.034). At the end of the follow-up, respectively, 60% (n = 34) and 47% (n = 33) patients had clinical recurrence (p = 0.07). CD-related hospitalisations were observed in, respectively, 37.5% (n = 21) and 18.8% (n = 13) with positive and negative margins (p = 0.02). Fourteen patients (25%) with positive intestinal margins were reoperated at the end of the follow-up compared with 5 patients (7%) with negative margins (p = 0.04). Multi-variate analysis confirmed that positive intestinal margin was independently associated with CD-related hospitalisation (Odds Ratio (OR), 2.5 (CI 95%, 1.1–5.5), p = 0.03) and surgical recurrence (OR, 4 (95% CI, 1.3–12.5), p = 0.01).

Conclusions: Positive histological margin, as defined by the presence of erosion, ulceration, chorion infiltration by neutrophils polynuclears, cryptic abscesses or cryptitis, was associated with an increased risk of clinical and surgical recurrence after ileocaecal resection for Crohn's disease.

P693

Vedolizumab treatment for pouch inflammation

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Background: Pouchitis is the most common complication in UC patients following total proctocolectomy with ileal pouch anal anastomosis surgery, with a reported cumulative prevalence ranging from 23% to 46%. Oral antibiotic therapy is the mainstay treatment, however, 10–15% of patients with pouchitis develop chronic antibiotic-dependent/refractory pouchitis or Crohn's-like disease of the pouch (CLDP) requiring treatment escalation to immuno-modulatory or biologic therapy. Our aim was to evaluate the safety and efficacy of vedolizumab in patients with antibiotic-dependent/refractory pouchitis.
Methods: We performed a retrospective chart review of patients with chronic antibiotic-dependent or refractory pouchitis who were treated with vedolizumab (300 mg at week 0, 2, 6 and 14) and were followed at the Tel Aviv Medical Center. Data collected included demographics, Pre and post-pouch therapy, modified pouch disease activity index (mPDAI) and serum C-reactive protein (CRP). The effectiveness of vedolizumab treatment was based on mPDAI and CRP level at Weeks 14 and 22.
Results: We identified 10 patients (7 males, median age 58 years) after IPAA with chronic antibiotic-dependent or refractory pouchitis, who were treated with vedolizumab; their baseline characteristics shown in Table 1. Of these patients, 7 had concomitant pre-pouch ileal inflammation and 3 had cuffitis. Six of these patients were previously treated with TNF-inhibitors for their pouch inflammation. The mean mPDAI dropped from 6.7 (range 5–10) to 3.6 (range 2–7), this was statistically significant ($p = 0.05$), as shown in Table 2 and graph 1. CRP levels remained stable throughout Week 22 (mean 9.85, range 2.1–20.7). No serious side effects were recorded, and all patients were off antibiotic therapy.
Conclusions: Vedolizumab is both safe and effective in patients with antibiotic-dependent/refractory pouchitis, and in patients with concomitant pre-pouch ileitis.

P694

Genetic predisposition and thiopurine-induced pancreatitis in inflammatory bowel disease patients

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Background: Thiopurines, Azathioprine and 6-Mercaptopurine, remain an important treatment in both Crohn's disease (CD) and ulcerative colitis but are responsible for several side effects, such as acute pancreatitis (AP) in 3 to 7% of cases. The underlying mechanism of this dose-independent immune-mediated allergic reaction is still unknown. Genetic variability of enzymes intervening in thiopurine metabolism is known to influence adverse events linked to thiopurines. Results for inosine triphosphate pyrophosphatase (ITPA) are controversial. Recent studies on HLA polymorphism demonstrated a significant link between single-nucleotide polymorphism (SNP) rs2647087 and thiopurine-induced pancreatitis (TIP).[1,2]
Methods: Out of 59 patients from five Belgian hospitals with a history of TIP, 42 met the eligibility criteria for AP linked to thiopurine with a positive temporal relationship (< 4 weeks after thiopurine exposure) and exclusion of other causes of AP. A fully custom PCR amplicon-based target enrichment kit was developed based on the TruSeq Custom amplicon (TSCA) technology from Illumina (Illumina, San Diego, CA, USA). The design of the kit targeted ITPA, HLA-DQA1-HLA-DRB1, but also ABCC4, TPMT, MTHFR and GSTM1, known to intervene in thiopurine metabolism.
Results: Our cohort showed high rates of known risk factors for TIP such as CD (88.1%), women (73.8%) and smoking habits (50%). AP were mild or moderate and no early or late complication regarding AP was reported. Hospitalisation rate was 42.9% with a median stay of 6.1 ± 5.43 days. No significant link between ITPA, ABCC4, TPMT, MTHFR, GSTM1 polymorphism and TIP could be found. However, in this cohort, SNP rs2647087 located on HLA-DQA1-HLA-DRB1, was found in high proportions (Allele frequency (AF)=0.476). This AF is similar to Heap et al.'s findings (AF = 0.48–0.49) who demonstrated a significant link between this SNP and TIP (OR = 2.59, $p = 2 \times 10^{-16}$) [1] and slightly lower than Wilson et al.'s results (AF = 0.69) (OR = 15.83, $p = 0.0001$).[2]
Conclusions: TIP is a serious adverse event with important rate and duration of hospitalisation. Prevalence for HLA variant rs2647087 in this TIP cohort is significantly high. Results are similar than in previous studies where heterozygous and homozygous variants experienced a significant increased risk of TIP. Genotyping rs2647087 could be implemented in daily practice when discussing treatment options. Together with TPMT testing, it could be an interesting tool for guiding the physician and the patient in deciding whether or not it is appropriate to initiate thiopurine therapy. No association between ITPA polymorphism and TIP was observed.

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P695

Feasibility and safety of strictureplasties performed by laparoscopic approach for complicated Crohn's disease: A prospective observational cohort study

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Background: Laparoscopy (LP) is considered the gold standard for the surgical treatment of complicated Crohn's disease (CD). Conventional and non-conventional strictureplasties (SP) are indicated as a valid alternative to resection for fibrotic strictures, but such a complex and often multiple suturing has been considered until now the prerogative of open surgery. Since no data are available in the literature, aims of the present study is to assess feasibility and safety of SP performed by laparoscopic approach.
Methods: Data of all the patients undergoing surgery for CD were entered into our prospective database (ProSaDS-CD). A prospective protocol for laparoscopic approach was started in 2007. We compared patients treated by LP and by open approach (OP) in terms of preoperative patients' characteristics; number, site, and type of diseased segments; surgical procedure; perioperative complications and long-term results. All the consecutive, unselected patients with at least one small bowel location of CD at primary surgery were included. Pure colonic or recurrent disease were exclusion criteria. Clavien–Dindo classification was used for postoperative complications. Follow-up was performed at 3, 6 and 12 months after surgery, and then every year or in case of necessity.
Results: Between January 1995 and January 2018, 1166 patients entered the ProSaDS-CD. 557 met the inclusion criteria. LP and OP groups consisted of 297 and 260 patients, respectively. Overall conversion rate was 5.3%. Postoperative recovery was faster, and duration of surgery and hospital stay shorter in VL group ($p < 0.05$). Morbidity (Clavien–Dindo III or IV) and mortality rates were 4.3% and 0,3% in VL group and 4.2% and 0.7% in OP group (ns). No differences were present in terms of patients' history and clinical characteristics. In VL group 653 segments were involved (min 1 – max 25), and 290 bowel resections (52.3%), 146 conventional SP (26.4%), and 118 non-conventional SP (21.3%) were performed. In OP group were performed 228 bowel resections (46.4%), 143 conventional SP (29%), and 121 non-conventional SP (24.6%), for a total of 468 locations (min 1 – max 21) (ns). The mean length of diseased bowel, resection, and bowel sparing were 30.5 ± 26.2 cm, 23.6 ± 17.5 cm, and 23.3% (VL); and 24.5 ± 20,3 cm, 19.3 ± 14.5 cm, and 20.8% (OP) (ns). Mean follow-up was 6.3 ± 3.2 years.
Conclusions: This is the first study comparing the use of SP in open and laparoscopic surgery. No differences were found in term of safety and efficacy, number and type of SP, and bowel sparing. VL group had faster recovery and shorter duration of surgery and hospital stay.

P696

Long-term prognosis and predictive factors for surgical treatment of intestinal lesions in patients with Behcet's disease

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Background: Behcet's disease with intestinal lesions, known as intestinal Behcet's disease (Int BD), is a manifestation of the disease that is often treated with immunosuppressive therapy, such as anti-tumour necrosis factor (TNF)α agents. However, some with Int BD cases are refractory to medical treatment and require surgery, though predictive factors indicating that have yet to be established. The aim of this study was to evaluate predictive factors for surgery (in principle, hand-sewn end-to-end anastomosis) as well as long-term prognosis in patients with Int BD.
Methods: Int BD was diagnosed according to the Japanese diagnostic criteria for BD. This single-centre retrospective study was conducted at our referral institution for IBD surgery between January 2000 and December 2017. Patients who underwent an emergency operation due to perforation prior to a definitive diagnosis were excluded.
Results: A total of 42 (22 males) patients with Int BD were included. Their median age was 39 years (range 11–76) and the duration of disease was 4.3 years (0.1–16.1). Lesion location was ileocaecal in 26 (61.9%), ileum and colon in 10 (23.8%), and colon in 6 (14.3%) patients. Five (11.9%) were also complicated with oesophageal lesions. For medical treatment, 5-aminosalicylates were given to 31 (73.8%), corticosteroids to 30 (71.4%), anti-TNFα agents to 26 (61.9%), immunomodulators to 22 (52.4%), and colchicine was given to 20 (47.6%) patients. An intestinal resection was performed in 25 (59.5%) cases. The median time from initiation of medical treatment to surgery was 19.6 months (2.4–192.9 months). The cumulative operation rate after obtaining a definitive diagnosis was 19.1% at 1 year, 23.8% at 3 years, and 28.9% at 5 years. Postoperative complications were surgical site infection in 11 (26.2%) patients, including 2 with an intraabdominal abscess and 1 with a ruptured suture, and bowel obstruction was seen in 3 (7.1%). Intestinal lesion recurrence was confirmed in 13 patients, of whom 8 underwent a re-operation. The cumulative re-operation rate after the first surgery was 8.6% at 1 year, 23.0% at 3 years, and 31.5% at 5 years. Predictive factors for surgery shown by univariate analysis were corticosteroids administration (OR, 4.6; $p = 0.03$), colchicine administration (OR, 3.6; $p = 0.05$), higher CRP (OR, 1.2; $p = 0.01$), lower haemoglobin (OR, 0.8; $p = 0.16$), and non-administration of an anti-TNFα agent (OR, 0.2; $p = 0.04$), while non-administration of an anti-TNFα agent (OR, 0.1; 95% CI, 0.01–0.61; $p = 0.04$) was the only predictive factor for surgery in multi-variate analysis.
Conclusions: Surgery and a re-operation are sometimes needed during the clinical course of Int BD. Administration of an anti-TNFα agent with appropriate timing may be effective to avoid surgery.

P697

Pneumocystis jirovecii pneumonia in IBD patients treated with immunomodulator(s)

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Background: *Pneumocystis jirovecii* Pneumonia (PJP) is a very rare life-threatening pulmonary fungal infection that occurs in immunocompromised individuals including patients with inflammatory bowel disease (IBD). Prophylaxis for PJP is recommended in IBD patients treated with triple immunomodulators where one agent is a calcineurin inhibitor or an anti-TNFα [Ref1] but there is no consistency in a preventive approach in patients with double or single immunomodulators. Our aim was to describe the immunosuppressive treatment profile of IBD patients infected with PJP and the outcome of the disease.
Methods: Cases of PJP were retrospectively collected through the COllaborative Network For Exceptionally Rare case reports of the European Crohn's and Colitis Organization (ECCO CONFER). All ECCO members were invited to report cases of PJP. Data were collected through a case report form.
Results: A total of 15 PJP infections were reported in 14 IBD patients (9 ulcerative colitis and 5 Crohn's disease including 10 men and 4 women). The median age at PJP diagnosis was 55 years (IQR 44–80). Diagnosis was performed by a positive PJ polymerase chain reaction on the bronchoalveolar lavage in 87% of the cases and by a microscopic direct examination in 7% (unreported in 1 patient). One patient was co-infected by HIV and 57% were non-smokers. Immunosuppressive therapies at the time of diagnosis included steroids (n = 11), thiopurines (n = 9), infliximab (n = 3), cyclosporin (n = 2), methotrexate (n = 1) and tacrolimus (n = 1). Two PJP (13%) occurred in patients on triple immunosuppression, 9 patients (60%) had a double immunosuppressive treatment, 3 patients (20%) were on monotherapy and PJP in the HIV patient occurred in absence of immunosuppressive treatment (Table 1). None of the patients diagnosed with PJP had received prophylaxis. All patients were treated by trimethoprim/sulfamethoxazole or atovaquone and 5 required an intensive care unit stay. Two patients (14%) died and 1 patient had a recurrent episode 16 months after initial treatment. Evolution was favourable for the others.

Immunosuppressive treatment exposure in IBD patients	n=14
Monotherapy	**n=3**
Steroid monotherapy	n=2
Thiopurine monotherapy	n=1
Double immunosuppression	**n=9**
Steroid + thiopurine	n=4
Steroid + infliximab	n=1
Steroid + methotrexate	n=1
Steroid + tacrolimus	n=1
Infliximab + thiopurine	n=2
Triple immunosuppression	**n=2**
Steroid + thiopurine + cyclosporin	n=2

Table 1. Immunosuppressive treatment in IBD patients at time of PJP (HIV patient excluded).

Conclusions: This case series reports PJP in IBD patients while on single or double immunosuppression highlighting the risk in this population. Identifying risk factors for PJP infection in the IBD patients is essential to provide a case-by-case prophylaxis.

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P698

Persistence, clinical effectiveness and safety of vedolizumab in the post-marketing real clinical practice in Italy: a double-centre, 2-year experience in Crohn's disease and ulcerative colitis patients

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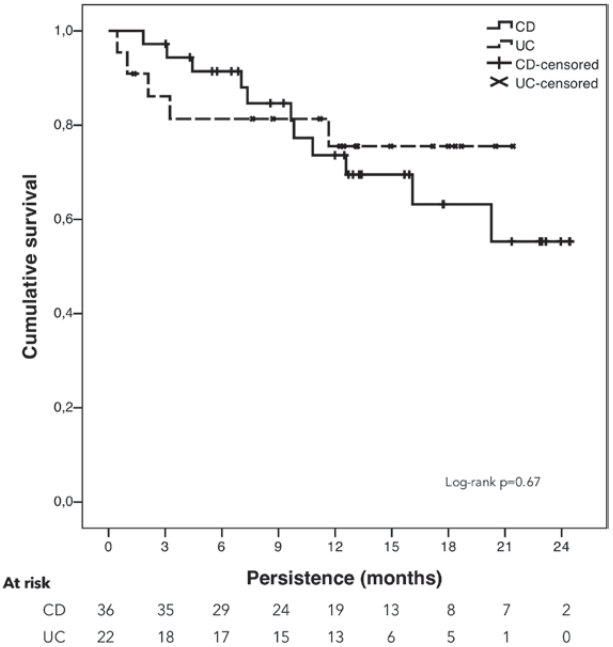
Background: Data on clinical effectiveness of vedolizumab (VDZ) for the treatment of refractory Cronh's disease (CD) and ulcerative colitis (UC) in real clinical practice in Italy are still limited. Our aim was to evaluate VDZ treatment persistence and safety in the post-marketing era.
Methods: This retrospective study included adult patients with CD and UC treated with VDZ as first and second–line therapy, from June 2016 to October 2018. The Kaplan–Meier method was used to calculate the cumulative probability of treatment persistence and the bivariate Cox proportional hazard model was used to find predictors of treatment withdrawal. Biochemical parameters at baseline and 12 months were compared by the Wilcoxon-signed rank test. Adverse events (AEs) were reported as number per patients-year (PY) of exposition.
Results: We included 58 patients, 36 CD and 22 UC, of which 10/58 (17.2%) were first-line treatments. At the observation, 16/58 patients (27.4%) discontinued VDZ, 11 CD and 5 UC; only 1 patient (CD) withdrew because of remission, 11 (9 CD and 2 UC) withdrew because of failure and 4 (1 CD and 3 UC) because of AEs. Median VDZ persistence was 12.5 (IQR 10.8) and 12.4 (IQR 10.9) months in CD and UC patients, respectively. The cumulative probability of treatment persistence was 91.4%, 73.6%, 63.2% and 55.3% at 6, 12, 18 and 24 months in CD patients and 81.3%, 75.5% and 75.5% at 6, 12 and 18 months in UC patients.



Kaplan–Meyer curves showing the cumulative probability of vedolizumab treatment persistence in Crohn's disease and ulcerative colitis patients.

Baseline C-reactive protein significantly increased the risk of withdrawal (HR 1.2, 95% CI 1.1 – 1.3, p = 0.01). At Week 14, 54/58 patients persisted in therapy: 32/54 patients (59.3%) were steroid-free and 35/54 (64.8%) reached a clinical response; the clinical

remission rate was low (22.2%), but it increased up to 41.7% and 50% at 6 and 12 months. Overall, 18 patients completed a colonoscopy/magnetic resonance at 12 months and 5/18 (27.8%) reached a deep remission. The median White blood cells and platelets count significantly decreased from baseline to month 12 (p = 0.01). The incidence rate of AEs and severe AEs was 28/100 PY and 3.3/100 PY, respectively. The majority of them were delayed reactions (88.2%); joint pain (13.5/100 PY) and acute diarrhoea (3/100 PY) were the most common AEs and severe AEs, respectively.

Conclusions: More than half of CD and 2/3 of UC patients treated with VDZ were persistent over 24 and 18 months, respectively; safety was fairly good. Nevertheless, the low rate of clinical remission at Week 14 could be explained by its gut-selective mechanism of action, which requires more time to reach deep remission.

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Faecal microbiota transplantation as treatment for recurrent clostridium difficile infections: a single-centre experience

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Background: *Clostridium difficile* infection (CDI) is a significant complicating factor in inflammatory bowel disease (IBD). IBD patients with CDI appear to flare worse than their non-IBD counterparts. Faecal microbiota transplantation (FMT) is recently recommended to effectively treat recurrent CDI (rCDI). Despite, FMT is still not a routine procedure in most centres. We describe our experience of FMT to treat rCDI in IBD patients and other indications, with focus on the identification of risk factors for FMT failure.

Methods: Patients were included retrospectively (2012–2018) if (I) CDI was confirmed in the faecal sample according to the ESCMID algorithm and (II) patients failed ≥2 antibiotics for CDI or had ≥2 laboratory-confirmed CDI recurrences. Demographic and clinical data were collected (Table 1).

Baseline patient characteristics		
Sex (Women)		60.6%
Age (Years) (Median, IQR)		57.8 (23-73.5)
Charlson Morbiditeits Index (Median, IQR)		3 (2-5)
Body mass index (kg/m^2) (Median, IQR)		22.6 (19.6-25.9)
Smoking	*Smoker*	6.1%
	Ex-smoker	33.3%
	Non-smoker	60.6%
Underlying gastro-intestinal problem		45.50%
Inflammatory bowel disease	*Crohn's disease*	15.2%
	Ulcerative colitis	9.1%
Proton pump inhibitor intake		42.40%
Corticosteroïd use		39.40%
Immunomodulator use		39.40%
Predisposing infection		69.70%
Hospital aquired infection		60.60%
Severe *Clostridium Difficile* infection (based on the SHEA/ISDA guidelines)		18.20%
Amount of antibiotic treatments before first FMT (Median, IQR)		5 (4-6)
Amount of FMT's (Median, IQR)		1 (1-2)
Days between first positive sample and first FMT (Median, IQR)		216 (136-349)
Relationship with donor	*Relative*	88.6%
	Friend	11.4%
Failed previous vancomycin taper therapy		100%

Table 1. Overview of the demographic and clinical baseline characteristics

FMT success was defined as resolution of diarrhoea within 48 h, for ≥8 weeks. Statistical analyses were performed in JMP.

Results: We included 33 rCDI patients in which 8 IBD patients, 8 post-transplant patients and 1 multiple-sclerosis patient. Fifteen/33 patients were on immunosuppressive therapy during their first FMT. FMT success was seen in 24/33 patients (72.7%) after 1 FMT. This success ratio was not significantly different in IBD patients (Fisher exact test p = 0.37), post-transplant patients (p = 0.94), or for all immunocompromised patients combined (p = 0.741). Relapses were observed in 9/33 patients (27.3%) within 8 weeks and in 3/33 patients (9.1%) later on. Nine relapsed patients underwent a second FMT which was successful in 5 patients (4 received a different donor). The remaining 3 patients were successfully treated with a vancomycin based scheme. FMT was not efficacious in 7/33 patients. The overall cumulative success ratio was 78.8% with minimal side effects in 6/44 FMTs (13.6%). None of the demographic and clinical variables was significantly correlated with success after ≥1 FMTs. The use of a related donor tended to show a higher effectiveness after 1 FMT (p < 0.053). The presence of a predisposing infection treated with antibiotics gave a trend (p < 0.068) to a lower efficacy.

Conclusions: FMT is efficacious for rCDI, also in IBD and other immunocompromised patients. Our FMT success ratios and percentage of side effects are comparable to literature. Stratification of eligible patients for FMT can be useful. However, FMT failure was not associated with any risk factor or patient group. Donor faeces from a relative appears to increase FMT efficacy and multiple FMT treatment seemed to be less effective for patients with a predisposing infection.

P700

The efficacy of colesevelam to treat bile acid malabsorption in Crohn's disease: data from TOPPIC trial

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Background: Bile acid malabsorption (BAM) associated diarrhoea is a significant clinical issue in patients post ileocaecal resection secondary to Crohn's disease resulting in a reduced quality of life.

This study aimed to assess the efficacy of Colesevelam, as a useful symptomatic treatment for diarrhoea in these patients.

Methods: This is a post hoc analysis of the TOPPIC trial. The trial randomised 240 patients, 44 of these patients formed our study population based on the medications for our study. The four intervention groups we analysed are; Colesevelam alone (n = 17), Cholestyramine alone (n = 10), Loperamide alone (n = 12) and both Colesevelam and Loperamide (n = 5). A Wilcoxon Signed Rank Test was performed to analyse if there was a statistically significant difference between pre- and post-drug intervention in the following four outcomes; liquid stool frequency per week, CDAI value, IBDQ score and SF-36 score.

Results: Patients treated with Colesevelam monotherapy had a reduction in stool frequency from pre to post treatment: media$n$ = 33/week (IQR 45.5, 25.5) vs. median = 14/week, (IQR 40, 5.5) ; p = 0.038. Similarly, Cholestyramine group had a reduction in stool frequency from median 17/week (IQR 32.25,10.25) vs. median 7.5/week, (IQR 12.75,4.25); p = 0.008. The other two groups were not associated with a reduction in stool frequency. Additionally, only the patients treated with Colesevelam monotherapy had a reduction in CDAI from pre to post treatment: median 213 (IQR 261, 8147) vs. median 118 (IQR 229.3, 60); p = 0.013. Finally, only

Colesevelam monotherapy was associated with improvement in quality of life score, specifically the SF-36, from pre to post treatment: median 118 (IQR 122, 102.5) vs. median 121 (IQR 127.5, 118.5); $p = 0.005$.

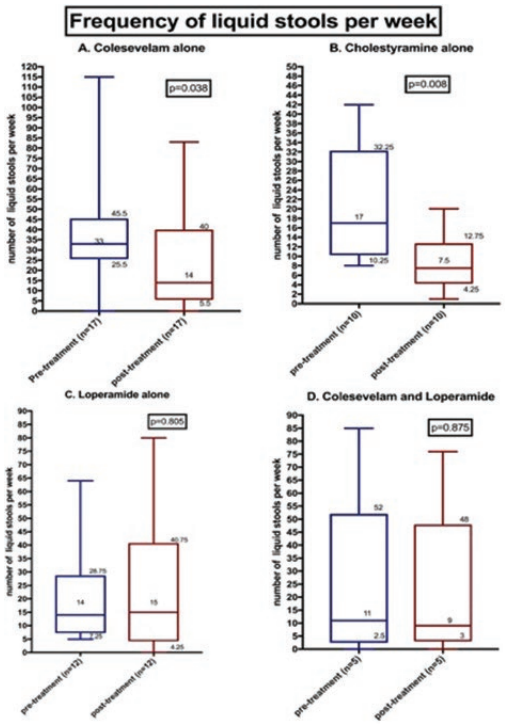

Figure 1. (A–D) Graphs representing the change in liquid stool frequency per week pre- and post-treatment in four different medication groups.

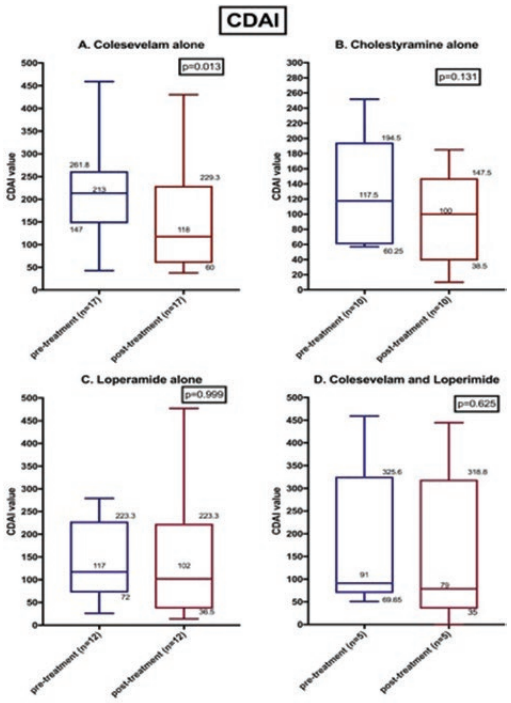

Figure 2. (A–D) Graph representing the change in CDAI index pre and post treatment in four different medication groups.

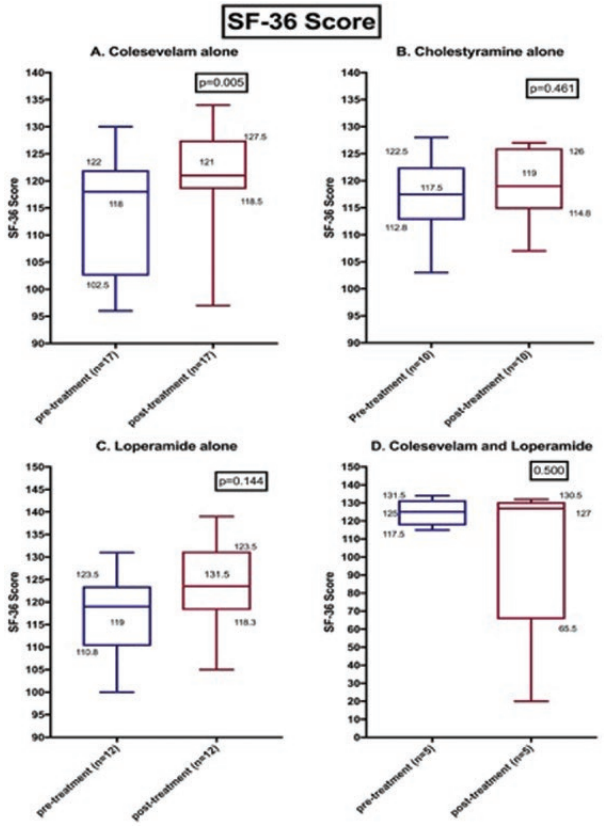

Figure 3. (A–D) Graph representing the change in SF-36 score pre and post treatment in four different medication groups.

Conclusions: We have demonstrated that Colesevelam is an effective treatment for post-operative BAM in Crohn's disease. Both Colesevelam and Cholestyramine were associated with a reduction in stool frequency but only Colesevelam was associated with a reduction in CDAI and an improvement in quality of life.

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P701

The comparative safety of different intravenous iron preparations in inflammatory bowel disease: a systematic review and network meta-analysis

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Background: Anaemia occurs with an estimated prevalence of ca. 74% in patients with IBD, causing increased morbidity and hospitalisation rates and impacting quality of life. Oral iron compounds cause gastrointestinal side effects and therapy adherence is poor. Modern intravenous (IV) iron compounds have been shown to be safe and effective in IBD. ECCO IBD guidelines recommend IV iron

therapy for severe anaemia and in patients intolerant or unresponsive to oral iron. We compared the tolerability of different IV iron therapies for IDA in IBD [ferric carboxymaltose (FCM), ferumoxytol (FOX), iron sucrose (IS), iron isomaltoside (ISM) and iron dextran (IDX)] in a systematic review and network meta-analysis (NMA).

Methods: A literature search was performed up to August 2018 in PUBMED, SCOPUS, Web of Science and the Cochrane Library. Primary outcome measure was the pooled total of drug-related AEs and SAEs as % of safety population. Secondary outcome was identification of the most common AEs. Bayesian NMA was performed to calculate the tolerability of each iron therapy relative to all comparators. Results were presented as OR in relation to AE rate.

Results: 2730 papers were found. After duplication removal and detailed review, 24 eligible studies were included: 4 RCTs (NMA) and 20 others (systematic review only). No eligible studies for FOX and no RCTs for IDX were found. Bayesian NMA was performed on 4 eligible RCTs (n = 1052). No statistically significant difference was found between different IV iron products or oral iron (vs. oral iron: OR = 0.87, 95% CrI [0.43; 1.7] for FCM, OR = 0.80, 95% CrI [0.36; 1.8] for IS, OR = 1.5, 95% CrI [0.64; 3.7] for ISM). The systematic review (n = 2619) showed overall AE rates of 83/1028 (8.1%) for FCM, 78/481 (16.2%) for IS, 89/475 (18.7%) for ISM and 10/83 (12%) for IDX. Pooled rates of drug-related SAEs were 0.1%, 2.2%, 0.0%, 1.1%, for FCM, IS, IDX and ISM, respectively. For oral iron, AE/SAE rates were 22.6%/1.4%.

Conclusions: While the systematic review indicates FCM to be associated with fewer AEs, as also suggested most recently by a Dutch trial,[1] statistical significance was not reached due to sparsity of data from RCTs. Although hypophosphatemia is suspected to be associated with IV iron administration, especially FCM, it was temporary and asymptomatic, if reported. No severe hypophosphatemia-related bone manifestations occurred in the RCTs or other prospective studies. Further comprehensive trials are needed for head-to-head comparison of the safety of different IV iron substances.

Reference

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P702

Off-label drug use in patients with inflammatory bowel disease: a national survey among tertiary care centres

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Background: In daily clinical practice, drugs are commonly prescribed outside the terms of product license, also known as off-label prescribing. Off-label drugs create alternative treatment options, but are associated with unknown safety risks since they are underevaluated for unlicensed indications. The use of off-label drugs for the treatment of inflammatory bowel diseases (IBD) has not been characterised. We aimed to assess the proportion and characteristics of off-label prescribing for IBD in tertiary care in the Netherlands.

Methods: A prospective database of IBD patients from all university hospitals in The Netherlands was used to collect data on (historical) drug prescriptions for IBD and demographics. Drugs were classified as off-label if they were unlicensed for Crohn's disease and/or ulcerative colitis. Uni- and multi-variate analyses were used to identify patient-specific characteristics predictive of increased off-label use.

Results: A total of 12 651 historical and current drug records for the induction and/or maintenance treatment of 4583 IBD patients (59% female and 62% Crohn's disease) were available in the database. Of these, 2374 (19%) were considered off-label drug prescriptions. Out of 4583 IBD patients, 1477 (32%) were exposed to off-label drugs. Commonly prescribed off-label IBD drugs were mercaptopurine (18%), beclomethasone (12%), thioguanine (4%) and allopurinol (3%). Off-label prescriptions were more common in ulcerative colitis than Crohn's disease (37% vs. 29%, $p < 0.001$). Smokers and patients exposed to multiple (≥5) types of drugs during their disease course were more likely to be exposed to off-label drugs (smoking 33% vs. 27% and multiple (≥5) drug use 66% vs. 22%, both $p < 0.001$).

Conclusions: About 19% of prescriptions for IBD were off-label and one-third of IBD patients, especially patients with ulcerative colitis, were exposed to off-label drugs. Future studies are needed to evaluate the consequences of off-label prescriptions for the treatment of IBD.

P703

The real-world long-term effectiveness of vedolizumab in inflammatory bowel diseases: a single-centre observational study

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Background: The effectiveness of vedolizumab (VDZ) in real-world practice is under evaluation. We aimed to report the effectiveness of VDZ on intestinal and articular symptoms after 10 and 52 weeks of treatment, and at the end of follow-up.

Methods: All consecutive patients with moderate–severe Crohn's disease (CD) or ulcerative colitis (UC) who started a treatment with VDZ from July 2016 to December 2017 were entered in a prospectively maintained database. The following clinical end-points were set at 10 and 52 weeks: steroid-free remission (Harvey–Bradshaw Index < 5 for CD and Mayo Partial Score < 2 for UC without steroids use), and response (absence of steroid-free remission, but reduction of Harvey–Bradshaw Index ≥3 for CD and Mayo Partial Score ≥2 for UC compared with baseline). Patients with steroid-free remission and response were deemed as having clinical benefit. In patients with active spondyloarthropathy (SpA) at baseline, the response on articular symptoms was defined as disappearance of objective signs of arthritis and resolution of pain.

Results: 169 patients (112 with CD and 57 with UC) were included. At Week 10, a steroid-free remission was achieved in 44 out of 169 patients (26.0%), and a response in 35 (20.7% - overall clinical benefit: 46.7%), while at 52 weeks a steroid-free remission was achieved in 30 out of 128 patients (23.4%), and a response in 18 (14.1% - overall clinical benefit: 37.5%). The median follow-up was 47.0 weeks (148.39 person-years), and the failure-free survival was 60.4% at 1 year. Semi-parametric Cox model showed that patients with CD had a higher risk of treatment failure compared with patients with UC (HR 2.06, 95% CI: 1.05–4.05, $p = 0.036$). After 10 weeks, a response on articular symptoms was reported in 12 out of 39 patients (30.8%) with active SpA at baseline, and in 12 out of 16 patients (75.0%) at Week 52. At Week 10, the only factor that was marginally associated with the articular response was the clinical benefit on intestinal symptoms (OR 5.07, 95% CI: 0.97–31.70, $p = 0.055$), while the coexistence of axial and peripheral SpA was associated with a reduced response rate compared with peripheral manifestations only (OR 0.13, % CI: 0.02–0.64, $p = 0.021$). Overall, 67 adverse events were reported (incidence rate: 45.2 per 100 person-years). Twenty (11.8% of patients) adverse events leading to treatment discontinuation were reported: 11 arthritic flares, 5 subjective perceptions of intolerance, 2 infusion reactions, one pneumonia, and one prostate cancer.
Conclusions: In this large cohort, VDZ provided good effectiveness on intestinal symptoms, particularly in patients with UC. A subset of patients reported improvement also on articular symptoms, especially in cases of peripheral SpA.

P704

Association between trough levels of vedolizumab and therapy outcome in a cohort of patients with inflammatory bowel disease

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Background: Vedolizumab(VDZ) is an α4β7 integrin antagonist for the treatment of IBD. The role of VDZ therapeutic drug monitoring has not been clearly defined. We aimed to investigate the association between VDZ trough levels and therapy outcome in a cohort of patients with inflammatory bowel disease (IBD) and the association between VDZ trough levels and clinical and biochemical variables.
Methods: IBD patients receiving VDZ were identified in a cross-sectional study where serum samples were not collected at a pre-specified time point. Ulcerative colitis(UC) and Crohn's disease(CD) clinical activity was quantified using Mayo clinical subscore (MCS, remission MCS ≤ 1) and Harvey–Bradshaw Index (HBI, remission HBI < 5). VDZ and antibody-to-vedolizumab (AVA) concentrations determined by Prometheus® Anser® laboratories using non-radiolabelled liquid-phase mobility shift assays. p-values < 0.05 were considered significant.
Results: *N* = 35 IBD patients included (57% UC, 54% male, median age(range) 44.3 years(17.7–76.2), 9% receiving immunomodulators, 83% prior anti-TNF. 34/35 patients had trough VDZ level performed during maintenance therapy. Median(range) trough VDZ concentration 9.5 µg / ml(0 – 25). 0/35 subjects had detectable AVAs. No association between MCS or HBI defined remission and trough VDZ concentrations was observed $p = 0.38$ and $p = 0.83$, respectively. No difference in trough VDZ concentrations observed comparing by IBD phenotype($p = 0.50$); prior biologic exposure($n = 0.37$); or concomitant immunomodulator use($p = 0.68$). CRP and albumin levels were not correlated with trough VDZ concentrations, correlation coefficient –2.2($p = 0.36$) and 0.21($p = 0.36$) respectively.
Conclusions: In a real-world study of IBD patients receiving VDZ no clear association between VDZ trough levels and therapy outcome was observed. Significant immunogenicity was not observed supporting the use of VDZ monotherapy in uncomplicated patients. Further study is required to determine the utility of therapeutic drug monitoring in VDZ-treated patients.

P705

Incidence and risk factors of micronutrient deficiency in the patients with inflammatory bowel disease in Korea: folate, vitamin B12, 25-OH-vitamin D, ferritin

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Background: Inflammatory bowel disease (IBD) patients are vulnerable to micronutrient deficiencies due to diarrhoea-related gastrointestinal loss and lack of dietary intake from anorexia related to disease activity. According to the European Society for Clinical Nutrition and Metabolism (ESPEN) guideline, patients with IBD should be regularly checked for micronutrient deficiencies and certain defects should be adequately corrected. However, there is still limited number of studies on the incidence and risk factors of micronutrient deficiency.
Methods: We retrospectively analysed 105 IBD patients who underwent micronutrient examination including folate, vitamin B12, 25-OH-vitamin D, ferritin from March 2016 to March 2017. In addition, all of these patients had follow-up blood tests 6 months later at single tertiary university hospital.
Results: In the deficiency group, 76 (72.4%) patients had a deficiency in one of the four micronutrients (folate, vitamin B12, 25-OH-vitamin D, and ferritin), and 29 (27.6%) were in the non-deficient group. Deficiency group showed significantly higher rate of young age (mean ± standard deviation [SD], 38.7 ± 14.5 vs. 54.4 ± 15.0; $p < 0.001$), incidence of deficiency in Crohn's disease (CD) (CD, ulcerative colitis [UC], and intestinal Behcet's disease [BD]; 78.9% vs. 14.5% vs. 6.6%; $p < 0.001$), use of azathioprine (35.5% vs. 10.3%; $p = 0.011$) and anti TNF agents (50.0% vs. 20.7%; $p = 0.006$) compared with non-deficient group. On the multi-variate analysis, CD (Hazard ratio [HR], 3.600; 95% confidence interval [CI], 1.057–12.253; $p = 0.040$) and intestinal BD (HR, 15.469; 95% CI, 1.081–221.359; $p = 0.044$) were determined to be significant independent factors for micro-nutrient deficiency compared with UC.

Conclusions: In conclusion, the incidence of micro-nutrient deficiency is high (72.4%), and CD and intestinal BD were associated with higher risk of deficiency than UC. Therefore, in IBD patients, especially the patients with CD and intestinal BD, need more attention in micro-nutrition.

P706

Patient knowledge towards biological treatment in inflammatory bowel diseases: a cross-sectional survey

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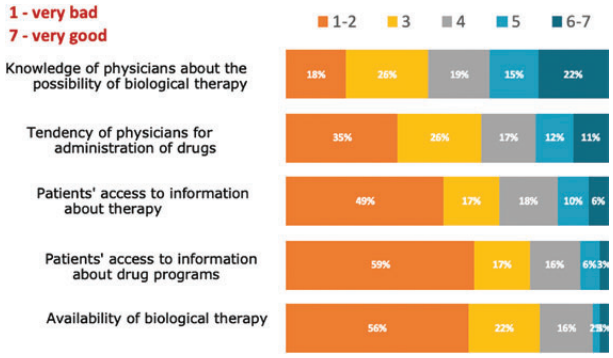
Background: Previously, it has been demonstrated in many chronic conditions, including inflammatory bowel diseases (IBD), that better patient knowledge about pathology and treatment improves the course and management of the disease. The aim of this study was to assess the actual knowledge of IBD patients' about the risks and benefits associated with biologic therapies, patients experience with therapy, patients awareness about therapy availability, and expectations of ideal biological therapy.

Methods: The study was conducted in collaboration with Polish IBD Patients Association in the period from February 2018 to May 2018. A cross-sectional, internet questionnaire-based study was conducted in 152 IBD patients: 84 patients with Crohn's disease (CD) and 68 patients with ulcerative colitis (UC). The questionnaire covers three domains of IBD, including diagnosis, therapeutic options, and disease course.

Results: 51% (n = 78) of enrolled IBD patients reported feeling unwell at the time of the study. In our study in 62% (n = 94) of subjects during the last 12 months exacerbation of the disease requiring medical intervention were observed. Forty-two per cent (n = 64) of patients were hospitalised during this period due to exacerbation of the disease or its complications. The 97% (n = 147) of IBD patients investigated in our study reported that they heard about biological therapy and 54% (n = 79) of them had personally used biological therapy. In our study, the improvement in health as a result of biological therapy in 65% (n = 99) of current and 51% (n = 78) in the past treated patients was observed. In the case of patients treated in the past, 45% (n = 68) of them managed to achieve full clinical remission of the disease. Thirty-seven per cent (n = 65) of respondents as a result of treatment completely discontinued steroid and 32% (n = 49) could reduce their dose. The main reasons for not using biological therapy reporting by investigated patients were: the lack of proposals for treatment (47%), the effectiveness of current therapies (45%), failure to meet the inclusion criteria for the drug program. Seventy-two per cent (n = 109) of respondents reported that they believe that biological therapy should be administrated earlier and 36% (n = 55) of patients believe that the biological therapy is associated with a high risk of side effects.



Selected aspects related to the availability of biological therapy in inflammatory bowel disease patients

Conclusions: Knowledge about the use of biologic therapies in IBD patients in Poland is still unsatisfactory. An immediate need exists for patient and physician education about biological therapies and clinical trials to ensure educated and informed decisions are made about biological drug use.

P707

38 Weeks treatment of UC patients with different daily doses of mesalazine

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Background: In everyday practice, the management of UC patients is not limited to a 6 week induction period. Patients in clinical remission will continue treatment to maintain remission and avoid recurrence. For non-remitters or for patients with clinical response, the treating physician faces several choices. He could maintain the same treatment for a longer period or increase the dosage of the initial therapy or just switch to another therapeutic class. In this analysis, we present the results of maintaining UC patients on 3.2 g/day or 4.8 g/day for a longer period than the short 8 weeks of induction.

Methods: 737 patients (average MAYO 7.7 at screening) completed an 8 week randomised induction period with 3.2 g/day of mesalazine. 675 patients entered an open-label extension for a total of 38 weeks (including induction period). They were separated into 3 groups: remitters, responders and non-responders to 8 weeks of 3.2 g/day. They, respectively, received 1.6 g/day, 3.2 g/day or 4.8 g/day of a new 1600 mg mesalazine tablet.

Results: 44% of all patients achieved clinical and endoscopic remission at Week 38. 53.8% of all patients achieved an endoscopic remission (MES ≤1, Mayo Endoscopic Score) at Week 38. 45.7% patient had a history of distal disease (proctitis and proctosigmoiditis). Similar endoscopic remissions were achieved in patients with any disease extent history including patients with distal disease of ulcerative colitis (Figure 1).

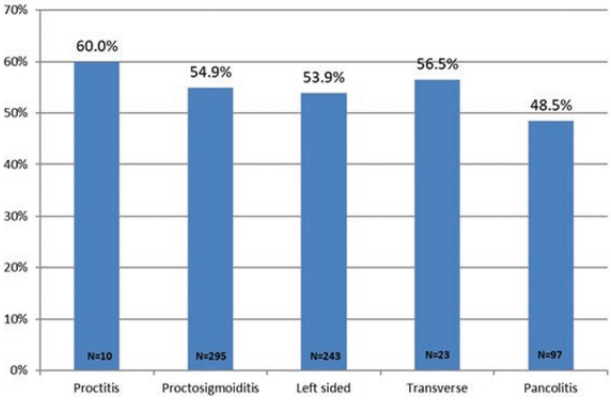

Figure 1: Mucosal healing at Week 38. 133 (65.8%), 108 (39.4%) and 59 patients (29.6%) achieved clinical and endoscopic remission at Week 38 with 1.6 g/day, 3.2 g/day and 4.8 g/day, respectively. 142 (70.3%), 93 (33.9%) and 61 (30.7%) patients achieved clinical remission (Stool score of 0 and rectal bleeding score of 0) at Week 38 with 1.6 g/d, 3.2 g/day and 4.8 g/day, respectively. 143 (70.8%), 138 (50.4%) and 82 (41.2%) patients achieved endoscopic remission (MES ≤1) at Week 38 with 1.6 g/day, 3.2 g/day and 4.8 g/day, respectively. 76 (37.6%), 64 (23.4%) and 27 (13.6%) achieved endoscopic remission (MES = 0) at Week 38 with 1.6 g/day, 3.2 g/day and 4.8 g/day, respectively.

TEAE incidence was similar between the 1.6 g/day, 3.2 g/day and 4.8 g/day treatment groups (29.2%, 26.6% and 19.1%, respectively).

Conclusions: Patients who did not respond to 3.2 g/day, either partially or fully, could benefit from a longer treatment period or even a 4.8 g/day of mesalazine to achieve total clinical and endoscopic remission with a similar and good safety profile. High endoscopic remission was also found in patients with distal disease extent.

P708

Prospective study to predict psychological morbidity in young people with inflammatory bowel disease using novel risk assessment tool

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Background: Psychological morbidity in inflammatory bowel disease (IBD) is common with a reported prevalence of up to 50% and far reaching impact on quality of life as well as on education and employment. Young people living with IBD face the additional challenge of being at a pivotal point in their development. Prediction of future development of psychological morbidity in young people with IBD would identify those at greatest risk and enable early intervention. The aim of this study was to identify risk factors which predict psychological morbidity in young people aged 16–24 years using a novel risk assessment tool (IBD-RAPID).
Methods: Patients were recruited to a questionnaire-based study either online or face-to-face from outpatient services. Measures of anxiety and depression (HADS), IBD specific health-related quality of life (IBDQ) and the IBD-RAPID were made at baseline (T1) and at 6-months (T2). Correlations were identified between baseline factors and outcome measures of anxiety, depression and health-related quality of life (HRQoL) at T2. Regression analysis identified T1 items predictive of the development of each outcome. Sensitivity and specificity analysis was performed to identify the strength of the models when accounting for age, gender and baseline psychological morbidity.
Results: 132 participants were recruited either online or in clinic and completed IBD-RAPID and outcome measures at T1 (median age 21 years, 65.9% female). High levels of psychological morbidity at T1 were identified: anxiety (n = 76/112, 67.9%), depression (n = 38/113, 33.6%), and impaired HRQoL (n = 115/125, 92%). Self-harm (n = 30/132, 22.7%) and suicidal ideation (n = 24/131, 18.3%) were reported at T1. N = 49/132 (37.1%) of participants completed IBD-RAPID at T2, with significant differences at baseline between completers and non-completers. Regression analysis controlled for baseline age, gender and psychological morbidity. Living with a stoma predicted development of depression (f^2 = 0.60) and feelings of sadness/hopelessness combined with impaired well-being predicted the development of a lower health-related quality of life (f^2 = 0.42). Impaired well-being predicted the development of anxiety when taking sample size into account (f^2 = 0.31).
Conclusions: IBD-RAPID is a novel tool to predict psychological morbidity in young people with IBD. In this first prospective study in this cohort, key risk factors for development of anxiety, depression and lower HRQoL have been identified – but also a high attrition rate. These findings can be incorporated into current practice and provide the basis for optimising further validation studies and their design.

P709

Early measurement of serum cytokines as predictor of clinical and endoscopic outcome to vedolizumab in patients with ulcerative colitis

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Background: Ulcerative colitis (UC) is characterised by inflammatory cell infiltration of the colonic mucosa with release of pro-inflammatory cytokines. Vedolizumab (VDZ) has been developed to block integrin α4β7 to prevent the homing of activated leucocytes into the inflamed bowel through vascular endothelium. At present, there is a lack of data on the variations of serum cytokine patterns during VDZ treatment in UC patients. Our aim was to correlate serum cytokine levels with treatment outcome in terms of mucosal healing (MH) and clinical remission (CR).
Methods: Patients treated with VDZ for moderate–severe UC were enrolled, excluding primary non responders. A blood sample was drawn before VDZ infusion at week 0, 6 and 22, and serum IFN-γ, IL-1β, TNF, IL-6, IL-8, IL-10, IL-12, IL-17A, IL-22 and IL-23 were assessed by a fluorescence assay. At the same time points, faecal calprotectin (FC) and C-reactive protein were assayed. A colonoscopy was performed at baseline and at Week 54, where MH (Mayo Endoscopic Score ≤1) and CR (Partial Mayo Score ≤1) were evaluated. IBD-Q questionnaire was performed at week 0, 6, 22 and 54 to evaluate patient-reported-outcomes.
Results: Out of 27 enrolled patients, 6 (22%) experienced loss of response during the first year of treatment. At Week 54, MH was achieved in 12 patients (44%) and CR in 17 (63%). A high value of IL-8 at week 0 correlated with MH ($p < 0.01$) after 1 year. A decrease in serum IL-6 and IL-8 at Week 6 correlated with MH ($p < 0.05$ and $p < 0.001$, respectively) and CR ($p < 0.05$ for both) after 1 year. At Week 22 the reduction of IL-8 and TNF correlated with MH ($p < 0.001$ and $p < 0.01$, respectively) after 1 year, and the decrease in IL-6, IL-8 and TNF correlated with CR ($p < 0.01$ for IL-6 and IL-8, $p < 0.05$ for TNF) after 1 year. A significant correlation was found also among FC ≤150 mg/g at Week 6 with MH and CR ($p < 0.001$ for both) after 1 year. IBD-Q results were correlated to MH and CR only at Week 54.
Conclusions: Basal serum levels of IL-8 as well as its decrease over time displayed the best correlation with the therapeutic response to VDZ. In combination with FC and, to a lesser extent, IL-6 and TNF, IL-8 monitoring could help clinicians to implement a better management of patients under treatment with VDZ.

P710

The use of first-line biologics in patients with Crohn's disease in Norway from 2011 to 2016

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Background: Treatment of Crohn's disease (CD) is preference based and might also be affected by drug costs. In Norway, biosimilar infliximab entered the market in 2014 at a reduced cost of 40% compared with the original product. We have previously shown an increase in the use of biologics for inflammatory bowel disease (IBD) between 2011 and 2014. In the present study, we aimed to assess whether there was a change over time in the proportion of patients receiving biologics between 2011 and 2016 and if the preferred first-line biologic changed after the introduction of biosimilar infliximab.
Methods: Data were collected from the Norwegian Patient Registry (NPR) and the Norwegian Prescription Database (NorPD). The study cohort was defined as all patients with at least two registered K50 (CD) within 1 year between 2011 and 2016. Patients were followed for 1 year after identification of first diagnosis code. The use of biologics is recorded with ATC codes for each patient in NPR and NorPD. The ATC codes do not distinguish between biosimilars and originators. Patients were stratified by the year of first diagnosis in order to examine change over time.
Results: A total of 4972 patients were included in the study. The total use of biologics stratified by year is shown in Figure 1. The proportion of patients receiving biologics within 1 year of diagnosis increased significantly from 21% in 2011 to 33% in 2016 ($p < 0.0001$). The proportion of patients receiving adalimumab as their first biologic after 1 year of diagnosis was 11% in 2011 compared with 4% in 2016. Opposed to this, the use of infliximab increased from 10% in 2011 to 28% in 2016. From 2011 to 2013, adalimumab was the preferred first-line biologic and this changed to infliximab after 2014.

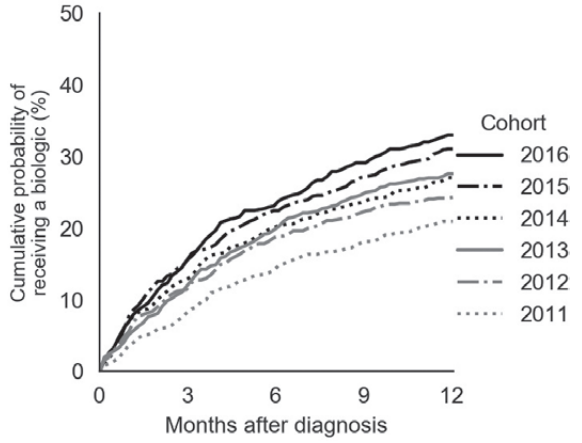

Figure 1. Cumulative probability of receiving a biologic within 1 year of diagnosis.

Conclusions: There was a significant increase in the proportion of patients who received biologics within the first year of diagnosis between 2011 and 2016. After the introduction of biosimilars in 2014, infliximab became the preferred first-line biologic.

P711

The real-life experience of vedolizumab therapy in the OBSERV-IBD cohort: a 3-year prospective observational multi-centre cohort study

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Background: Population-based studies have confirmed effectiveness and safety of vedolizumab in treating patients with UC and CD, but data beyond 1 year are laking. Herein, we provide effectiveness and safety data of vedolizumab therapy in the OBSERV-IBD cohort with a 3-year follow-up period.
Methods: Between June and December 2014, 173 patients (64 males; median age 34.7 [IQR: 27.9–45.4] years) with CD and 121 with UC (67 males; median age 40.1 [29.8–54.4] years) were treated with vedolizumab therapy. Among them, 149 were still treated with vedolizumab beyond Week 54 (78 patients with CD and 71 with UC). Disease activity was assessed using the Harvey–Bradshaw Index for CD and the partial Mayo Clinic score for UC. Clinical remission was defined as HBI ≤4 for CD patients and a partial Mayo Clinic score < 3 with a combined stool frequency and rectal bleeding subscore of ≤1. The steroid-free clinical remission rates were computed at Weeks 81, 108, 135 and 162 to the whole population included at week 0. The probability of persistence of vedolizumab therapy was studied with Kaplan–Meier method, log-rank test and Cox regression model.
Results: A total of 92 patients completed the 162-week maintenance period, including 43 in the CD group and 49 in the UC group. In the CD group, steroid-free clinical remission rates at Weeks 81, 108, 135 and 162 were 30%, 24%, 24% and 20%, respectively. In the UC group, steroid-free clinical remission rates at Weeks 81, 108, 135 and 162 were 40%, 33%, 34% and 36%, respectively. Vedolizumab dose optimisation occurred up to 59% and 52% up to week 162 in patients with CD and UC, respectively. The 1-, 2- and 3-year persistence rates of vedolizumab were 48.5%, 31.4% and 26.3% in patients with CD and 61.0%, 49.9% and 42.9% for UC, respectively. In the CD group multi-variate analysis, the persistence of vedolizumab was significantly decreased in patients with history of perianal disease (OR = 0.62, 95% CI[0.43–0.90], p = 0.01) and increased in patients with an age at induction of vedolizumab therapy > 35 years (OR = 1.47, 95% CI[1.01–2.13], p = 0.005). In the UC group multi-variate analysis, the persistence of vedolizumab was significantly decreased in patients with partial Mayo Clinic score > 6 at week 0 (OR = 0.43, 95% CI[0.25–0.74], p = 0.003) and in patients with UCEIS > 5 at week 0 (OR = 0.55, 95% CI[0.32–0.94], p = 0.03). No new safety signal was identified.

Conclusions: In the OBSERV-IBD cohort study, vedolizumab was able to maintain steroid-free clinical remission in approximately one third of patients with UC and CD up to Week 162. Loss of response resulting in discontinuation of vedolizumab occurred in approximately 10% of the patients per year.

P712

Tofacitinib efficacy in patients with moderate to severe ulcerative colitis: Subgroup analyses of OCTAVE Induction 1 and 2 and OCTAVE Sustain by 5-aminosalicylates use

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Background: Tofacitinib is an oral, small-molecule JAK inhibitor approved in several countries for the treatment of ulcerative colitis (UC). The efficacy and safety of tofacitinib were demonstrated in three Phase 3 trials (OCTAVE Induction 1 and 2, NCT01465763 and NCT01458951; OCTAVE Sustain, NCT01458574) in patients with moderate to severe UC [1]. In this post-hoc analysis, we explored tofacitinib efficacy for patients with (c5-ASA) and without (n5-ASA) concomitant 5-aminosalicylates use.

Methods: In OCTAVE Induction 1 and 2, patients received placebo or tofacitinib 10 mg twice daily (BID) for 8 weeks; clinical responders were re-randomised into OCTAVE Sustain for 52 weeks and received placebo, tofacitinib 5 or 10 mg BID. c5-ASA were permitted at entry, provided doses were stable ≥4 weeks prior to and during the trials. Remission and mucosal healing were summarised at Week 8 (OCTAVE Induction 1 and 2) and Week 52 (OCTAVE Sustain) by c5-ASA status. Generalised linear models were used to compare the adjusted treatment effects between 5-ASA subgroups (Tables 1 and 2).

Results: A smaller proportion of c5-ASA patients had prior tumour necrosis factor inhibitor (TNFi) and immunosuppressant failure compared with n5-ASA patients, at baseline of OCTAVE Induction and Sustain (OCTAVE Induction 1 and 2: TNFi failure 42.7% vs. 74.5%; immunosuppressant failure 69.4% vs. 78.3%; OCTAVE Sustain: TNFi failure 36% vs. 70%; immunosuppressant failure 67.9% vs. 80%). For both c5-ASA and n5-ASA subgroups, a higher proportion of tofacitinib-treated patients achieved efficacy endpoints, compared with placebo-treated patients, at Week 8 of OCTAVE Induction 1 and 2 and Week 52 of OCTAVE Sustain (Tables 1 and 2). Without controlling for baseline variables, higher treatment effects were observed within the c5-ASA subgroup compared with the n5-ASA subgroup; however, when controlled for prior TNFi and immunosuppressant failure (and baseline remission status in OCTAVE Sustain), the differences were not statistically significant in treatment effects between the 5-ASA subgroups in terms of adjusted odds ratios (Tables 1 and 2).

Conclusions: When controlling for prior UC treatment status, efficacy of tofacitinib, based on adjusted odds ratios, was similar regardless of 5-ASA status. This analysis is limited by subgroup size differences.

	c5-ASA, n/N (%)	n5-ASA, n/N (%)	p value (c5-ASA vs n5-ASA)[c]
Remission[a]			
Placebo	11/167 (6.6)	3/67 (4.5)	
Tofacitinib 10 mg BID	130/650 (20.0)	29/255 (11.4)	
Unadjusted difference from placebo (95% CI)	13.4 (8.6, 18.3)	6.9 (0.6, 13.2)	
Adjusted odds ratio (95% CI)	3.7† (1.9, 7.1)	2.8 (0.8, 9.4)	0.6724
Mucosal healing[b]			
Placebo	26/167 (15.6)	6/67 (9.0)	
Tofacitinib 10 mg BID	217/650 (33.4)	54/255 (21.2)	
Unadjusted difference from placebo (95% CI)	17.8 (11.2, 24.4)	12.2 (3.7, 20.7)	
Adjusted odds ratio (95% CI)	2.8† (1.8, 4.4)	2.7† (1.1, 6.7)	0.9599

[a]Remission was defined as a total Mayo score of ≤2 with no individual subscore >1, and a rectal bleeding subscore of 0
[b]Mucosal healing was defined as a Mayo endoscopic subscore of 0 or 1
[c]Between-subgroup comparisons of the adjusted odds ratios (c5-ASA vs n5-ASA)
Odds ratios and p values were obtained based on the logistic regression model
Remission status = TNFi failure + prior immunosuppressant failure + treatment + 5-ASA + treatment*5-ASA
†p<0.05 vs placebo
5-ASA, 5-aminosalicylates; BID, twice daily; c5-ASA, concomitant 5-aminosalicylates;
CI, confidence interval; N, number of patients in the treatment group; n, number of patients who met endpoint criteria; n5-ASA, no concomitant 5-aminosalicylates; TNFi, tumour necrosis factor inhibitors

	c5-ASA, n/N (%)	n5-ASA, n/N (%)	p value (c5-ASA vs n5-ASA)[c]
Remission[a]			
Placebo	15/130 (11.5)	3/44 (6.8)	
Tofacitinib 5 mg BID	48/128 (37.5)	9/48 (18.8)	
Unadjusted difference from placebo (95% CI)	26.0 (15.9, 36.0)	11.9 (-1.4, 25.3)	
Adjusted odds ratio (95% CI)	4.8† (2.5, 9.3)	3.4 (0.8, 13.7)	0.6557
Tofacitinib 10 mg BID	55/125 (44.0)	16/48 (33.3)	
Unadjusted difference from placebo (95% CI)	32.5 (22.2, 42.8)	26.5 (11.2, 41.8)	
Adjusted odds ratio (95% CI)	6.4† (3.3, 12.4)	7.4† (2.0, 28.3)	0.8483
Mucosal healing[b]			
Placebo	19/130 (14.6)	3/44 (6.8)	
Tofacitinib 5 mg BID	54/128 (42.2)	9/48 (18.8)	
Unadjusted difference from placebo (95% CI)	27.6 (17.1, 38.1)	11.9 (-1.4, 25.3)	
Adjusted odds ratio (95% CI)	4.4† (2.4, 8.2)	3.3 (0.8, 13.4)	0.7130
Tofacitinib 10 mg BID	64/125 (51.2)	16/48 (33.3)	
Unadjusted difference from placebo (95% CI)	36.6 (25.9, 47.2)	26.5 (11.2, 41.8)	
Adjusted odds ratio (95% CI)	6.5† (3.5, 12.0)	7.2† (1.9, 27.2)	0.8899

[a]Remission was defined as a total Mayo score of ≤2 with no individual subscore >1, and a rectal bleeding subscore of 0
[b]Mucosal healing was defined as a Mayo endoscopic subscore of 0 or 1
[c]Between-subgroup comparisons of the adjusted odds ratios (c5-ASA vs n5-ASA)
Odds ratios and p values were obtained based on the logistic regression model
Remission status = TNFi failure + induction remission + prior immunosuppressant failure + treatment + 5-ASA + treatment*5-ASA
†p<0.05 vs placebo
5-ASA, 5-aminosalicylates; BID, twice daily; c5-ASA, concomitant 5-aminosalicylates;
CI, confidence interval; N, number of patients in the treatment group; n, number of patients who met endpoint criteria; n5-ASA, no concomitant 5-aminosalicylates; TNFi, tumour necrosis factor inhibitors

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P713

Long-term efficacy of endoscopic balloon dilatation using single-balloon enteroscopy in patients with Crohn's disease

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Background: Small bowel stenosis is the most frequent reason for surgery in the clinical course of Crohn's disease (CD). Although there are some reports showing the efficacy of endoscopic balloon dilatation (EBD) for gastrointestinal stenotic lesions, the data confined to small bowel stenosis is limited. Therefore, we investigate the effectiveness of EBD on small bowel stenosis in CD using single-balloon enteroscopy.
Methods: Among 252 CD patients (921 examinations) who underwent single-balloon enteroscopy at our University Hospital from November 2005 to December 2017, we performed EBD for small bowel stenosis for 91 CD patients (276 EBD sessions). We investigated the long-term efficacy of EBD, EBD complications, and factors related to surgical intervention. During this study period, we were given the opportunity to use prototype single-balloon enteroscope with passive bending mechanism. We also assess the usefulness of passive bending mechanism when performing EBD in patients with CD.
Results: The average age at initial EBD was 37 years old. The cumulative surgery-free rate using Kaplan–Meier analysis was 79.7% after 3 years, 76.0% after 5 years and 73.0% after 10 years. Multi-variate analysis was performed on factors contributing to surgical intervention by Cox regression analysis. As a result, long stenosis (≥2 cm), unsuccessful EBD was the significant factors for surgery. Primary stenosis (de novo) and secondary stenosis (anastomotic) were not associated with surgery. As for complication, there were two cases of localised peritonitis and two perforation requiring surgery in 276 EBD sessions. Among patients who underwent EBD, 25 patients underwent EBD more than twice with both conventional SIF-Q260 and prototype scope with passive bending mechanism. The depth of insertion was significantly longer by using prototype single-balloon enteroscope with passive bending mechanism.
Conclusions: A relatively high cumulative surgery-free rate was obtained over a long period of time by EBD for small bowel stenosis using single-balloon enteroscopy in CD patients. Length of stenosis is the significant factor related to surgical avoidance. Prototype single-balloon enteroscope with passive bending mechanism is useful in EBD for small bowel strictures of CD.

P714

Efficacy and safety of infliximab retreatment in luminal Crohn's disease: a multi-centre, prospective, observational cohort (REGAIN) study

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Background: Although the therapeutic arsenal in Crohn's disease (CD) is expanding, reintroducing an anti-TNF treatment previously discontinued is still questionable. Data on retreatment after intolerance or loss of response remain controversial. The objective of this study was to describe the efficacy and safety of infliximab (IFX) reintroduction in luminal CD after stopping for loss of response or intolerance.
Methods: We conducted a prospective multi-centre observational cohort study including adult patients with active luminal CD in whom IFX therapy was reintroduced after at least 6 months of discontinuation. The reasons for the initial discontinuation of IFX could be a loss of efficacy after an initial response in a patient treated for at least 6 months (secondary loss of response) or intolerance to IFX regardless the previous duration of treatment. At baseline, patients had a clinically (CDAI>150) and objectively active CD (C-reactive protein level> 5 mg/l and/or faecal calprotectin>250 µg/g and/or endoscopic activity and/or radiological activity). The reintroduction schedule included three IFX infusions at weeks 0, 4, and 8, after a systematic premedication. Maintenance treatment was administered every 8 weeks. The primary endpoint was the efficacy of IFX retreatment at Week 26 defined by a CDAI < 150 in the absence of IFX discontinuation or use of corticosteroid therapy, surgery, or other biologic. Efficacy and tolerance of IFX retreatment were evaluated over a 12-month period.
Results: From June 2015 to June 2018, 96 patients were included in 16 centres. Reasons for the initial discontinuation of IFX were secondary loss of response in 47 patients (49%), intolerance in 21 patients (22%) and other reasons in 28 patients (29%). At Week 26, 34 patients (35%) reached the primary endpoint. No significant difference was observed between rates of clinical remission at Week 26 in patients with initial secondary loss of response and those with IFX intolerance (38% and 33%, $p = 0.9$, respectively). Thirty-seven patients (36%) had an intolerance reaction to retreatment with IFX on average after 3 infusions, requiring drug discontinuation in 31 (30%) cases. Optimisation of IFX treatment by increasing doses and/or frequency of infusions was necessary in 45 patients (47%) during the 12-month follow-up period. Nor the presence of anti-drug antibodies at baseline neither IFX trough level at Week 8 were predictive of IFX retreatment failure.
Conclusions: IFX retreatment is safe and efficient in more than one third of CD patients regardless the reason of prior discontinuation (loss of response or intolerance). Early pharmacokinetics at retreatment cannot predict subsequent IFX intolerance or failure at retreatment.

P715

Real-world tofacitinib effectiveness and safety in patients with refractory ulcerative colitis

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Background: OCTAVE phase III trials confirmed the efficacy of tofacitinib, an oral Janus kinase inhibitor (JAK), over placebo for induction and maintenance of remission in patients with moderately to severely active ulcerative colitis (UC). Along this and before it was approved, tofacitinib was administered to a number of patients. Here, we further evaluated the real-world results of tofacitinib in patients with refractory UC (inadequate response, loss of response or intolerance to corticosteroids, immunosuppressant, antagonists to tumour necrosis factor (anti-TNF), vedolizumab or ustekinumab).
Methods: From December 2016 through August 2018, we conducted a multi-centre, retrospective study including all patients with active UC treated with tofacitinib induction therapy (10 mg twice daily) in France. The primary end point was survival without colectomy at Week 24. Secondary end points were survival without tofacitinib interruption and steroid-free clinical remission at Week 24. Disease activity was assessed using the partial Mayo Clinic score. Remission was defined by a total Mayo score ≤ 2 without any sub-score > 1, and the clinical response was defined by the decrease in the Mayo score ≥3 points and ≥30% compared with the inclusion and decrease in the rectal bleeding sub-score ≥1 or absolute sub-score ≤ 1. Survival analyses were performed using the Kaplan–Meier method.
Results: Among 37 patients treated with tofacitinib, 23 (62%) had pancolitis. All patients had been previously treated with TNF antagonist, 26 (70%) with two or more anti-TNFs and 36 (97%) with vedolizumab. Median total Mayo score at baseline was 9 (range 4–11). Median follow-up was 24 weeks (IQR). Non-parametric Kaplan–Meier estimator showed a survival without colectomy of 77% (n = 26) at Week 24 (CI 95%, 58.9%–87.8%); survival without treatment interruption was 62.6% (n = 25) at Week 24 (44.3%–76.4%) and 58.2% (n = 9) at Week 48 (39.2%–73.1%). Clinical response occurred in 15 (41%) patients including 12 (32%) who were in steroid-free clinical remission at Week 24. Adverse events occurred in 10 (27%) patients, of whom 5 (13.5%) were serious, corresponding to infections, and 3 (8.1%) adverse events were herpes zoster infections. No deaths were reported.
Conclusions: In this highly selected refractory population with moderate to severe UC, tofacitinib achieved steroid-free remission in one-third of patients at Week 24, and colectomy was avoided in more than 75% of cases at 6 months. Safety profile was consistent with those reported in the pivotal tofacitinib studies.

P716

The use of tacrolimus in patients with ulcerative colitis resistant to standard medical therapy

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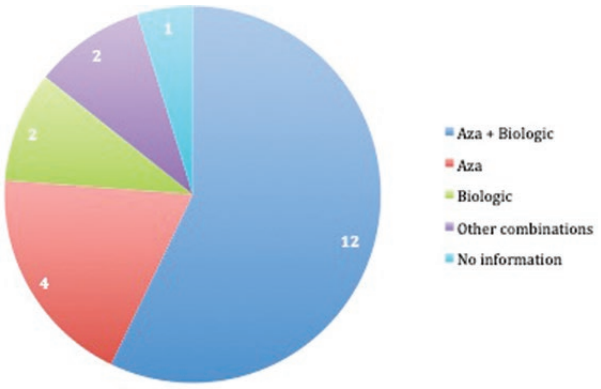
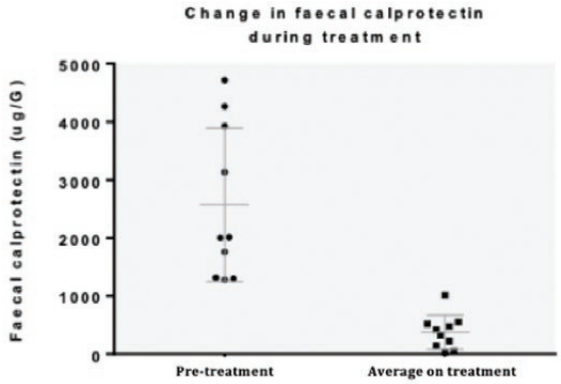
Background: ECCO guidelines support the use of tacrolimus in selected adult or paediatric patients with ulcerative colitis (UC) resistant to standard therapy. Despite these guidelines, in our experience tacrolimus is used infrequently. We present the outcomes of 21 UC patients commenced on tacrolimus at Kings College Hospital NHS Trust.
Methods: The King's College Hospital electronic patient records database was searched, including all records from January 2011 to October 2018. The search was performed using the terms, 'ulcerative colitis' and 'tacrolimus'. All records were interrogated to collect retrospective data.
Results: Our search yielded a total of 275 patients. 191 were excluded as they were on tacrolimus for an indication other than UC. A further 59 were discounted as tacrolimus was never commenced. Four were removed where tacrolimus topical ointment was used. Twenty-one UC patients (16 adult, 5 paediatric) treated with tacrolimus were identified. Mean age was 29 years (range 9–62), M:F 13:8, 13 Caucasian, 4 Afro-Caribbean, 2 Asian and 2 unspecified. Eighty-one per cent had pancolitis, 3 left-sided disease and 1 proctitis. Previous therapies are summarised in Figure 1. All patients had previously been treated with 5-aminosalicylates and steroids.



The number in each section of the pie chart indicates the number of patients on each combination. Aza – Azathioprine; Biologic – either: infliximab, adalimumab, vedolizumab or golimumab; Other combinations - mycophenolate mofetil, and mercaptopurine.

Mean duration on tacrolimus was 11 months (median 5; range, 0 – 66). 2 patients were primary non-responders and 9 terminated therapy due to adverse drug effects such as tremor, nausea and renal toxicity. 10 (48%) patients had a sustained clinical response remaining on tacrolimus for a mean of 21 months. 1 remains on tacrolimus currently, but 9 patients have had disease recurrence, with 6 patients requiring a colectomy, at an average of 16 months after starting tacrolimus. Faecal calprotectin (FCP) was used as an objective measure of disease activity. In patients on tacrolimus for a sustained period (n = 10), there was a significant reduction in FCP. Mean FCP levels pre- and during treatment were 2574 and 381, respectively (mean difference 2193, CI 1157 to 3237, p = 0.001) [Figure 2].



Comparison of patient faecal calprotectin levels before treatment and average levels on tacrolimus treatment.

Conclusions: If tolerated, tacrolimus can be an effective treatment option for patients with ulcerative colitis. This response was maintained for an average of 21 months, with a significant drop in faecal calprotectin levels.

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The use of combination biologic therapy in inflammatory bowel disease: A single tertiary-centre experience

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Background: Biologic therapy has revolutionised the care of inflammatory bowel disease (IBD). More recently, newer biologics have been approved. Despite multiple options, clinical remission rates at 1 year are approximately 40% for any single biologic agent. In addition, questions surround the efficacy of newer agents in controlling extra-intestinal manifestations (EIMs). This has raised interest in whether combination biologic therapy with agents of different mechanisms of action (MOA) can be used safely to increase overall efficacy and to control EIMs. The aim was to describe the clinical experience in IBD patients treated with combination biologic therapy at the University of Calgary IBD unit.

Methods: A retrospective single-centre cohort study was performed at the University of Calgary of adult (≥18 years) IBD patients receiving combination biologic therapy All patients received 'add on' biologic therapy either to control medically refractory disease or to treat EIMs not controlled by a single agent. Safety and efficacy of the combination biologic therapy was assessed.

Results: We identified 10 patients (9 Crohn's disease (CD), 1 ulcerative colitis (UC)) were treated with combination biologic therapy with mean follow-up of 64.8 weeks (range 10–118 weeks). All patients had failed > 3 previous biologics, All patients had a biologic added to existing biologic therapy. Primary indication to add a second biologic was medically refractory disease in 6 and control of EIMs in 4. Combinations of biologics used included: vedolizumab and adalimumab (n = 3); vedolizumab and infliximab (n = 3); vedolizumab and golimumab (n = 2); vedolizumab and certolizumab (n = 1); and ustekinumab and infliximab (n = 1). Of the 6 who were on dual biologic therapy for medically refractory disease 3/6 (50%) demonstrated clinical improvement, and 3/6 (50%) demonstrated endoscopic response. Two patients (1 CD; 1 UC) underwent intestinal resection, but neither experienced a postoperative complication.The four whose primary indication was to control EIMS; anti-TNF therapy was added to vedolizumab and all patients had complete resolution of their EIMs. One patient developed community acquired pneumonia (CAP) on high-dose steroids, golimumab, and vedolizumab. All other combinations were well tolerated during the follow-up period.

Conclusions: In this small, highly selective cohort of patients with IBD, a variety of combinations of biologic therapy were well tolerated. One patient developed CAP. The combination proved to be a successful strategy to control EIMs when anti-TNF therapy was added to vedolizumab. Further studies are needed to assess the comparative efficacy of combination strategies and long-term safety compared with single agents.

P718

Risk of tuberculosis in patients with inflammatory bowel disease receiving biologics using two interferon-γ release assays as monitoring

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Background: Screening and treatment of latent tuberculosis infection (LTBI) before starting biological therapy in patients with inflammatory bowel disease (IBD) has decreased the risk of active tuberculosis. However, among patients with a negative baseline screening there is still a risk of developing tuberculosis. Positive conversion of tuberculin skin test and/or Interferon Γ Release Assay (IGRA) have been observed during biological treatment; however, there are not enough data to recommend monitoring for tuberculosis in this setting. Our aim was to assess the likelihood of detecting a positive seroconversion of a IGRA in IBD patients with negative baseline LTBI screening

Methods: Prospective, single-centre study in IBD patients attended at a Spanish IBD unit between 2009 and 2018. Patients with normal chest radiography, negative tuberculin skin test (most patients with booster), and one or two negative IGRAs (QuantiFERON/T-SPOT-TB) at baseline, and that receiving biological treatment, were included in the study. Two IGRAs were performed once a year during treatment with biologics. In all patients we assessed TB cases occurring during follow-up.

Results: 250 patients were included (191 Crohn´s disease, 52 ulcerative colitis, 7 unclassified colitis), 137 males, mean age at the IBD diagnosis 30.5 years, mean age at the LTBI screening 38.2 years. In total, 8 patients (3.2%) (95% CI 1.5–6.4) presented a positive seroconversion of an IGRA (4 patients the first year, 1 the second year, 1 the third year, 1 the fourth year and 1 the fifth year). Four patients presented positive seroconversion of T-SPOT-TB, 2 patients presented positive seroconversion of QuantiFERON and, 2 patients positivized both IGRAs. Six of 741 T-SPOT-TB tests (0.81%, 95% CI 0.33–1.8) vs. 4 of 797 QuantiFERON tests (0.50%, 95% CI

0.1- 1.3) were positive (p not significant). After a follow-up of 949 patient-years, one patient developed an active tuberculosis; the overall incidence of active tuberculosis was 0.11 per 100 patient-years. The patient was asymptomatic and, Mycobacterium tuberculosis was isolated in sputum after two IGRAs resulted positive. Other seven patients with seroconversion were treated with isoniazid during biological therapy.

Conclusions: In an area of low incidence of tuberculosis, annual monitoring with two IGRAs in patients with IBD receiving biologics and who have had negative baseline LTBI screening is associated with a very low risk of active tuberculosis.

P719

Update of a network meta-analysis of efficacy and safety of different intravenous iron compounds in patients with IBD and anaemia

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Background: Iron deficiency anaemia (IDA) is a frequent complication of IBD and associated with reduced quality of life and increased hospitalisation rates. Modern intravenous (IV) iron compounds are evidentially safe and effective in IBD patients, facilitating rapid correction of haemoglobin (Hb) levels and iron store repletion. ECCO guidelines recommend IV iron therapy in IBD patients with IDA. Slight variances in core size, composition and density of the carbohydrate shell cause variances in the efficacy and tolerability of IV iron formulations. Here, we searched for new data to augment a first network metaanalysis (NMA) and systematic review of IV iron preparations [ferric carboxymaltose (FCM), ferumoxytol (FOX), iron sucrose/saccharate (IS), iron isomaltoside (ISM) and iron dextran (IDX)] approved in IBD, carried out in 2016.[1]

Methods: Using the same methodology, we searched PUBMED, SCOPUS, Web of Science and Cochrane databases to identify articles published from Jul 2016 to August 2018. Primary outcome measure was haematopoietic response (% of patients), defined as Hb normalisation increase of ≥2 g/dl. Secondary outcomes included total adverse events (AEs) as % of safety population.

Results: We found 151 studies including 4 prospective observational studies (2 FCM, 2 ISM) which were added to the systematic review, making 18 in total. Eligible studies on FOX were not found. No new studies eligible for the NMA of 4 studies were identified. The updated systematic review included 7 studies (n = 798) for FCM, 2 (n = 78) for IDX, 8 (n = 508) for IS, and 3 (n = 423) for ISM. Overall response rates were FCM; 599/798(78%), IDX; 33/78(42%), IS; 344/508(68%), ISM; 265/423(63%). All IV iron products were reported to be well tolerated: overall rates of AEs and serious AEs were 66/836 (7.9%) and 1/836 (0.1%) for FCM; 10/83 (12%) and 0/83 for IDX; 72/471 (15.3%) and 1/471 (0.2%) for IS; 54/454 (12.7%) and 5/424 (1.2%) for ISM, respectively. Only FCM was significantly more effective than oral iron (OR = 1.9, 95% CrI [1.1;3.2]). IS and ISM also had better response rates than oral iron (insignificant). p-values of < 0.05 for the node-splitting analysis of the Bayesian analyses indicated insignificant inconsistency.

Conclusions: Our findings indicate that FCM remains the most effective IV iron formulation as monotherapy, followed by iron sucrose. In addition, FCM tended to have a better safety profile, with fewer AEs. The totality of evidence showed that further studies are unlikely to overturn this result. Nevertheless, evidence from comprehensive head-to-head studies is needed to establish the comparative efficacy of different IV iron compounds in IBD patients with IDA.

Reference

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P720

Efficacy of exclusive enteral nutrition for induction and partial enteral nutrition for maintenance of remission in newly diagnosed paediatric and adolescent Crohn's disease

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Background: Exclusive enteral nutrition (EEN) is beneficial for inducing remission in children, and is recommended as the first-line therapy for inducing remission for newly diagnosed paediatric patients with CD. However, the long-term effectiveness of enteral nutrition (EN) therapy, including partial enteral nutrition (PEN), has not been systematically investigated. This study aimed to investigate the efficacy of EEN for inducing remission and PEN for maintaining remission in a retrospective, observational study.

Methods: We retrospectively reviewed the outcome of consecutive paediatric patients who were younger than 18 years and were newly diagnosed with active CD at our centre. The patients received EEN and PEN for inducing and maintaining remission from January 2000 to September 2018. The remission rate at Week 8 was evaluated according to the paediatric Crohn's disease activity index (PCDAI). The cumulative rate of maintaining remission was calculated using the Kaplan–Meier method. For evaluation of safety, any adverse event occurring after administration of enteral nutrition was considered.

Results: Fifty-one patients were enrolled. A total of 31 (61%) patients were boys and the median age at diagnosis was 14.0 years (range: 7.0–17.0 years). Seventeen of 51 (33%) patients received EEN therapy to induce remission. Fourteen (82%) of 17 patients achieved a clinical response and nine (53%) achieved clinical remission at Week 8. Twenty-four (47%) patients received PEN therapy to maintain remission after any induction therapy, including EEN, drug therapies, and intestinal resection. Among 24 patients who received PEN after a median follow-up of 4.2 years, the cumulative rates of maintaining remission were 58% at 1 year and 36% at 3 years. Induction therapy had no effect on the timing of relapse (log-rank test, p = 0.1946). No severe adverse events occurred.

Conclusions: EEN is effective for inducing remission. PEN may be effective for maintaining remission in newly diagnosed paediatric patients with CD, regardless of the type of the induction therapy. To the best of our knowledge, this is the first study to report the efficacy of EN therapy as maintenance remission therapy in newly diagnosed paediatric patients with CD, regardless of induction remission therapies.

P721

Effect of thalidomide on clinical remission in adult with refractory crohn disease, a multicentre, randomised, double-blind clinical trial

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Background: With the development of biological agents, the treatment of Crohn's disease (CD) have improved significantly. However, there are quite a part of CD patients for the treatment of biological agents is invalid or loss in the process of treatment response. Several clinical studies have small sample have evaluated the efficacy and safety of thalidomide in adult with Refractory CD, but the object of study is only limited in children and adolescents.
Methods: Patients were recruited in 2 Inflammatory bowel disease centres in China between August 2016 and October 2018. Adult aged 18 to 50 years were eligible for enrolment if they had active Refractory CD (after failure of steroids, Immunosuppressive drug or biological agent). Thalidomide,100 mg per day, or placebo once daily for 8 weeks. In an open-label extension, non-responders to placebo received thalidomide for an additional 8 weeks. All responders continued to receive thalidomide for an additional minimum 48 weeks. To determine whether thalidomide is effective in inducing remission in refractory CD.
Results: 25 patients were randomised to thalidomide and 25 to placebo. There were no significant difference between the two groups baseline. Clinical remission was achieved by significantly more patients treated with thalidomide (17/25 [68.0%] vs. 4/25 [16.6%], $p < 0.01$). The change in CRP were also more significantly in thalidomide than placebo(9.38 ± 20.6 mg/l vs. −5.08 ± 23.66, $p = 0.01$). Forty-seven patients who continue to receiving thalidomide after 8 week randomised, 57/5%(27/47) of them achieved clinical remission, and 9 patients had mucosal healing. Overall, 51.8%(14/27) patients maintain remission at 48th week, 2 patients remain mucosal healing. In the whole treatment process, there were 47 cases adverse drug reactions. The three most common kinds of adverse reactions were drowsiness, dermatitis and constipation. There were six patients had numbness symptoms, and four in them had abnormal electromyography.
Conclusions: In adult with refractory Crohn's disease, thalidomide compared with placebo resulted in improved clinical remission at 8 weeks of treatment. Thalidomide can induced and maintenance clinical remission and mucosal healing in refractory Crohn Disease. Although the incidence of adverse drug reactions was relatively high during the treatment of thalidomide, most of them were mild and well tolerated. Thalidomide can be useful and safely in the treatment with refractory Crohn Disease.

P722

Results of the STAR study: management of ulcerative colitis in private practice in france, in the first years following diagnosis

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Background: The STAR study was conducted to describe the management of ulcerative colitis (UC) in private practices in France and to compare real-life data with European guidelines.
Methods: STAR is an observational, retrospective, multicentre French study, conducted with private practice gastroenterologists. Data were collected in the medical records of patients, aged ≥18 years (yr), diagnosed with UC in the last 36 months (M) and followed-up for at least 12 M.
Results: Ninety physicians included 249 patients, median age 36 yr, 48.7% women and 11.8% smokers. Median UC duration was 17.7 M. The Montreal classification of UC extent was E1 41.5%, E2 39.4% and E3 19.1%. Mean disease severity perceived by physicians (EVA 0–100 mm) was 35.07 at diagnosis and 19.00 at last visit. Mean Partial Mayo Score (PMS) was 4.20 at diagnosis and 2.02 at last visit. PMS at diagnosis was 58.2% mild, 25.8% moderate, and 11.1% severe. At last visit PMS was 51.1% remission, 37.1% mild, 7.4% moderate and 4.4% severe. The first endoscopy at diagnosis showed 38.3% light activity, 54.7% moderate and 5.5% severe activity. During the first yr of treatment (trt), 76.8% patients had no endoscopy, 9.1% had colonoscopy, 4.1% rectoscopy and 10% sigmoidoscopy. In the first yr of trt, endoscopies showed healing in 28.3% patients, mild activity 39.6%, moderate 26.4% and severe 5, 7%. Trt was 5-ASA in 97.9% patients, steroids 44.9%, immunosuppressants 20.3%, anti-TNF 18.2%. At last visit, 37.3% patients were no longer receiving 5-ASA. Oral 5-ASA was prescribed in 39.7% patients, rectal 27.5% and both 32.8% patients. 5-ASA was effective from first M in 79% patients. Mean dose oral 5-ASA induction trt was 3.60 g/day. Sixty-seven per cent patients had optimal mesalazine induction trt (≥4 g/day) and 13.1% had lower dose than European recommendations (< 2.4 g/day). Mean oral 5-ASA maintenance dose was 2.14 g/day. Mean rectal induction dose mesalazine was 1.36 g/day. Median duration of oral induction trt was 83.5 vs. 48.5 d for rectal. 66.8% patients treated with 5-ASA first-line required no other drug class. 6.8% patients were hospitalised from diagnosis until the day of the visit. Since the diagnosis until the day of the last visit, 44.9% patients had steroids, 20.3% had immunosuppressants and 18.2% had at least one anti-TNF. Initiation of anti-TNF trt was not related to the severity of the disease at diagnosis (Mayo score 5).
Conclusions: 5-ASA is the gold standard trt in UC induction and maintenance management and was effective from the first M of trt. 1/5 patients were treated with immunosuppressants and 1/5 with anti-TNF indicating that many patients went directly from 5-ASA to anti-TNF without exposition to immunosuppressants. The very high use of anti-TNF in mild-to-moderate UC could partly be explained by 5-ASA underdosing.

P723

Incidence of hypophosphatemia in patients with inflammatory bowel disease treated with iron

isomaltoside or ferric carboxymaltose: results of a prospective cluster randomised cohort study

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Background: Iron deficiency (ID) and iron deficiency anaemia (IDA) are common complications in inflammatory bowel disease (IBD). ECCO guidelines states that high-dose IV iron is the treatment of choice. Ferric carboxymaltose (FCM; Ferinject®) and iron isomaltoside (IIM; Monofer®) are the high-dose iron preparations used in Europe. Hypophosphatemia is a reported side effect of both preparations and may give symptoms similar to clinical manifestations of IBD and ID/IDA. Previous publications suggest a higher risk of hypophosphatemia after FCM than IIM, but this has not yet been explored in prospective head to head studies. In this trial we investigate the occurrence of hypophosphatemia in an adult IBD population treated with either FCM or IIM.

Methods: A prospective cluster-randomised comparative two-centre study was conducted at Akershus university hospital (AHUS) and Oslo university hospital Ullevål (OUS Ullevål) over 1.5-years involving adult IBD patients with ID or IDA. Patients presenting at AHUS were treated with 1000 mg IIM and at OUS Ullevål they received 1000 mg FCM. At baseline, after 2- and 6-weeks clinical assessment of muscle function, quality of life, faecal, blood and urine tests were collected.

Results: 130 patients were recruited. Fifty-two patients at OUS Ullevål and 54 patients at AHUS were included in the per protocol analysis. Demographic data are shown in Table 1, the results on blood tests and faecal calprotectin are shown in Table 2. The incidence of hypophosphatemia at Week 2 and 6 were 72.5% and 21.6% in the FCM treatment arm compared with 11.3% and 3.7% in the IIM treatment arm ($p < 0.001$ and $p = 0.01$). The prevalence of moderate and severe hypophosphatemia in the FCM group was 56.9% and 13.7% compared with 5.7% and 1.9% in the IIM group, respectively. ($p < 0.001$ and $p = 0.05$). Details are presented in Table 3.

		Ferinject	Monofer	Total
	N	52	54	106
Sex	Women (%)	29 (56%)	25 (46%)	54 (51%)
	Men (%)	23 (44%)	29 (54%)	52 (49%)
	Age, mean (sd)	40.6 (14.1)	39.5 (13.5)	40.1 (13.7)
	Disease duration, years, mean (sd)	10.6 (9.8)	11.4 (10.6)	11.0 (10.2)
Prior surgery	Yes (%)	14 (27%)	14 (26%)	28 (26%)
	No (%)	38 (73%)	40 (74%)	78 (74%)
IBD	CD (%)	19 (37%)	28 (52%)	47 (44%)
	UC (%)	33 (63%)	26 (48%)	59 (56%)
	Mayo Score, mean (sd)	2.09 (2.3)	2.50 (2.4)	2.28 (2.28)
	HBI, mean (sd)	4.11 (4.7)	5.71 (5.2)	5.09 (5.02)
CD extension	Ileal (%)	7 (37%)	6 (21%)	13 (28%)
	Colonic (%)	2(11%)	7 (25%)	9 (19%)
	Ileocolonic (%)	10 (53%)	15 (54%)	25 (53%)
UC extension	Ulcerative proctitis (%)	9 (27%)	1 (4%)	10 (17%)
	Left sided UC (%)	11 (33%)	5 (19%)	16 (27%)
	Extensive UC (%)	13 (39%)	20 (79%)	33 (56%)

	Inclusion		First followup		Second followup	
	Ferinject	Monofer	Ferinject	Monofer	Ferinject	Monofer
Hb, mean (sd)	12.4 (1.6)	11.6 (1.8)	12.8 (1.4)	12.7 (1.5)	13.3 (1.4)	13.4 (1.5)
MCV, mean (sd)	86.5 (6.8)	81.4 (7.1)	87.9 (6.1)	83.9 (6.4)	89.1 (6.4)	84.6 (6.3)
MCH, mean (sd)	28.1 (3.0)	26.0 (2.9)	28.5 (2.9)	27.0 (2.6)	29.2 (2.7)	27.7 (2.5)
Trombocytter, mean (sd)	330.4 (113.1)	334.0 (108.6)	316.8 (106.4)	299.5 (76.9)	302.2 (106.6)	281.4 (87.3)
Reticulocytter, mean (sd)	57.8 (19.9)	45.9 (15.9)	91.3 (31.0)	71.9 (25.0)	63.3 (25.0)	43.4 (17.5)
Reticulocytter.Hb, mean (sd)	29.9 (4.1)	25.6 (5.6)	32.7 (3.4)	32.0 (3.9)	32.4 (4.0)	31.2 (3.7)
Serum.jern, mean (sd)	11.2 (6.1)	8.3 (5.8)	16.2 (6.7)	15.3 (6.7)	16.3 (6.5)	15.0 (12.6)
Transferrin.metning, mean (sd)	15.4 (7.9)	10.8 (7.4)	27.0 (10.6)	24.2 (10.4)	28.5 (11.5)	26.0 (28.1)
Transferrin.receptor, mean (sd)	4.0 (2.3)	6.5 (4.6)	3.2 (2.4)	4.8 (3.4)	3.2 (2.3)	3.7 (2.9)
CRP, mean (sd)	3.4 (4.1)	7.3 (12.4)	3.3 (4.9)	4.9 (7.6)	3.2 (4.8)	4.8 (6.4)
Kreatinin, mean (sd)	24.3 (21.9)	19.6 (28.0)	494.2 (204.9)	316.1 (139.7)	192.8 (107.1)	141.0 (131.8)
ALP, mean (sd)	78.2 (39.9)	76.3 (32.2)	78.2 (34.4)	78.5 (36.9)	76.4 (33.2)	77.6 (37.5)
Calcium, mean (sd)	2.31 (0.11)	2.33 (0.12)	2.24 (0.08)	2.35 (0.12)	2.33 (0.11)	2.36 (0.19)
Ionisert.Calcium, mean (sd)	1.21 (0.05)	1.23 (0.04)	1.20 (0.04)	1.23 (0.05)	1.21 (0.05)	1.25 (0.05)
Magnesium, mean (sd)	0.84 (0.07)	0.82 (0.08)	0.83 (0.06)	0.84 (0.08)	0.84 (0.07)	0.83 (0.08)
Fosfat, mean (sd)	1.07 (0.17)	1.15 (0.17)	0.65 (0.25)	1.07 (0.24)	1.00 (0.29)	1.14 (0.20)
Albumin, mean (sd)	42.7 (4.4)	41.7 (4.0)	43.3 (3.8)	42.5 (4.0)	44.2 (4.2)	42.9 (4.3)
Vitamin.25.D, mean (sd)	58.3 (24.4)	63.5 (21.9)	57.1 (23.1)	64.6 (20.0)	57.5 (20.8)	62.8 (21.1)
Calprotectin, mean (sd)	851 (1100)	1040 (1365)	-	-	726 (1205)	707 (956)
Calprotectin, median	298 (1100)	562 (1365)	-	-	364 (1205)	318 (956)

Time	Phosphate level	Ferric carboxymaltose (FCM; Ferinject®) No. of patients	Iron isomaltoside (IIM; Monofer®) No. of patients
Visit 2 (2 weeks)	Normal (>= 0.8 mmol/L)	13 (25%)	47 (89%)
	Mild (0.65 - <0.8 mmol/L)	9 (18%)	3 (6%)
	Moderate (0.33 - <0.65 mmol/L)	28 (55%)	3 (6%)
	Severe (<0.32 mmol/L)	1 (2%)	0 (0%)
	Missing	1	1
Visit 3 (6 weeks)	Normal (>= 0.8 mmol/L)	40 (78%)	52 (96%)
	Mild (0.65 - <0.8 mmol/L)	3 (6%)	1 (2%)
	Moderate (0.33 - <0.65 mmol/L)	7 (14%)	1 (2%)
	Severe (<0.32 mmol/L)	1 (2%)	0 (0%)
	Missing	1	0

Conclusions: This study shows a high incidence, severity and duration of hypophosphatemia in a real life IBD patient cohort after administration of a single IV dose of 1000 mg FCM. The presence of moderate to severe hypophosphatemia beyond 6 weeks is a clinical concern that needs further investigation. The results were significant compared with IIM.

P724

Vedolizumab use is not associated with increased malignancy incidence: GEMINI LTS study results and post-marketing data

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Background: Vedolizumab (VDZ) is a gut-selective antibody to α4β7 integrin approved for the treatment of moderate to severe Crohn's disease (CD) and ulcerative colitis (UC) in adults. Inflammatory bowel disease (IBD) and use of immunosuppressants are associated with increased risks of malignancy. We analysed the incidence of malignancy with VDZ using data from the GEMINI Long-Term Safety study (LTSS; NCT00790933) and post marketing data.

Methods: Malignancies from the LTSS, and those reported in the VDZ Global Safety Database from 20 May 2014 (first approval of VDZ) to 19 May 2018, were identified using Medical Dictionary for Regulatory Activities terms. The number of patients with a malignancy in the LTSS (excluding malignancies within 1 year of VDZ initiation) was indirectly standardised against the number expected, using age- and sex-specific IBD rates from Optum's Clinformatics Data Mart database (CDMD), a de-identified claims database.

Results: Of 2243 patients followed up for 7746 patient-years in the LTSS, 31 experienced a malignancy (17 CD, 14 UC); this was fewer than expected from the CDMD (31 vs. 62; ratio: 0.50 [95% CI: 0.34–0.71]; $p < 0.0001$; Table 1). The most common malignancies were renal and bladder (6) and lower GI (5). Prior anti-TNF agent use was

reported in 61% of these patients and concomitant immunomodulator use in 39%. In the post-marketing setting, 299 malignancies were reported in 293 patients in the context of 208 050 patient-years of exposure (including malignancies within 1 year of VDZ initiation; Table 2): the most common were lower GI (59) and lymphoma (33). Prior and/or concomitant anti-TNF agent or other immunomodulator use was reported in 47% and 20% of these patients, respectively; 24% had no data on prior/concomitant treatment.

Malignancy[a]	Number of patient-years	Observed number of patients with event[b]	Expected number of patients with event[c]	Ratio of observed to expected (95% CI)	*p* value
Breast	3721	2	11.19	0.179 (0.022–0.646)	0.0021*
Central nervous system	7746	2	1.47	1.364 (0.165–4.926)	0.8615
Gynaecological	3721	1	2.54	0.394 (0.010–2.194)	0.5588
Hepatic	7745	2	2.09	0.955 (0.116–3.449)	1.0000
Lower GI tract[d]	7745	5	11.92	0.419 (0.136–0.979)	0.0427*
Lymphoma	7746	1	7.28	0.137 (0.003–0.766)	0.0115*
Mouth and throat	7745	1	1.49	0.673 (0.017–3.750)	1.0000
Multiple myeloma	7746	1	2.13	0.470 (0.012–2.617)	0.7446
Prostate	4024	2	8.29	0.241 (0.029–0.871)	0.0219*
Renal and bladder	7744	6	4.51	1.331 (0.488–2.896)	0.5973
Respiratory	7740	4	4.40	0.908 (0.247–2.325)	1.0000
Soft tissue sarcoma	7746	1	0.97	1.036 (0.026–5.771)	1.0000
Thyroid	7743	3	3.19	0.940 (0.194–2.747)	1.0000
All cancers	7732[f]	31	62.46	0.496 (0.337–0.705)	< 0.0001*

*p < 0.05.
[a]Patients randomized to vedolizumab in GEMINI I. GEMINI II and GEMINI III continued to receive vedolizumab in the LTSS, whereas patients randomized to placebo switched to receiving vedolizumab; other patients, who enrolled directly into the LTSS, were vedolizumab-naïve before treatment in the LTSS.
[b]Malignancies were identified using MedDRA version 20.0 System Organ Class 'neoplasms benign, malignant and unspecified (including cysts and polyps)'. Benign neoplasms, basal cell carcinoma, haemangioma, neurilemmoma, all non-melanoma skin cancers, and malignancies with diagnoses reported before, or within 1 year after, the start of vedolizumab treatment were excluded. The corresponding follow-up time for excluded malignancies was not used in the analysis.
[c]Patients with more than one malignancy in a single site were only counted once.
[d]The expected number of patients with malignancies in the LTSS was estimated by indirectly standardizing against age- and sex-specific malignancy rates in patients with inflammatory bowel disease in Optum's Clinformatics Data Mart database.
[e]Including colorectal and anal cancers.
[f]Survival time was measured up to time of failure or the end of study follow-up. As a result, the total number of patient-years is reduced versus values of each site individually.
GI, gastrointestinal; LTSS, Long-Term Safety study.

	Indication					
Malignancy[a]	Crohn's disease	Ulcerative colitis	Unspecified inflammatory bowel disease	Not reported	Other (including off-label)	Total
Bone	0	1	0	0	0	1
Breast	11	10	0	2	1	24
Central nervous system	4	3	0	1	0	8
Ear, nose and throat	6	4	0	1	0	11
Gallbladder, bile duct and pancreatic	10	5	0	0	0	15
Gynaecological	2	3	0	0	0	5
Haematological	6	5	0	0	3[b]	14
Hepatic	3	0	0	2	0	5
Lower GI tract[c]	21	34	2	2	0	59
Lymphoma	11	14	1	5	2	33
Neuroendocrine	2	3	0	0	1	6
Oesophageal and gastric	2	0	0	2	0	4
Prostate	2	6	0	1	0	9
Renal and bladder	18	4	0	2	0	24
Respiratory	7	12	0	4	0	23
Skin (melanoma)	4	1	0	3	1	9
Skin (unspecified/other)	12	5	0	3	0	20
Thyroid	4	3	1	2	0	10
Unspecified malignant neoplasm	9	3	1	4	1	18
Unspecified GI neoplasm	0	1	0	0	0	1
Total	**134**	**117**	**5**	**34**	**9**	**299**

[a]Malignancies were identified using MedDRA version 21.0 System Organ Class "neoplasms benign, malignant and unspecified (including cysts and polyps)". Benign neoplasms, colon adenomas, non-malignant skin melanomas, and malignancies with diagnoses reported before the start of vedolizumab treatment were excluded; this time period differed from that used for the GEMINI Long-Term Safety study because 126 (42%) of the malignancy reports did not contain data on the start date of the malignancy with respect to vedolizumab therapy initiation and 128 malignancies (43%) were reported to occur within 1 year of the start of vedolizumab treatment.
[b]This includes one event each for two patients with graft-versus-host disease.
[c]Including colorectal and anal cancers. GI, gastrointestinal.

Conclusions: The number of observed malignancies in the LTSS was lower than expected from the CDMD. As observed numbers are small, individual malignancy data should not be over-interpreted, and the limitation that standardisation does not correct for other potential confounders (e.g. smoking and body mass index) should be considered. Although limitations of post-marketing safety reports, including incomplete data and voluntary reporting of events, must be considered when interpreting post-marketing data, the number of malignancies with VDZ appeared low.

P725

A prospective study of planned switch from Infliximab originator remicade to biosimilar inflectra: a multi-centre Irish experience

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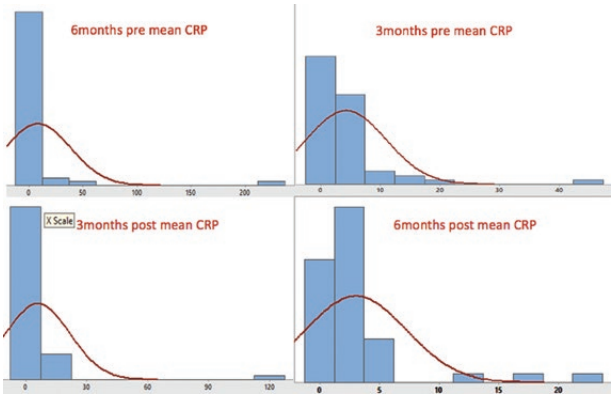
Background: Infliximab (IFX) biosimilars were approved in 2013 by the EMA. Since then, studies have shown the efficacy of IFX biosimilars appear similar to Remicade when patients are switched. The main reason for switch to bio-similar is the associated cost reduction with recent reports of cost savings up to 69%. Our aim was to prospectively assess the efficacy, safety and patient satisfaction when patients were switched from Remicade to Inflectra.
Methods: This is an open-label, non-inferiority, prospective cohort study from two Tertiary Irish hospitals involving patients with IBD >18 years receiving Remicade who were switched to Inflectra between October 2017 and August 2018. Data were collected at intervals of 3 months. Patient CRP, faecal calprotectin, IFX trough levels and antibodies (Abs) to IFX were collected.
Results: 74 patients were included in the study. Sixty-nine per cent (n = 51) had Crohn's disease. Fifty-seven per cent (n = 42) were male. Mean values for CRP at 3 monthly intervals starting 6 months prior to switching are 8.6 (CI: 0.08, 17.09), 4.3 (CI: 2.6, 6.1), 4.4 (CI: 2.9, 5.8), 5.9 (CI: 1.7, 10.2), respectively, and 3.1 (CI: 1.7, 4.4) at 6 months post switch for Centre 1. Student T-test comparing pre and post switch CRP was insignificant (p = 0.475), that is, showing no significant change. There was no difference in IFX levels pre and post switch (p = 0.72) and no new clinically significant Abs were detected. There were no crisis IBD admissions and no infusion reactions.



Mean CRP Pre and Post switch

Conclusions: Our study demonstrates the efficacy of switching to biosimilar without concern regarding safety or immunogenicity. There was no change in clinical remission rates following the switch. The majority of patients remained on Inflectra at 6 months and the switch resulted in a significant cost reduction. We aim to collect further 6 and 12 month data prior to the congress.

P726

Trough levels of infliximab better correlate with combined mucosal and transmural healing than clinical remission in Korean patients with Crohn's disease on infliximab maintenance therapy

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Background: Studies on correlations between trough levels of infliximab (TLIs) and levels of antibody to infliximab (ATI levels) with combined mucosal and transmural healing as well as clinical remission in Crohn's disease (CD) in non-Caucasians are still lacking.

Methods: TLIs and ATI levels were measured using prospectively collected serum samples drawn from CD patients on infliximab (IFX) maintenance therapy for more than 1 year at Asan Medical Center, South Korea, from August 2017 to August 2018. We analysed correlations between TLIs/ATI levels and combined mucosal and transmural healing as well as clinical remission. TLIs/ATI levels according to concomitant immunomodulator use were also evaluated.

Results: This study included 629 serum samples drawn from 348 patients. Two hundred and thirty-six patients were males (67.8%). The median age at diagnosis of CD and at starting IFX was 21.0 years (interquartile range [IQR], 17.0–29.0) and 28.0 years (IQR, 22.0–35.0),, respectively. Clinical remission (Crohn's disease activity index [CDAI] < 150) was observed in 81.9% (515/629 samples) and combined mucosal and transmural healing was observed in 29.5% (84/285 samples). TLIs differed significantly between two groups divided by a cut-off value of ATI level as 9 μg/ml-eq (2.541 μg/ml [IQR 1.193–4.598] in ATI-negative samples [n = 590 {93.8%}] vs. 0.004 μg/ml [IQR 0.001–0.021] in ATI-positive samples [n = 39 {6.2%}], p < 0.001). TLIs showed significant differences between groups with or without combined mucosal and transmural healing (3.765 μg/ml [IQR 1.807–5.203] vs. 1.554 μg/ml [IQR 0.416–3.952], p = 0.001) but not between groups with or without clinical remission (2.454 μg/ml [IQR 1.182–4.455] vs. 1.498 μg/ml [IQR 0.152–4.223], p = 0.126). There was no difference in TLIs and ATI levels according to concomitant immunomodulator use at the time of measuring TLIs/ATI levels, during induction period and continuously from induction period to the time of measuring TLIs/ATI levels (Table 1).

	TLIs (μg/ml)		ATI levels (μg/ml-eq)	
	Non-use	Use	Non-use	Use
At the time of measuring TLIs/ATI levels	2.537 (1.315–4.805)	2.213 (0.708–4.310)	0.001 (0.001–0.046)	0.001 (0.001–0.101)
	p = 0.331		p = 0.273	
During induction period	2.351 (0.826–4.741)	2.304 (0.910–4.356)	0.001 (0.001–0.012)	0.001 (0.001–0.118)
	p = 0.225		p = 0.524	
Continuously from induction period to the time of measuring TLIs/ATI levels	2.293 (0.826–4.741)	2.396 (0.910–4.325)	0.001 (0.001–0.067)	0.001 (0.001–0.118)
	p = 0.373		p = 0.642	

*Median (interquartile range)

TLIs/ATI levels according to concomitant immunomodulator use.

TLIs above 5.49, 7.16 and 9.04 μg/ml (area under the receiver-operating characteristic curve = 0.665) identified patients on deep healing with specificities of 85%, 90% and 95%, respectively.

Conclusions: TLIs better correlated with combined mucosal and transmural healing than clinical remission in Korean CD patients on IFX maintenance therapy. There was no difference in TLIs/ATI levels according to concomitant immunomodulator use.

P727

Quality of life and disease activity in children and adolescents with inflammatory bowel disease

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Background: inflammatory bowel diseases (IBD) have a major impact on quality of life (QoL). Clinical scores used in routine clinical practice do not take into account patients and families' perceptions of social lives. The main objective of this study was to evaluate QoL perceived by patients and their parents and to define the concordance among patients, parents, and physician' perception. As secondary outcomes, we aimed at assessing the impact of disease duration on QoL and the effectiveness of a psychological therapy

Methods: All consecutive children with IBD and their parents followed-up at the Pediatric Gastroenterology and Endoscopy Unit of the Department of Pediatrics of Sapienza University of Rome were recruited from June 2017 to June 2018. At each routine visit, disease activity was evaluated by the treating physician by the Physician Global Assessment (PGA). Two scores for measuring health-related QoL were administered to all patients: the Pediatric Quality of Life Inventory (PedsQL) and the IMPACT III, a 35-item self-administered questionnaire with a total score ranging from 35 (poor) to 175 (best). One or both parents completed the IMPACT III questionnaire. A subgroup of patients and their families started a psychological support

Results: One hundred twenty-one children and their parents entered the study. Mean IMPACT III was 136.55 ± 19.06 for patients and 126.59 ± 21.26 for parents (p < 0.0001), regardless of disease activity. Parents had worse perceptions mainly in the emotional and social domains, compared with their children (p < 0.0001 and p < 0.001, respectively). Disease activity evaluation was similar between patients and physician, with a negative correlation between PGA and IMPACT III (r = 0.4971; p < 0.0001). Patients with moderate/severe disease had a worse perception of QoL compared with those with an inactive and mild disease (p < 0.0001). No statistically significant difference was found based on disease duration (less or more than 1 year) (IMPACT III patients 140 ± 17.46 vs 135.06 ± 19.77; p = 0.106; parents 130.97 ± 20.7 vs. 124.75 ± 21.34; p = 0.07). Twenty patients and their families started a psychological therapy. No significant difference was found in the perception of QoL following the psychotherapy (IMPACT III patients 134.55 ± 17.73 and 140.1 ± 16.41; p = 0.162. Parents 123.67 ± 20.49 vs. 130.74 ± 22.74; p = 0.16).

Conclusions: Our study suggests that parents of children with IBD have a significantly lower perception of QoL compared with their children, independent of disease duration and activity. Children with a severe disease have a poor QoL perception, which is correlated with physician disease assessment. Psychological support was not correlated with a significant QoL improvement, probably due to the small sample size and the short study follow-up.

P728

Effectiveness and quality of life (QoL) of Ustekinumab (UST) therapy in a Real-world Setting in Germany – First Results of the RUN-CD Study

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Background: RUN-CD study is an investigator initiated, ongoing, non-interventional trial on biologics in Crohn´s Disease (CD) patients in Germany with a prospective documentation of effectiveness in induction and maintenance therapy of biologics, especially of UST. Aim of this analysis was to compare steroid-free remission rates and QoL in CD-patients after a 16 week-long induction phase of UST vs. other biologic-therapies.
Methods: From 04/2017- 09/2018 334 CD patients from 42 gastroenterology practices and hospitals with IBD-experience from all over Germany completed induction phase (Week 16) of the RUN-CD study. We compared steroid-free remission rates (i.e. HBI < 4 and no systemic use of steroids or budesonide during the last 8 weeks) in patients with UST vs. other biologics therapies. Anxiety/depression as marker of QoL was assessed by EQ-5D at baseline as well as at Week 16. T-test and χ^2-test were used to compare the UST- and other biologic-group. Level of significance was set at $p < 0.05$ (two-sided).
Results: 174 CD-patients received a new UST therapy while 160 patients were newly treated with another biologic (Infliximab: 38.1%; Adalimumab: 46.0%; Vedolizumab: 15.9%). Baseline characteristics were well balanced between both groups (UST/other biologics; p>0.05): males: 42%/48%, mean (SD) age [years]: 41 ± 14/43 ± 15, smokers: 31%/24%, mean (SD) disease duration [years]: 13 ± 10/11 ± 11, extraintestinal manifestations: 41%/39%, stenosis: 30%/33%. Perianal fistula was more frequent in patients with UST therapy (32% vs. 23%; $p < 0.05$ Steroid-free remission rates after induction phase in patients with UST and other biologic therapies were 45.4% vs. 49.4% ($p > 0.05$), respectively. Concomitantly, we found a significant reduction of patients who were anxious or depressed with 48.0% at baseline to 36.4% at Week 16 in the UST group and from 48.8% to 34.5% in the group of other biologics (reduction in both groups: $p < 0.05$; difference between groups: $p > 0.05$). In the UST group 21 patients were biologic-naïve and 54 were biologic-experienced with one previous biologic treatment; in the group with other biologics, these were 115 and 33 patients. Stratified to biologic-naïve and biologic-experienced with one previous biologic treatment, steroid-free remission rates were 47.6% (UST) vs.. 49.6% and 51.9% (UST) vs. 54.6% (p>0.05).
Conclusions: In this real-world setting remission as assessed by symptom scores rates or QoL, respectively, were similar between patients receiving UST and other biologic therapies. Surprisingly the clinical effectiveness in biologics-naïve patients was not superior to biologics-experienced CD patients.

P729

Faecal calprotectin and faecal immunochemical test have different values depending on mucosal status in patients with ulcerative colitis

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Background: Although faecal calprotectin (Fcal) and faecal immunochemical test (FIT) have been to be associated with endoscopic disease activity in ulcerative colitis (UC), the values of each marker depending on the mucosal status are not well known. This study evaluated the differences between two faecal markers depending on the mucosal status in UC.
Methods: A total of 174 results, obtained in simultaneous examination with endoscopy and faecal tests, were retrospectively evaluated for 127 UC patients from March 2015 to February 2018. The usefulness of faecal markers as a surrogate marker of endoscopic disease activity and the difference between faecal markers depending on the mucosal status was statistically evaluated. Endoscopic disease activity of UC was analysed by Mayo endoscopic subscore (MES) and ulcerative colitis endoscopic index of severity (UCEIS).
Results: Both faecal markers showed statistically significant correlation with MES (r = 0.678 for Fcal ($p < 0.001$) and r = 0.635 for FIT ($p < 0.001$)) and UCEIS (r = 0.711 for Fcal ($p < 0.001$) and r = 0.657 for FIT ($p < 0.001$)). Fcal was significantly superior to FIT in predictive accuracy for endoscopic disease activity (AUC; 0.863 vs. 0.765 in MES ($p < 0.001$) and AUC; 0.847 vs. 0.757 in UCEIS ($p < 0.001$). FIT was significantly superior to Fcal in sensitivity for complete mucosal healing (98.0% vs. 78.4% in MES, 94.9% vs. 74.6% in UCEIS).
Conclusions: Both Fcal and FIT were well correlated with endoscopic disease activity in UC patients. Fcal was more accurate correlation with endoscopic disease activity in patients with active inflammation, while FIT was more sensitive in predicting the achievement of complete mucosal healing.

P730

Short and long-term outcome of acute severe colitis

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Background: The acute severe colitis is a serious complication of inflammatory bowel disease(IBD). It can lead to colectomy and death. Its medical treatment has been step forward within the last decades. Hence, an improvement of the prognosis of this life-threatening disease has to be proven.
Methods: All patients admitted for acute severe colitis have been retrospectively enrolled, between the years 2000 and 2018. Demographic , clinical, laboratory and endoscopic data were gathered. Standard therapy based on intravenous corticosteroids was initially led in all patients. Short and long-term evolution has been reported, precising the rate of proceeding to cyclosporine or infliximab and referral to colectomy.
Results: 62 patients with acute severe colitis were reviewed (median age: 31 years (12–60 years); 34 females and 30 males). There were 57.8% with ulcerative colitis, 34.4% with Crohn's disease and 6.3% with indeterminate colitis. 54.7% of severe colitis occur on an already known underlying IBD. 25.7% of them were not receiving

any immunosuppressive therapy. A super-imposed infection was reported in 5 patients (Salmonella in three cases and CMV in two cases). Forty-four patients (68.8%) responded to a first-line treatment. Among patients with steroid-refractory colitis (20 patients), urgent colectomy was performed in 5 cases , 10 patients received infliximab(5 mg/kg on days 0, 14 and 42) and 5 patients received cyclosporin (2 mg/kg per day). Ninety per cent of patients given infliximab had a clinical response compared with 80% given ciclosporin. These two drugs have equivalent efficacy as a rescue therapy in steroid-refractory acute severe colitis (p = 0.59). After a median follow-up of 76 months, colectomy- free survival rates at 1 and 5 years were, respectively, 77% and 63%. Cumulative incidence of first infliximab use at 1 and 5 years was, respectively, 12% and 32%. Two patients died due to severe septique complications.

Conclusions: The first severe flare of IBD responds often to steroids. Our study further confirms a similar efficacy of both infliximab and ciclosporin as a rescue therapy. Colectomy rate and mortality are still high in acute – phase. Nevertheless, the long-term prognosis is excellent.

P731

Characteristics and follow-up on body composition, physical activity and quality of life in paediatric patients with inflammatory bowel disease

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Background: Paediatric inflammatory bowel disease (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC) is associated with malnutrition and weight loss affecting body composition (BC). Characteristic symptoms of IBD are abdominal pain, arthralgia and fatigue leading to impaired physical activity (PA), affecting muscle, bone strength and quality of life (QoL). According To the best our knowledge, there is no other follow-up study analysing BC, PA, and QoL, therefore the aim of this study was to characterise these parameters in newly diagnosed CD and UC patients, and to follow them for a 6 month long period of time.

Methods: BC, PA and QoL was detected in IBD patients (n = 57, range: 10–18 years). Our patients were divided into four groups: newly diagnosed CD patients (nCD: n = 20; mean age: 13.3 ± 2.2 years), newly diagnosed UC patients (nUC: n = 14; mean age: 13.6 ± 2.3 years), and CD (btCD: n = 12; mean age: 15.6 ± 2.5 years) and UC patients (btUC n = 11, mean age: 15 ± 3.6 years) receiving biologicals. BC, including fat-free mass (FFM), and body fat mass (BFM) and skeletal muscle mass (SMM) was measured via bioelectrical impedance, using the InBody 720 device. PA was assessed with the Physical Activity Questionnaire (PAQ) and QoL with the validated IMPACT-III questionnaire. Patients were measured at the time of the diagnosis (M0), after 2 months (M2) and after 6 months of the diagnosis (M6). According to healthy controls BC data (n = 307, mean age: 14.28 ± 2.1) FFM, BFM and SMM z-scores were calculated via the LMS method.

Results: BMI and FFM index (FMMI) increased between M0 and M2 in nCD group. Between M2 and M6 weight, BMI, FFMI and SMM index (SMMI) increased further. weight z-score, BMI z-score and FFM z-score also increased during the 6-month follow-up. In the nUC group BMI, weight, FFM SMMI and QoL was higher at M2 compared with M0. In btUC group, BMI, FFMI, weight z-score, BMI z-score and BFM z-score increased significantly between M2 and M6. According to weight z-score, BMI z-score and FFM z-score, the highest number of under- or malnourished children (under -1 score) were in nCD group (8/20, 8/20, 10/20). The lowest number of under- or malnourished children were in btCD group (weight: 1/12, BMI: 4/12, FFM: 1/12).

Conclusions: Our data suggest that nCD patients have the worst nutritional status, which improves in the first 6 months after diagnosis. Patients, with a longer disease course, had better nutritional status.

P732

Endoscopic Balloon Dilation Of Symptomatic Intestinal Crohn's disease Strictures: Long-Term Data On Efficacy And Safety In A Cohort Of Patients Followed-up For 10 Years.

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Background: Crohn's disease (CD) is a chronic disease frequently complicated by obstructive symptoms secondary to development of intestinal strictures. In the medium-short-term period endoscopic through-the-scope (TTS) balloon dilation offered a valid therapeutic alternative in those with intestinal symptomatic strictures. Data on long-term efficacy and safety are still lacking. We present data from a cohort of CD patients treated with balloon dilation and followed for up to 10 years.

Methods: In 2011 we published data on a cohort of CD patients with symptomatic naïve or post-operative intestinal strictures treated effectively with endoscopic TTS balloon dilation (1–2–3 years cumulative symptom-free rates of 76%, 55% and 46%). In this cohort last balloon dilation was performed in December 2008 and 4 out of 37 patients underwent surgery. We followed-up the remaining 33 patients to the present day. Data on obstructive symptoms relapse, hospitalisation, surgical recurrence and safety were collected.

Results: We collected data on 28 out of 33 patients (5 patients were lost at the follow-up): 16 male (57%), 27/28 patients had a post-operative stricture. Twenty-three patients (82%) have suffered from a clinical relapse (obstructive symptoms) through the follow-up, while 5 (18%) were in clinical remission: 7 (25%) were treated with mesalamine/steroids as needed, 6 (21%) with immunosuppressants and 15 (54%) with biological therapies. Fifteen/23 symptomatic patients (65%) underwent a new balloon dilation: 1 dilation in 6 patients, 2 dilations in 4, and more than 2 dilations in the remaining 5 patients; no complications after the re-dilation were recorded. Eight/23 symptomatic patients (25%) did not undergo a new balloon dilation: 4 were treated conservatively (steroids) while 4 were operated-on due to severe intestinal obstruction not

suitable for endoscopic dilation. In patients treated with a new dilation, 60% (9/15) avoided new surgery at the end of the follow-up (75.8 ± 38.9 months). Seventeen patients (61%) were hospitalised during the follow-up (in 10 patients hospitalisation was scheduled to perform surgical intervention rather than an obstructive flare). Final overall surgical rate was 36% (6 patients in those re-dilated and 4 in those not re-dilated) with 64% of patients 'free from surgery' with or without new endoscopic balloon dilations.

Conclusions: Data from this long-term study shows that balloon dilation is an effective and safe procedure to treat CD symptomatic strictures. After an initial effective balloon dilation the sustained clinical benefit through the follow-up was over 60% considering that in those with obstructive symptoms relapse balloon dilation can be safely repeated limiting the need for surgery to just 1/3 of the patients.

P733

Comparative Analysis of Monotherapy and Combination Biological Therapy for Crohn's disease and ulcerative colitis: Results from a Multi-Country Study in Europe

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Background: To assess patterns of biological monotherapy and combination therapy usage in Crohn's disease (CD) and ulcerative colitis (UC) patients across the EU5 (UK, Germany, France, Spain, Italy) over the period of 4Q2017 (4Q17) to 3Q2018 (3Q18), and the effects on remission rates.

Methods: Data from Ipsos Autoimmune Therapy Monitor, a multicentre medical chart-review study of CD and UC patients was conducted among physicians (mostly gastroenterologists) from EU5 to collect de-identified data on patients currently on a biologic/biosimilar or discontinued from one within past 3 months. Physicians were recruited from a large panel to be geographically representative in each country. Patient charts of ~4–6 successive patients visiting each centre/practice during study periods 4Q17 and 3Q18 were selected and stratified based on biologic use (monotherapy or combination therapy). Demographics, clinical characteristics, treatment patterns and disease status (incl. assessment of 'disease remission', per physician clinical judgement) was collected and analysed using descriptive statistics.

Results: In 4Q17, 194 physicians abstracted data on 1037 CD and 713 UC patients; in 3Q18, 207 physicians abstracted 1148 CD and 745 UC patients. CD combination therapy rates remained stable over time (4Q17: 30.8%, 3Q18: 30.6%). In UC patients, the proportion receiving combination therapy decreased slightly over time (4Q17: 49.9%, 3Q18: 46.8%) The proportion of immunologic naïve CD combination therapy patients increased over time (4Q17: 15.0%, 3Q18: 27.1%, $p \leq 0.01$), similar increase was also seen in UC patients (4Q17: 31.2%; 3Q18: 43.8% ($p \leq 0.01$)). The rate of combination therapy with steroid use remained stable among CD patients (4Q17: 36.1%; 3Q18: 40.7%), however, increased among the UC patients (4Q17: 23.0%; 3Q18: 33.8%, $p \leq 0.05$). Significant increase in remission rates were seen among the CD patients on monotherapy (4Q17: 75.3%, 3Q18: 80.1%, $p \leq 0.05$), however, rates remained stable for combination therapy patients (4Q17: 58.0%, 3Q18: 58.8%). Remission rates among monotherapy UC patients remained stable (4Q17: 71.1%, 3Q18: 76.5%) but there was a significant decrease in remission rate among combination therapy patients (4Q17: 73.0%, 3Q18: 64.5%, $p \leq 0.05$).

Conclusions: In this study, there was a significant increase in combination therapy use among biologic naïve CD and UC patients from 4Q17 to 3Q18 suggesting that physicians are taking a more progressive approach to treating patients. However, CD patients on monotherapy showed better remission rates compared with others patient groups. Further study on treatment patterns and potential confounders impacting the remission rates is warranted.

P734

Combining endoscopic and histological activity for predicting response to treatment

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Background: Biological therapy (both anti-TNF and anti-integrins) currently represents the best treatment for moderate-to-severe ulcerative colitis (UC). Clinical trials and real life studies have reported their ability in achieving clinical, endoscopic and, recently, histological remission. However, about 60% of patients fail to achieve remission or failing to respond or have adverse events, so need 'switching'or 'swapping' strategies or surgery. It would be valuable to be able to predict which patients will respond to these drugs. Data regarding the predictive role of endoscopy and histology are scarce. Aim was to assess the role of endoscopy and histology in predicting response to biological drugs.

Methods: We conducted a single-centre retrospective analysis on adult patients with moderate-to-severe active UC who underwent biological treatment, enrolling only patients with full endoscopic and histological assessment at baseline and at control time (at 48 weeks). Endoscopic and histological disease activity were assessed with the Mayo Endoscopic Subscore (MES) and the Nancy Histological Index (NHI), analysing the worst colonic segment. Clinical response to treatment was defined as a partial Mayo Score (PMS) < 2. Statistical analysis included Fisher exact test and Receiver-operator characteristic (ROC) curves (a p value less than 0.05 was considered significant).

Results: Thirty adult patients referring to a single IBD Unit (Negrar Hospital) were enrolled. At baseline 63.3% (19/30) of patients were MES =3 while 36.7% (11/30) were MES=2. NHI was 4 in 60% (18/30) of patients, 3 in 33.3% (10/30) of patients and 2 in 6.7% (2/30) of patients. 46.7% (14/30) of patients were treated with Infliximab, 13.3% (4/30) with Adalimumab, 33.3% (10/30) with Golimumab and 6.7% (2/30) with Vedolizumab. At control time 30% (9/30) of patients achieved clinical remission, 26.3% (5/19) with MES=3 (of these, 4 with NHI=4 and 1 with NHI < 4) and 36.4% (4/11) with MES=2 (all with NHI < 4) at baseline. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of MES alone were 44.4%, 66.7%, 36.4% and 73.7%, respectively. The area under the ROC curve (AUROC) was 0.56. When MES=2 was analysed with NHI, sensitivity, specificity, PPV

and NPV were 71.4%, 100%, 66.7% and 100%, respectively. The AUROC was 0.86. When MES=3 was analysed with NHI, sensitivity, specificity, PPV and NPV were 20%, 64.3%, 16.7% and 69.2%, respectively. The AUROC was 0.42.

Conclusions: The combination of histology, evaluated using the NHI, and endoscopy, evaluated with MES, above all for moderate disease (MES), could identify patients who may not respond to biological treatment.

P735

Immunogenicity differences between anti-TNF drugs

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Background: The aim of this study was to determine the prevalence of immunogenicity in patients receiving anti-TNF drugs (infliximab and adalimumab) in our hospital and to analyse if there are differences in terms of immunogenicity between these drugs.

Methods: We conducted a retrospective observational study between May 2015 and October 2018, in a reference hospital area (330 beds). We included all patients diagnosed with inflammatory bowel disease that received treatment with infliximab or adalimumab and the serum levels of these drugs between May 2015 and October 2018. The variables studied were: sex, age, number of serum samples collected, main diagnosis, previous biologic therapy, serum drug concentrations and antibody levels. Antibody levels were performed in patients who had undetectable serum concentrations of the drug. We used χ^2 test to compare the association between categorical variables.

Results: We included 181 cases (151 patients), of which 62.5% were male, the mean age was 42.6 (SD: 14.5) years. 73.2% had Crohn's disease. A total of 468 drug serum levels were collected, 61.1% infliximab (22.7% biosimilar) and 38.1% adalimumab. The adalimumab and originator infliximab mean serum trough level was 7.2 (SD: 4.3) µg/ml and 7.2 (SD:4.5) µg/ml, respectively, vs. 8.3 (SD: 7.8) µg/ml for biosimilar infliximab (p = 0.790). The prevalence of immunogenicity was 24/181 cases (13.3%). In terms of immunogenicity, no significant difference was found between infliximab vs. adalimumab (16% vs. 9.9%, respectively, p = 0.227). Similarly, there were no significant differences between originator infliximab vs. biosimilar infliximab (13.6% vs. 19.5%, respectively; p = 0.425). The median adalimumab antibody levels was 993.5 (DE:2199.4) AU/ml, 199.3 (DE:305.7) AU/ml for originator infliximab and 83.21 (78.9) AU/ml for biosimilar infliximab. The median time for antibodies appearance was 15.2 weeks (SD: 11.9) for adalimumab and 20.5 weeks (SD: 20.5) for infliximab, with no significant difference between them (p = 0.47).

Conclusions: The introduction of drug monitoring for anti-TNF drugs, including drug concentration and antidrug antibody level testing represents a fundamental mainstay for the optimisation of these treatments. In our study, we identified a similar anti-TNF antibody levels to other published series. There are no significant differences between both anti-TNF drugs in terms of immunogenicity. Furthermore, we found no significant difference in the mean concentration of the drug between originator infliximab and biosimilar infliximab nor a significant difference in terms of immunogenicity, suggesting that biosimilar infliximab is a cost-effective alternative to the reference product.

P736

Characteristics of polymeric formula and mode of delivery of exclusive enteral nutrition have no effect on disease outcome and weight gain in children with Crohn's disease

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Background: This study aimed to evaluate the difference in the mode of exclusive enteral nutrition (EEN) delivery (orally or via nasogastric (NG) tube) and type of polymeric formula (with taste vs. tasteless and isocaloric vs. hypercaloric) on the disease outcome and nutritional status in children with Crohn's disease (CD).

Methods: This was a single-centre retrospective study which included all CD patients which were initially treated with EEN in the period from October 2007 to November 2017. All patients received polymeric formula which was based on physicians and child preference provided orally or via NG tube.

Results: A total of 92 CD patients were included in the study (mean age 13.6 ± 3.0 years; 45.7% female). Overall 42 (45.7%) patients received EEN via NG tube until the end of EEN period. Remission was achieved in 71 (77.2%) children. There was no difference in the EEN failure, remission duration, inflammatory markers and weight gain at the end of EEN period between oral intake and NG tube groups.

	Oral (n = 50)	NG tube (n = 42)	p
EEN failure (n, %)	12 (24)	9 (21.4)	0.808
Weight change after EEN (kg, mean ± SD)	0.1 ± 2.8	0.4 ± 2.8	0.252
CRP change after EEN (mg/l, mean ± SD)	–21.6 ± 5.8	–36.3 ± 6.8	0.1

Difference between patients treated with exclusive enteral nutrition (EEN) and corticosteroids at diagnosisNone of the factors including age, type of formula (with taste vs. tasteless and isocaloric vs. hypercaloric) and mode of delivery (orally vs. trough NG tube for the whole duration of EEN) were associated with EEN failure.

	HR	95% CI
Age	1.011	0.742–1.378
Enteral formula with taste	0.412	0.086–1.960
Hypercaloric (1.5 kcal/ml) enteral formula	2.5	0.377–16.588
NG tube for the duration of EEN	1.001	0.286–3.504
Energy intake via EEN (kcal/kg body weight)	0.964	0.907–1.025

Risk factors at diagnosis associated with exclusive enteral nutrition (EEN) failure.

Conclusions: This study failed to demonstrate any benefit in the provision of EEN via NG tube in paediatric patients with CD.

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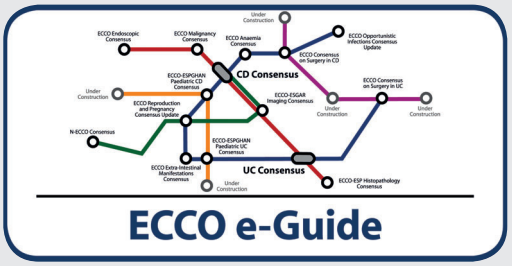

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P737

SPOSIB SB2: A Sicilian prospective observational study of patients with inflammatory bowel disease treated with infliximab Biosimilar SB2 (Flixabi®): interim analysis

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Background: No data on the recently introduced Infliximab (IFX) biosimilar SB2 (Flixabi®) in inflammatory bowel diseases are available.
Methods: SPOSIB SB2 is a multi-centre, observational, prospective study performed among the cohort of the Sicilian Network for Inflammatory Bowel Disease (SN-IBD). All consecutive patients with Crohn's disease (CD) or ulcerative colitis (UC) starting IFX Biosimilar SB2 (Flixabi) from the introduction of the drug in Sicily (March 2018) to September 2019 (18 months of enrolment) were or will be eligible. The primary end-point is the assessment of safety, in terms of rate of serious adverse events. Secondary end-points include the evaluation of efficacy, in terms of proportion of patients achieving steroid-free clinical remission and partial response at 8 weeks and at the end of follow-up. Herein we report preliminary data of the first 6 months of the study (March 2018–September 2018).
Results: 77 patients (median age 39 years; CD 50.6%, UC 49.4%) were included. Forty-six patients (59.7%) were naïve to anti-TNFs. Sixty-six patients (85.7%) were not previously exposed to IFX, while 8 patients (10.4%) switched form IFX originator to SB2, and 3 (3.9%) from IFX biosimilar CT-P13 to SB2. The cumulative number of infusions of SB2 was 215, the mean follow-up was 2.2 ± 1.7 months (median 1.8 months, interquartile range: 0.4–3.8 months), and the total follow-up time was 14.2 patient-years (170.8 patient-months). Serious adverse events occurred in 7 out of 77 patients (9.1%), with an incidence rate of 49.3 per 100 person-years, and six of them caused the withdrawal of the drug. In details, three infusion reactions, three arthritic flares/arthralgias, and one case of flu-like syndrome were reported. The efficacy of IFX biosimilar SB2 was evaluated in 35 patients who completed at least 8 weeks of follow-up using time-to-event methods for censored observations: 17 patients (48.6%) had steroid-free remission after 8 weeks, 8 patients (22.8%) achieved a partial response, while 10 patients had no response (28.6%). Among the 25 patients with steroid-free remission or response at Week 8, the efficacy rates were 96.6%, 89.1%, and 72.8% after 12, 16, and 20 weeks of therapy, respectively.
Conclusions: These are the first data worldwide on the use of IFX biosimilar SB2 in IBD. Our preliminary results showed that efficacy and safety of SB2 seem to be overall similar to those reported for IFX originator and IFX biosimilar CT-P13. Anyway, these data need to be confirmed at the end of the study, when more patients and a longer follow-up will be available.

Epidemiology

P738

The budget impact of early dose optimisation with golimumab in ulcerative colitis in the UK

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Background: The PURSUIT study found that ulcerative colitis patients who were non-responders (based on full Mayo score) to subcutaneous golimumab treatment at Week 6 may benefit from receiving a dose of 100 mg golimumab from Week 6 onwards, with 28% of non-responders at Week 6 becoming responders by Week 14. The aim of this study was to assess the budget implications of optimising a patient's dose at Week 6 compared with other first-line therapies as per current clinical practice
Methods: A decision tree model was designed to follow a patient's response to first-line treatment and to track a patient's progression through subsequent line of therapy. The budget impact model only considered drug costs from the perspective of the UK NHS. In total three lines of therapy were covered by the decision tree over a 1 year time horizon. Patients could have first-line treatment with one of the three treatment strategies; golimumab (current treatment practice), golimumab (dose optimisation based on the PURSUIT trial) and adalimumab. Within each of the comparator treatments dose escalation was considered, based on the median time to escalation and proportion of patients receiving dose escalation. Subsequent therapy for golimumab patients was adalimumab and patients who received adalimumab as a first-line therapy received golimumab as a second-line therapy. Response rates, time to loss of response and treatment costs were taken from published data sources. The cost of golimumab was equal between 50 mg pack and 100 mg pack. The model used assumption for second-line response rates; this has been tested in sensitivity analysis.
Results: The use of dose optimisation for golimumab does not increase expenditure of drug costs compared with golimumab (single dose) with a cost saving of £42 per patient per year. When comparing dose optimisation for golimumab to adalimumab, golimumab was cost saving over 1 year of treatment with cost saving of £2138 per patient. The number of patients in a response health state was similar across all three treatments (47.7%, 47.6% and 45% for golimumab (single dose), golimumab (dose optimisation) and adalimumab, respectively.
Conclusions: The implementation of dose optimisation at Week 6 for golimumab was cost saving compared with golimumab (current treatment practice) or adalimumab. The analysis highlights the need for immediate implementation of the updated GLM label in clinical practice for potentially more cost savings.

P739

The progression of inflammatory bowel disease throughout Latin America: a systematic review

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Background: The incidence and prevalence of ulcerative colitis (UC) and Crohn's disease (CD) is stabilising in the Western world, but increasing in developing countries. Epidemiological data on IBD is lacking from Latin American countries. The aim of this systematic review is to summarise the clinical and epidemiological information on IBD arising from countries in Latin America.

Methods: Three databases (MEDLINE, EMBASE, SciELO) were searched until September 12, 2018 for clinical or epidemiological data on IBD from all Latin American countries and territories. We assessed the following outcomes: incidence and prevalence; ratio of patients diagnosed with UC vs. CD (ratios greater than 1 favour UC); phenotype as defined by the Montreal Classification; proportion of population prescribed IBD medications (i.e., steroids, 5-ASA, immunomodulators, and anti-TNF agents); and proportion of intestinal resections. Choropleth maps of the UC:CD ratio were created using Jenks Natural Breaks.

Results: We identified 1434 abstracts with 126 articles selected for full-text review, and 61 articles were used for data extraction. Incidence and prevalence of IBD is steadily rising throughout Latin America. For example, the incidence of CD in Brazil rose from 0.08 in 1988 to 0.68 (1991–1995) to 5.5 per 100 000 in 2015. The highest reported prevalence of IBD is in Argentina (2007) at 15 and 82 per 100 000 for CD and UC, respectively. The UC:CD ratio exceeds 1 in all regions throughout Latin America with the exception of Brazil where the states of Alagoas, Rio de Janeiro, and Mato Grosso do Sul reported more CD than UC patients

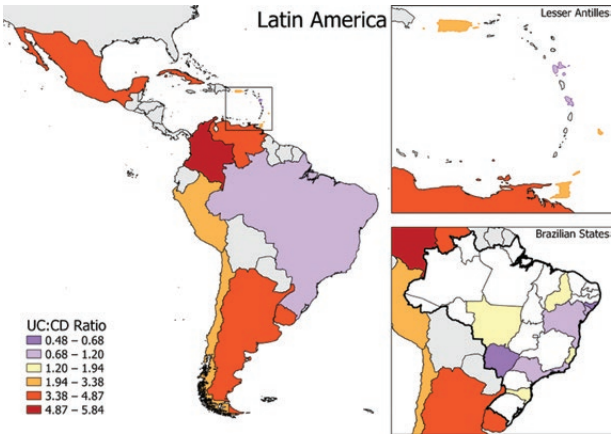

Figure 1. UC:CD ratio map.

The proportion of patients prescribed anti-TNF has steadily risen for CD (e.g. Brazil: 29.6% in 2005–2012 to 43.4% in 2014), but not UC (e.g. Brazil: 4.5% in 2014). Surgery for IBD is overall declining. In contrast, other regions showed stable colectomy rates pre- and post-introduction of anti-TNF for UC: e.g. in Peru, colectomy for UC 6.9% in 2001–2003 and 6.2% in 2004–2014

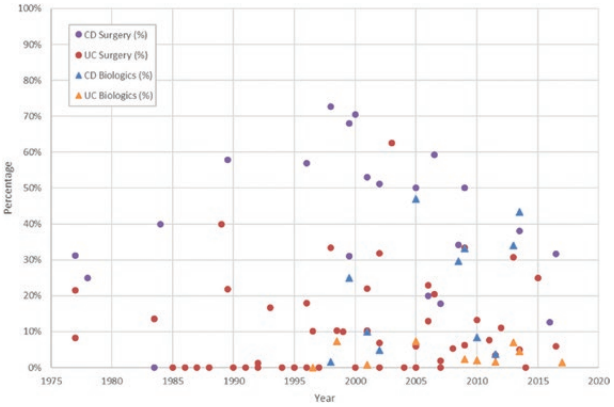

Figure 2. Proportion of Crohn's disease (CD) and ulcerative colitis (UC) patients prescribed anti-TNF therapy and undergoing an intestinal resection in Latin America.

Conclusions: The burden of IBD is expanding throughout Latin America. Heterogeneity between countries may offer important clues into the pathogenesis of IBD, as well as identify regions requiring standardisation in management and healthcare delivery. Additional population-based epidemiologic studies are needed to better define the evolving burden of IBD throughout Latin America.

P740

Sexual quality of life in inflammatory bowel disease: a multi-centre, national-level study

J. Roseira*[1], F. Magro[2], S. Fernandes[3], C. Simões[3], F. Portela[4], V. Ana Isabel[5], M. Patita[5], C. Leal[6], P. Lago[7], P. Caldeira[8], T. Gago[8], P. Currais[9], A. Sampaio[10], C. Dias[2], H. Tavares de Sousa[11], on behalf of GEDII

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Background: The impact of inflammatory bowel disease (IBD) in sexuality is one of patient's main concerns. Most studies narrowly focus on sexual organic disfunction rather than patient-perceived sexual quality of life. Our aim was to address sexual quality of life in IBD and population controls.

Methods: After an initial pilot study in 2016, the authors conducted a multi-centre, cross-sectional case–control design study, using an anonymous self-administered questionnaire. This multi-modal questionnaire included sociodemographic data and four validated instruments: The Short IBD Questionnaire (SIBDQ), Social Desirability Scale (SDS), Sexual QoL Questionnaire-Male/Female (SQoL-M/F), Nine-item Patient Health Questionnaire (PHQ-9). Results were compared against healthy controls.

Results: 869 patients (575 Crohn's disease, 294 ulcerative colitis) and 398 population controls fulfilled the questionnaire. Patients' gender (52.7% women vs. 47.3% men) and clustered age (47.5% < 40 years old vs. 49.8% ≥40 years old) were adjusted. There was no difference

for the SDS for IBD and controls (7 vs. 7; $p = 0.49$), meaning the reliability of responses was homogeneous. IBD patients reported a poorer SQoL (men: 77.3 vs. 83.8, $p = 0.007$; women: 70.4 vs. 81.6, $p < 0.001$) and a higher incidence of depression (6 vs.5; $p < 0.001$) than controls. 189 patients scored for moderate–severe depression indicators. For IBD, SQoL was correlated with health-related QoL (HRQoL) measured by the SIBDQ (men: $r = 0.48$, women: $r = 0.45$; $p = 0.00$), and negatively correlated with depression symptoms (men: $r = -0.47$, women: $r = -0.48$; $p = 0.00$). Similarly, perianal disease was associated with a poorer HRQoL and a higher incidence of depression. However, perianal disease did not impact SQoL for male or female patients. Looking closer into the IBD and controls' SQoL scores, male patients struggled with frustration, depression, anxiety and embarrassment. As for female patients, frustration, depression, anxiety, embarrassment, lack of pleasure and confidence loss were reported. In linear regression analysis for men, SQoL was associated with age, marital status and depression (β −1.87 [IC 95% −2.20 −1.53]; $p < 0.001$). In women, SQoL was associated with depression (β −1.81 [IC 95% −2.11 −1.51]; $p < 0.001$) only.

Conclusions: IBD patients reported a poorer sexual QoL than healthy controls. Moderate–severe depression was highly reported in IBD and was negatively correlated with SQoL. Similarly to what is reported for disease activity in other studies, perianal disease did not impact SQoL. Patients concerns on sexuality were mostly about emotional issues and self-esteem.

P741

Fine-scale geographic distribution and ecological studies of Crohn's disease in France (2007–2014)

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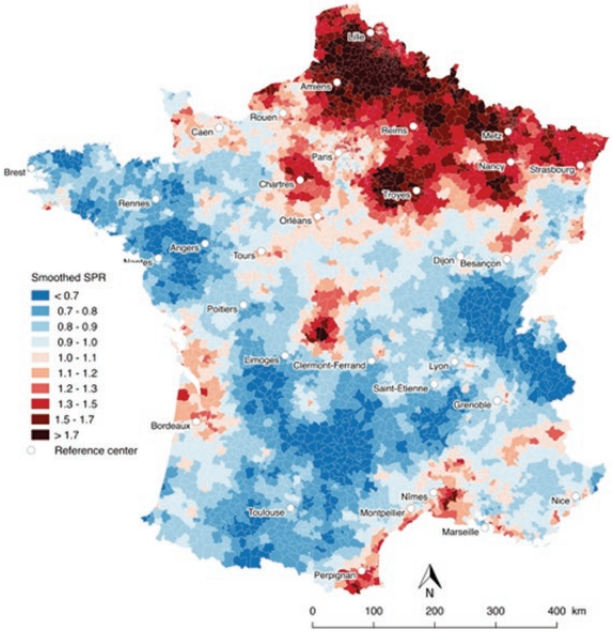
Background: A significant geographical variation in the incidence of Crohn's disease (CD) suggests the role of environmental factors in its pathogenesis. The objectives of this work were (i) to study the spatial distribution of CD cases in France from the database of the Programme de Médicalisation des Systèmes d'Information (PMSI), (ii) to study the factors associated with spatial heterogeneity and (iii) to identify clusters of high-prevalence.

Methods: Patients with a CD diagnostic code were searched in the PMSI database between 2007 and 2014. To study the spatial distribution of prevalence for this period, a fine-scale spatial unit (5610 units at the national level) was used. The results were expressed as standardised prevalence ratio (SPR). An ecological regression measured the association between the risk of CD and spatial unit characteristics, such as access to the nearest reference centre, urbanisation and rurality, deprivation index (FDep index), latitude, and distance from polluting facilities. Elliptical spatial scan statistics were used to search high-prevalence clusters.

Results: A total of 129089 patients with CD have been identified, with a national prevalence in 2014 of 203/100000 inhabitants. Significant spatial heterogeneity has been found ($p \leq 0.0001$) (Figure 1). Ecological regression revealed a significant association between the risk of CD and the highest deprivation index (Relative Risk (RR) = 1.05[1.02–1.08]) and urbanisation (RR=1.08[1.05–1.15]). The spatial analysis detected 16 clusters with a CD relative risk ranging from 1.40[1.31–1.50] to 1.90[1.65–2.19].



Geographical distribution of age-and-gender Standardised Prevalence Ratios of Crohn's disease in France, 2007–2014.

Conclusions: The French geographical distribution of CD is not uniformly distributed. Sixteen clusters with high-risk of CD have been identified. The poorest populations and industrialised areas were associated with a higher risk of developing CD.

P742

Iranian Registry of Crohn's and Colitis (IRCC): first nation-wide IBD registry in Middle East, a study protocol

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Background: A recent nation-wide study of inflammatory bowel disease (IBD) from Iran revealed a rapidly increasing incidence and prevalence. The best epidemiologic study to assess the burden and improve the care of IBD is a Population-based registry. The Iranian Registry of Crohn's and Colitis (IRCC) was established recently to answer the needs. We aimed to report the design, methods of data collection, and aims of IRCC to enlighten the strengths and limitations of this project.

Methods: IRCC is multi-centre prospective registry, which is established with collaboration of about 100 gastroenterologists who are providing care for IBD patients in different provinces of Iran. Minimum data set for IRCC was defined according to an international consensus on standard set of outcomes for IBD. The questionnaire was designed accordingly in order to make the data collection feasible in clinical setting. Feasibility of study was tested using a pilot study on 553 IBD patients with a web-based questioner. During and after the pilot study many revisions was made on questionnaire and software according to feedback of registrars and members of IRCC. The reliability of each section of questionnaire evaluated by Cronbach's α. For testing effect of any risk factor or specific condition or treatment on subtypes of IBD or disease activity we used chi square test and ANOVA. P-value less than 0.05 considered significant.

Results: In pilot study, 312 (56.4%) of participants were male and mean age was 38 years (Standard deviation = 12.8) and 378 (68.35%) patients had ulcerative colitis, 303 (54.7%) had college education and 358 (64.74%) were of Fars ethnicity. Among this sample, 68 (12.3%), 44 (7.9%), 13 (2.3%) of participants were smokers, hookah and opium users, respectively. History of appendectomy was reported in 58 (10.48%) of patients. The most consumed drug was 5-ASA (94.39%). The reliability of each section of questionnaire were checked and most sections had α>0.6. We established a well-designed registry with standard data set in order to better study IBD in Iran.

Conclusions: To best of our knowledge, IRCC is the first national level IBD registry running in Middle East and could become a reliable infrastructure for national and international research on IBD and at the same time improve the care of IBD patients and provide national information for policy makers to better plan for controlling IBD in Iran.

P743

Bone mineral disease is insufficiently evaluated in patients with inflammatory bowel disease at risk of metabolic bone disease: results from a Danish population-based inception cohort study

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Background: Patients with inflammatory bowel disease (IBD) including Crohn's disease (CD) and ulcerative colitis (UC) are at risk of developing metabolic bone disease. No general agreement regarding osteoporosis screening by Dual-energy X-ray absorptiometry (DXA) in IBD patients exists. The aims were to investigate the screening strategy, incidence and risk factors of osteoporosis in a well-defined prospective population-based inception cohort.

Methods: Between 2003 and 2004 all incident patients diagnosed with CD and UC in a clearly defined Copenhagen area were included and followed until 2015. Data regarding hospitalisation, diagnosis and treatment were collected from patient files and national registries. Data were compared with a control population (1:20). Poisson's regression model was performed for osteoporosis and a combined variable of osteoporosis and osteopenia with several covariates.

Results: A total of 513 patients with IBD were included (213 CD, 300 UC). Overall, 297 (58%, CD: 144 [68%], UC: 153 [51%]) patients received ≥2 courses of steroids within a year, resulting in 624 patient-years where 2 or more courses of steroids where given within a year. Of those, only 65 (10.4%) cases of patient-years were followed by DXA within the same or next calendar year. Overall, 50 (9.7%, Table 1) IBD patients (CD: 21 [9.9%], UC: 29 [9.7%]) and 562 (5.5%, $p < 0.001$) controls were diagnosed with osteoporosis during follow-up (OR: CD: 1.9 [1.2–3.0], UC: 1.8 [1.2–2.7]). Age at diagnosis (IRR, CD: 1.05 [1.02–1.07], UC: 1.06 [1.04–1.10]) was significantly associated with the risk of osteoporosis.

When assessing low energy fractures, 6 (2.8%) CD and 10 (3.3%) UC patients had at least one; independent of steroid treatment (p>0.05). No significant difference was found compared with the control population (238 [2.3%], p = 0.5). Assessment of BMD, T- and Z-score found on DXA showed no significant differences between UC and CD patients at any bone site, nor in subgroups of disease phenotypes.

Table 1. Prevalence of osteoporosis and the frequency of Dual-energy X-ray absorptiometry in patients with inflammatory bowel disease. *Compared with those who did not fulfil the criteria in each respective subgroup.

	Frequency of DXA	*p-value	Prevalence of osteoporosis	*p-value
Overall (%)	123 (24.0)		50 (9.7)	
Female (%)	80 (30.4)	0.001	34 (12.9)	0.02
Patients with ≥1 course of steroids (%)	108 (30.8)	< 0.001	40 (11.4)	0.09
Patients with ≥2 courses of steroids within a year (%)	89 (30.0)	< 0.001	32 (10.8)	0.44
Age above 50 at diagnosis (%)	51 (37.5)	< 0.001	40 (29.4)	< 0.001
Age above 50 at diagnosis with ≥1 course of steroids within a year (%)	42 (48.3)	< 0.001	31 (35.6)	< 0.001
Age above 50 at diagnosis with ≥2 courses of steroids within a year (%)	34 (50.0)	< 0.001	24 (35.3)	< 0.001

Conclusions: In this population-based inception cohort with 10 years of follow-up, 10% of IBD patients were diagnosed with osteoporosis, bone mineral density among patients at risk of

osteoporosis receiving steroid treatment was inadequately evaluated. Increased attention to IBD patient at risk of metabolic bone disease must be prioritised and guidelines on this matter are warranted.

P744

A significant decline in surgical resections during childhood with increased prevalence of anti-TNF therapy in patients with paediatric inflammatory bowel disease

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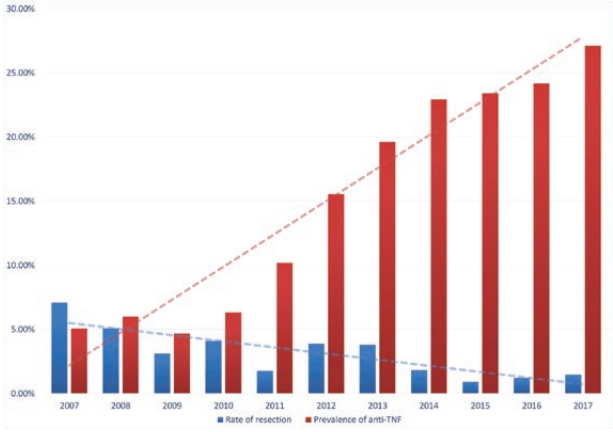
Background: The use of anti-tumour necrosis factor-α (anti-TNF) therapy has seen a rise over the last 15 years in paediatric inflammatory bowel disease (PIBD). Whether this has translated into preventing complications and avoiding surgery in childhood is less certain. Data from the Wessex PIBD cohort were analysed to assess for trends in anti-TNF therapy and surgical intervention.
Methods: All patients diagnosed with PIBD within Wessex from 1997–2017 were eligible. Prevalence of anti-TNF and yearly surgery rates (resection and perianal) during childhood (< 18 years of age) were analysed by Pearson's correlation, multiple linear regression and Fisher exact test.
Results: 825 children were included in the analysis (498 Crohn's disease, 272 ulcerative colitis, 55 IBDU), mean age at diagnosis 13.62 years (1.59-17.64 years), 327 (39.6%) female. The prevalence of patients treated with anti-TNF therapy increased from 5.05% to 27.11% (2007–17), $p = 0.0001$. Surgical resection rate per year fell significantly (7.07% to 1.46%, $p = 0.001$), driven by a decrease in resections for CD (8.9% to 2.3%, $p = 0.001$). There was no reduction in resection rate for UC ($p = 0.29$) (Figure 1).



The time from diagnosis to resection increased from 1.57 to 5.11 years, $p = 0.002$. Mean age at surgery was unchanged indicating patients undergoing surgery during childhood were younger at diagnosis (2007–2011= 13.05 years, 2013–2017=11.76 years, $p = 0.014$). There was no change in the rate of perianal surgery (Table 1).

Year	Patients under paediatric care	New diagnoses per year	Rate of resection per year	Average time to resection (years)	Average age at resection (years)	Rate of perianal surgery per year	Prevalence of anti-TNF treated patients	Median time to starting anti-TNF (years)
2007	198	52	7.07%	1.57	15.06	1.52%	5.05%	3.25
2008	217	47	5.07%	1.59	14.87	1.38%	5.99%	1.55
2009	257	67	3.11%	1.01	14.16	0.39%	4.67%	1.22
2010	269	47	4.09%	1.40	14.23	0.00%	6.32%	3.18
2011	285	58	1.75%	1.42	15.20	0.00%	10.18%	1.52
2012	309	64	3.88%	1.79	15.64	0.97%	15.53%	1.52
2013	316	51	3.80%	2.53	13.71	1.27%	19.62%	1.61
2014	327	58	1.83%	3.44	16.03	3.06%	22.94%	1.80
2015	329	56	0.91%	2.91	15.28	1.52%	23.40%	1.30
2016	327	56	1.22%	2.50	15.15	0.00%	24.16%	1.48
2017	343	71	1.46%	5.11	15.16	2.33%	27.11%	0.95

The incidence of surgery in those treated (16.1%) or untreated (12.2%) with anti-TNF agents was no different ($p = 0.25$). Subanalysis of patients started on early anti-TNF therapy (< 3 years post diagnosis) vs. late revealed a modestly significant reduction in the number patients undergoing surgical resection (11.6% and 28.6%, respectively, $p = 0.047$). A multiple linear regression model projected anti-TNF prevalence as the only significant predictor of surgical resection rate ($p = 0.011$).
Conclusions: There is an increase in the number of patients treated with anti-TNF therapy alongside a statistically significant decrease in the surgical resection rate. Despite this, children diagnosed at younger ages were still undergoing surgery during childhood. These data suggest that anti-TNF therapy may modify the natural history of IBD, reducing the need for surgical intervention.

P745

Incidence of indeterminate colitis in the EPIMAD registry decreases over the period 1988–2014

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Background: Inflammatory bowel disease unclassified (IBDU) represents 5–15% of new diagnosis of inflammatory bowel disease. However, IBDU is not well defined and high rate of reclassification in Crohn's disease (CD) or Ulcerative colitis (UC) is observed during follow-up. The objective of the present study was to evaluate the evolution of the incidence of IBDU over the period 1988–2014 in a population-based study and its reclassification rate during the follow-up.
Methods: All adults (> 17 years old) patients diagnosed with IBDU according to a validated and published algorithm[1] in the French population-based registry EPIMAD from 1988 to 2014, were identified. Follow-up was divided in 3 periods of 9 years (1988–1996, 1997–2005, and 2006–2014). Reclassification was defined as a modification of diagnosis during the follow-up.
Results: 24 304 IBD cases (> 17 years) were diagnosed, including 8449 (66.2%) CD, 3839 (30.1%) UC and 476 (3.7%) IBDU. IBDU concerned predominantly males compared with CD and UC population [(51.7% in IBDU population ($n = 246$) vs. 45.6% in CD plus UC population ($n = 5602$) ($p = 0.009$)], with an older age at diagnosis [(36 [26–51] in IBDU population vs. 30 [28–42] in CD plus UC

population ($p < 0.001$)]. IBDU rate among IBD diagnosis decreased significantly during the study period, from 6% (1988–1996) to 2% (2006–2014) ($p < 0.0001$). In the IBDU cohort, 334 (70.2%) only had one diagnosis; 132 (27.7%) had two and 10 (2.1%) had three during follow-up. IBDU reclassification occurred in 108 patients (22.7%). The median time for reclassification was 1 year (IQR [1 –2]) after the diagnosis. Eighty-nine patients (18.7%) were reclassified to CD or UC after a new flare. There was no significant modification of IBDU reclassification rate in CD or UC during the study period 17% (1988–1996) to 21% (2005–2014) ($p = 0.56$).

Conclusions: In this population-based study, IBDU incidence decreased significantly between 1988 and 2014, probably because of better diagnosis performances allowing CD and UC identification. These results suggest that IBDU may not be a real and significant clinical entity but a misclassification of colonic inflammatory bowel disease.

Reference

1. Gower-Rousseau *et al*. Incidence of inflammatory bowel disease in northern France (1988–1990). *Gut* 1994.

P746

Living with ulcerative colitis in Germany: quantifying the socioeconomic impact of moderate to severe ulcerative colitis

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Background: Ulcerative colitis (UC) often manifests in adults at a young age. Disease morbidity results in high societal costs due to the impairment on patients' ability to work. Previous European studies have estimated the cost of UC caused by work loss, but results varied greatly due to varying population characteristics and small sample sizes. Treatment options for inducing and maintaining clinical remission in moderate to severe UC include biologic therapies, and it is not known whether these have a beneficial effect on work impairment and/or societal cost due to UC. We present data from the Living with UC Study in Germany, comparing sick leave and benefits between patients with moderate to severe UC initiated on biologic therapy and general population matched controls.

Methods: A retrospective, longitudinal cohort design with comparator group was employed utilising de-identified German statuary health insurance (SHI) claims data within the Health Risk Institute (HRI) database. Adult patients (18+ years) with UC (ICD-10 K51) but without Crohn's disease (ICD-10 K50) were indexed from Jan 2013 to December 2015 on biologic therapy initiation (adalimumab, golimumab, infliximab, vedolizumab). Patients had to be continuously insured by SHI and have no record of biologic therapy in the prior 12 months. UC patients (cases) were matched 1:1 with respect to age, sex and comorbidities to controls from the HRI database without inflammatory bowel disease via a propensity score. The total number of sick leave days in the 24 months following indexing was calculated per-patient. Patients were classified as no leave, short-term leave (<6 weeks – employer pays wages) or long-term leave (≥6 weeks – sick benefits triggered). The amount paid in sick benefits (€) was also calculated. Descriptive analyses were reported.

Results: In total, 304 eligible cases were identified (mean age 42.9, 56.3% male). Data on sick leave and benefits for all cases and controls are presented in Table 1, with UC patients experiencing a significantly higher burden in terms of sick leave and benefits.

Conclusions: Long-term sick leave among patients with moderate to severe UC was higher vs. the matched general population. These data highlight a significant indirect cost burden associated with moderate to severe UC in spite of biologic therapy. This is further emphasised by the significantly higher degree of long-term sick leave in patients with UC vs. the general population, which results in a greater burden to the German healthcare system due to the significant amount of sick benefits.

	Cases (n=304)	Matched controls (n=304)	P-value
Sick leave			
No leave taken, n (%)	159 (52.3)	179 (58.9)	0.0001[a]
Short term, n (%)	107 (35.2)	115 (37.8)	
Long term, n (%)	38 (12.5)	10 (3.3)	
Days, mean (SD)*	39.2 (86.5)	12.6 (30.9)	<0.0001[b]
Sick benefits (€), mean (SD)**	832 (3,664)	89 (967)	0.0007[b]

[a] Chi-squared test; [b] Two-group t-test
** Includes patients who did not take any days of sick leave*
*** Costs representative of individual patients regardless of number of periods of leave and Includes patients who took less than 6 weeks of sick leave*

P747

A sharp increase of using biologics for IBD in Israel: a population- based report from the epiIIRN database

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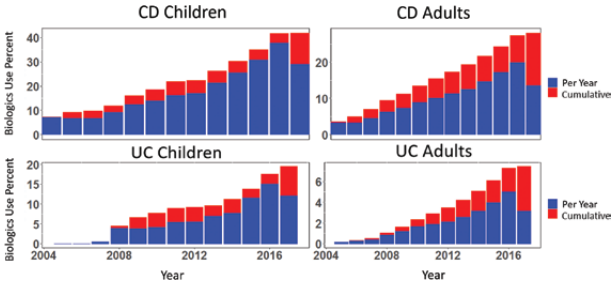
Background: The advent of biologics for inflammatory bowel diseases (IBD) has revolutionised the treatment of IBD over the last 15 years but the magnitude of their long-term effect is still unclear. Nevertheless, biologics use has been steadily increasing with their associated cost. We, thus, aimed to explore trends of use of biologics in all IBD patients in Israel for basing administrative planning of treatment algorithms.

Methods: IBD patients were identified within the epiIIRN database, a validated database of all IBD patients registered during 2005–2016 in 3 of 4 Israeli national health maintenance organisations (HMOs), covering 89% of the Israeli population. The identification of Crohn's disease (CD) and ulcerative colitis (UC) as well as date of diagnosis utilised previously validated algorithms. For incidence, we calculated the number of newly diagnosed IBD patients that commenced biologics within the first year of diagnosis.

Results: As of 2016, there were 3333/36 569 (9.1%) IBD patients treated with biologics and 7002/36 569 (19.1%) ever treated with biologics. The use of biologics steadily and sharply increased among

adults both in CD and UC (figure): from 280/8558 (3.3%) and 15/9735 (0.2%) in 2005 to 3640/18 300 (19.9%) and 844/16 830 (5%) in 2016 ($p < 0.001$),, respectively. The corresponding rates in children with CD and UC increased from 51/727 (7%) and 0/318 (0%) in 2005, to 366/969 (38%) and 80/531 (15%) in 2016. In 2016 adalimumab was used for CD in 63% of patients, infliximab in 29%, vedolizumab in 4.9% and others 3.1%. The corresponding figures for UC were infliximab 39%, adalimumab 30%, vedolizumab 29% and others 2%. The rate of patients who were commenced on biologics during the first year of diagnosis also sharply increased and continues to rise. In CD from 4.1% in 2005 through 8.6% in 2010, 11.8% in 2013 and 22.4% in 2016. In UC, the corresponding rates were 0.1%, 1.8%, 4.8% and 5.2%.



The Increase In The Use Of Biologics In Israel 2004–2017

Conclusions: The use of biologics continues to increases sharply in all IBD populations in Israel and the time to introduction shortens. Convincing data showing that this trend changes the natural history of the disease and in which patients are badly needed. This study was supported by a grant from the Leona M. and Harry B. Helmsley Charitable Trust.

P748

Retrospective study on incidence rates of NAFLD and advanced liver fibrosis in Crohn's disease and ulcerative colitis

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Background: Patients with inflammatory bowel disease (IBD) are at higher risk for non-alcoholic fatty liver disease (NAFLD) compared with general population. Complex pathogenesis of NAFLD in IBD may be related to disease-specific risk factors such as chronic inflammation, steroid exposure, drug-induced hepatotoxicity, malnutrition and alteration of gut microbiota, major emerging factor in the pathogenesis of NAFLD. The goal of the study was to compare incidence rates (IR) of NAFLD and advanced liver fibrosis (ALF) in patients with CD and UC.

Methods: This is a retrospective study on IBD patients without extra-intestinal manifestations and known liver disease. NAFLD was defined as Hepatic Steatosis Index (HSI) ≥36, and ALF was defined as FIB-4 ≥2.67. Active CD was defined using Harvey–Bradshaw Index ≥5 during follow-up. Incidence and predictors of NAFLD development were analysed using Kaplan–Meier and Cox regression analyses.

Results: In this retrospective study we included 250 IBD patients; 167 patients with CD and 83 patients with UC (median age 40 yr, 52.2% males) that were observed for a median of 4.6 years. During 639 persons-year (PY) in CD group, 61 (36.5%) patients developed NAFLD (IR 9.5/100 PY (95% CI, 7.3–12.2)). In UC patients over 212 PY, 30 (36.1%) developed NAFLD (IR 14.1/100 PY (95% CI, 9.5–20). When analysing liver fibrosis, over a 860 PY in CD group, 5 (2.9%) patients developed ALF (IR 0.6/100 PY (95% CI, 0.2–1.3), and over a 386 PY in UC Group 4 (4.8%) patients developed ALF (IR 1/100 PY (95% CI, 0.2–2.6). There was no difference between CD and UC in incidence rates of NAFLD ($p = 0.07$) and ALF ($p = 0.38$). Development of NAFLD in CD was predicted by disease activity (HR 1.47; 95% CI 1.05–2.1; $p < 0.05$) and disease duration (HR 1.45; 95% CI 1.06–1.8; $p < 0.05$), while in UC was predicted by disease activity (HR 1.67; 95% CI 1.2–2.4; $p < 0.05$).

Conclusions: NAFLD is frequent comorbidity in patients with CD and UC, which can lead to development or advanced liver fibrosis. Our results show that there is no difference in incidence rates of NAFLD and advanced liver fibrosis in different groups of IBD patients, even though there was a trend towards higher incidence rates of NAFLD in UC ($p = 0.07$). Disease activity and duration of IBD are predictors of NAFLD development. This study points out the complexity of disease-specific risk factors and importance of better stratifications of IBD patients at risk of NAFLD and development advanced liver fibrosis.

P749

Early environmental and lifestyle factors are associated with developing inflammatory bowel disease

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Background: The aetiology of inflammatory bowel disease (IBD), consisting of Crohn's disease (CD) and ulcerative colitis (UC), is complex with an interplay between genomic susceptibility, diet, microbiome and environmental factors. Differences in findings between studied populations are large, and it is likely that a large number of involved factors are unknown, while identification of modifiable risk factors is crucial. We executed a large population-based study evaluating known and possibly involved environmental factors.

Methods: IBD patients ($n = 674$) of the University Medical Center Groningen, the Netherlands, were asked to fill the validated Groningen IBD Environmental Questionnaire (GIEQ). [1] Here, we focus on 19 lifestyle factors. Patients were randomly matched based on age at diagnosis and sex to controls (1 to 2 case–control ratio) from the population-based LifeLines cohort study, who completed a comparable questionnaire. Logistic regression was applied to estimate the multivariable-adjusted effect of lifestyle factors on IBD (odds ratio; OR) and 95% confidence intervals. All models were corrected for age, sex and history of smoking. A $p < 0.05$ was

considered as nominal and a Bonferroni adjusted p-value < 0.0026 as statistically significant.

Results: CD and UC patients had high odds of being exposed to prenatal smoke exposure (OR1.9, 95% CI 1.4–2.6; 1.6, 1.2–2.2). CD patients were also more often former or current smokers (1.5, 1.0–2.2; 2.6, 2.0–3.4) than controls. The presence of more than three stressful life-events prior to diagnosis also increased risk of CD and UC (2.9, 1.9–4.5; 2.6, 1.7-4.0). Patients with IBD less often had a childhood cat or dog, with the strongest effect during the first year of life (all p-values < 0.00026). Also, patients less often used alcoholic beverages than controls yielding a protective OR for both diseases, red wine being the most protective factor in CD (0.3, 0.2–0.7).

Crohn's disease (n:323)	OR	95% CI	P-value	**Ulcerative colitis** (n:351)	OR	95% CI	P-value
Prenatal smoke exposure	1.89	1.38 – 2.59	**8.50e-5**	Prenatal smoke exposure	1.62	1.17 – 2.24	0.004
Receiving breastfeeding			0.072*	Receiving breastfeeding			
Never	1.0	Ref. group		Never	1.0	Ref. group	0.742*
Less than 3 months	0.51	0.34 – 0.77		Less than 3 months	0.80	0.52 – 1.23)	
More than 3 months	0.72	0.50 – 1.04		More than 3 months	1.06	0.72 – 1.56	
Pets in first year of life				Pets in first year of life			
Cat	0.38	0.37 – 0.54	**1.09e-7**	Cat	0.38	0.26 – 0.55	**2.93e-7**
Dog	0.41	0.29 – 0.57	**2.17e-7**	Dog	0.44	0.31 – 0.62	**3.00e-6**
Bird	0.45	0.24 – 0.85	0.014	Bird	0.17	0.06 – 0.45	**4.50e-4**
Guinea pig	0.25	0.03 – 1.90	0.18	Guinea pig	0.90	0.26 – 3.11	0.87
Living area 5 years of life			0.059*	Living area 5 years of life			0.032*
Farmhouse	1.0	Ref. group		Farmhouse	1.00	Ref. group	
Village rural area	1.30	0.79 – 2.13		Village rural area	1.72	0.98 – 3.00	
Small city/large village	0.76	0.44 – 1.29		Small city/large village	1.72	0.97 – 3.06	
Suburb of large city	2.07	1.15 – 3.72		Suburb of large city	2.24	1.17 – 4.28	
City center	2.10	1.06 – 4.15		City center	2.18	1.00 – 4.74	

* Indicates p-value of variable trend
All models are adjusted for sex, age and smoking status at diagnosis (current, former, never)

Table 1. Multi-variate-adjusted logistic regression models of the role of the early life exposures in risk of IBD development.

Crohn's disease (n:323)	OR	95% CI	P-value	**Ulcerative colitis** (n:351)	OR	95% CI	P-value
Lifestyle at time of diagnosis							
Smoking status			**6.40e-11***	Smoking status			0.998*
Never smoked	1.0	Ref. group		Never smoked	1.0	Ref. group	
Former smoker	1.52	1.04 – 2.22		Former smoker	1.36	0.97 – 1.92	
Active smoker	2.59	1.95 – 3.44		Active smoker	0.94	0.68 – 1.31	
Frequency of alcohol use			**4.30e-5***	Frequency of alcohol use			**1.27e-4***
None/<1 time per week	1.0	Ref. group		None/<1 time per week	1.0	Ref. group	
1-3 times per week	0.59	0.45 – 0.78		1-3 times per week	0.66	0.50 – 0.88	
4-7 times per week	0.47	0.29 – 0.75		4-7 times per week	0.45	0.28 – 0.71	
Type of alcohol consumed				Type of alcohol consumed			
Beer	1.02	0.68 – 1.53	0.94	Beer	1.69	1.14 – 2.51	0.009
White wine	0.44	0.25 – 0.79	0.005	White wine	0.69	0.40 – 1.17	0.17
Red wine	0.33	0.16 – 0.67	**0.002**	Red wine	1.30	0.82 – 2.06	0.27
Watching television			0.88	Watching television			0.078*
Less than 2 hours per day	1.0	Ref. group		Less than 2 hours per day	1.0	Ref. group	
2-4 hours per day	0.99	0.70 – 1.40		2-4 hours per day	0.94	0.65 – 1.35	
More than 4 hours per day	1.37	0.92 – 2.02		More than 4 hours per day	1.55	1.04 – 2.3	
Stress prior to diagnosis			**2.3e-5**	Stress prior to diagnosis			**7.0e-6**
0-1 stressful life-events	1.0	Ref. group		0-1 stressful life-events	1.0	Ref. group	
2-3 stressful life-events	1.32	0.98 – 1.76		2-3 stressful life-events	1.25	0.93 – 1.69	
More than 3 stressful life-events	2.61	1.70 – 3.99		More than 3 stressful life-events	2.92	1.92 – 4.46	
Meeting sleep recommendations**	1.07	0.74 – 1.57	0.713	Meeting sleep recommendations**	1.05	0.73 – 1.50	0.80
Living environment at time of diagnosis							
Pets at diagnosis				Pets at diagnosis			
Cat	1.07	0.82 – 1.41	0.61	Cat	1.02	0.77 – 1.35	0.88
Dog	1.21	0.92 – 1.59	0.18	Dog	1.03	0.77 – 1.38	0.82
Bird	1.77	1.05 – 3.01	0.03	Bird	0.98	0.52 – 1.85	0.94
Guinea pig	1.25	0.59 – 2.66	0.56	Guinea pig	1.50	0.75 – 2.99	0.25

* Indicates p-value of variable trend, ** sleep recommendation of 7 or more hours of sleep per night. OR indicates odds ratio, CI indicates confidence interval.
All models are adjusted for sex, age and smoking status at diagnosis (current, former, never), except 'Smoking status'.

Table 2. Multi-variate adjusted logistic regression models of the role of lifestyle at diagnosis in risk of IBD development.

Conclusions: A history of prenatal smoking and stress was associated with increased risk of IBD, whereas a history of a childhood cat or dog was associated with a lower risk of IBD. Identification of modifiable factors in the aetiology of IBD is crucial, especially for individuals at risk. Future studies are needed to confirm these findings and proof its applicability on risk reduction management of IBD.

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P750

Association between the use of antihypertensive agents and disease severity in patients with inflammatory bowel disease

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Background: Accumulating evidence suggests the implication of angiotensin II in the pathogenesis of inflammatory bowel diseases (IBD) via its role as an inflammatory mediator. Recent data highlight beneficial effects of angiotensin II receptor blockers (ARBs) in experimental colitis as a result of regulation of mechanisms of colonic inflammation, oxidative stress and apoptosis. The aim of the present study was to evaluate the prevalence of hypertension among Greek IBD patients and the possible impact of the use of anti-hypertensive medications on the IBD course.

Methods: This is a retrospective analysis of prospectively collected data from 425 consecutive IBD patients [251 males, 223 Crohn's disease (CD), age range 30–89 years, mean (±SD) age at diagnosis 41.6 ± 16.1 years and mean follow-up of 12.5 ± 9.1 years] derived from the IBD registries of 3 participating IBD referral Centres. The presence of hypertension and the use of anti-hypertensive agents were recorded in all patients. Clinical characteristics and IBD severity were compared between IBD patients with hypertension and age- and sex-matched IBD patients without concurrent hypertension.

Results: The prevalence of hypertension was calculated at 29.9% in Greek IBD patients. Among 127 IBD patients with concurrent use of anti-hypertensive drugs, 50 were on ARBs, 35 on angiotensin converting enzyme inhibitors and 39 on b-blockers or calcium-channel blockers. IBD patients on anti-hypertensives were found to use less frequently anti-TNFα ($p < 0.001$) or immunomodulators ($p = 0.001$), as well as to have lower rates of hospitalisation for relapse ($p < 0.001$) and a tendency for lower rates of IBD-related surgery ($p = 0.061$) compared with patients without any use of anti-hypertensives. After multivariate adjustment for gender, BMI, smoking history and IBD type, the use of anti-hypertensives remained significantly associated with mild disease as indicated by the absence of all the above parameters: anti-TNF-α or immunomodulator use, IBD-related surgery and >3 hospitalisations for relapse ($p = 0.004$). The use of ARBs was less frequently correlated with L2 CD ($p = 0.012$), anti-TNF-α ($p < 0.001$) or immunomodulators' use ($p < 0.001$) and with IBD-related hospitalisations ($p = 0.002$) compared with other classes of anti-hypertensive drugs.

Conclusions: The prevalence of hypertension in Greek IBD patients is 29.9%. The use of antihypertensive agents seems to be independently associated with mild disease. This association is stronger with the use of ARBs. Data from larger prospective studies are essential to further evaluate this finding.

P751

Perianal lesions in Crohn's disease: analysis of Epimad registry from 2007 to 2012

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Background: Perianal lesions (PL) affect up to 30% of Crohn's disease (CD) patients in the first two decades after diagnosis and are associated with poor outcomes. Data concerning evaluation and

clinical management of PL at diagnosis in prospective cohorts are scarce. Aims of the present study were to characterise CD patients with PL at diagnosis and describe their initial diagnostic and therapeutic management.
Methods: All CD patients diagnosed between 2007 and 2012 were extracted from the Epimad Registry, a French multi-centre prospective registry. PL were defined by the presence of fistula or abscess at CD diagnosis. The following variables were described using a cross-sectional analysis: clinical examination, perianal MRI, echo-endoscopy, examination under general anaesthesia (GA) and medical and/or surgical management within the first 3 months after CD diagnosis. Associated factors with PL at CD diagnosis were identified using a logistic regression.
Results: Among the 2906 patients with CD diagnosed from 2007 to 2012, 116 (4%) had PL at CD diagnosis. Forty-four per cent were women, the median age at diagnosis was 25 years (IQR: 19–39) and 45% had a previous history of PL. Ileocolonic CD (L3) was predominant in 51 patients (45%); one patient (1%) had only perianal involvement and 51% of patients presented rectal lesions. Patients could present one or more PL: 81% had fistula (including 12 rectovaginal fistulas) and 58% abscess; one patient (1%) had anal stenosis. An examination under GA was performed in 50% of patients, MRI in 34% of the patients and an echo-endoscopy in 1 case. Initial therapeutic management of CD: 63% of patients received antibiotics, 42% 5-ASA and 47% steroids. Twenty-seven per cent of patients received azathioprine, 29% anti-TNF therapy (90% infliximab) and 13 (12%) patients received a combination therapy. Surgery was performed in 64 patients (57%) with 41 abscess drainages, 25 seton drainages, 16 fistulotomy and 2 diverting ileostomy. Male sex ($p < 0.01$), luminal fistulising phenotype ($p < 0.0001$) and colonic location ($p = 0.01$) were significantly associated with the presence of PL at CD diagnosis.
Conclusions: In this large population-based study, the proportion of patients with PL at CD diagnosis was 4%. Male sex, fistulising phenotype, and colonic location were associated with the presence of PL at CD diagnosis. Surgery was performed in more than half of the cases. An immunosuppressant, an anti-TNF or a combination therapy were, respectively, prescribed in 27%, 29% and 12% of the cases, reflecting the current approach for treating CD patients with PL. Further exploration of the treatment options after CD diagnosis is warranted.

P752

Increased risk of hip fracture in patients with inflammatory bowel disease: a national registry-based nested case–control study

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Background: With rising rates of inflammatory bowel diseases (IBD) in the elderly population, management of co-morbidities such as osteoporosis is becoming increasingly important. Hip fracture is the most serious consequence of low bone mineral density and is associated with significant excess risk of mortality. Although metabolic bone disease is common among patients with IBD, data on fracture risk are limited and current evidence is ambiguous. Therefore, we sought to determine the risk of sustaining a hip fracture in an aged IBD population.
Methods: In a national database-registered nested case–control study, 56 821 hip fracture cases (HF) aged ≥50 years and 113 718 age-, sex-, and region-matched non-hip fracture controls were analysed. A history of IBD was assessed from data of all Austrian social health insurance funds between 2012 and 2016. Crude and adjusted logistic regression was used to assess the risk of hip fracture.
Results: A total of 531 patients were identified with IBD (25.0% men, mean age 81.2 years, SD 9.7). The prevalence of Crohn's disease (CD) was 211 and 67 per 100 000 among HF cases and controls, respectively. The prevalence of ulcerative colitis (UC) was 299 and 145 per 100 000 among HF cases and controls, respectively. Analysis adjusted for anti-osteoporotic treatment and use of glucocorticoids before fracture showed that IBD patients had increased risk of hip fracture (OR 2.37, 95% CI 2.00–2.81), while patients with CD revealed a higher hip fracture risk compared with the UC patients (OR 3.10, 95% CI 2.33–4.14 and OR 2.02, 95% CI 1.63–2.51, respectively).
Conclusions: Aged patients with IBD had twice the risk of hip fracture compared with general population.

P753

Increased risk of ulcerative colitis in patients with periodontitis: a nationwide population-based study

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Background: Periodontitis is a chronic inflammatory status of periradicular tissues caused by an infection of endodontic origin. Periodontitis is caused by the interaction between microbiota in the root canal and host immune system. Periodontitis can occur in patients with inflammatory bowel disease (IBD) treated with immunomodulators or biologic agents. However, the effect of periodontitis on IBD is unclear. The aim of this study was to assess the risk of IBD in patients with periodontitis.
Methods: We performed a nationwide, population-based study using claim data from the National Healthcare Insurance Service-National Health Screening Program in Korea. Included were people aged 20 or older who participated in the national health screening program at least once in the index year 2009 (n = 9,950.548). Periodontitis was defined as diagnosed within 2 years before the index year according to ICD-10 code. We compared patients with periodontitis to individuals without periodontitis matched by age, sex and body mass index (BMI). The end point was newly diagnosed IBD that met both of ICD-10 codes (K50 for Crohn's disease (CD) and K51 for ulcerative colitis (UC)) and V code for rare intractable diseases (V130 for CD and V131 for UC) until December 31th, 2017. We exclude IBD patients who were diagnosed within 1 year from the index year (lag period).
Results: Patients with periodontitis had higher risk of UC than populations without periodontitis matched by age, sex, smoking, drinking,

physical activity and BMI (Hazard ratio [HR], 1.090; Confidence interval [CI], 1.022–1.162; $p < 0.0001$). According to a subgroup analysis of the periodontitis group, the risk of UC was significantly higher in patients who were over 50 years old, heavy drinkers and current smokers (HR, 1.987; CI, 1.123–3.515). However, the risk of CD in patients with periodontitis was not increased compared with the general population.

Conclusions: Patients with periodontitis are at an increased risk of UC compared with individuals without periodontitis.

P754

Ovarian reserve in reproductive age women with Crohn's disease

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Background: Crohn's disease incidence is rising year by year, and the young patients with high-risk. So more and more people begin to pay close attention to fertility, pregnancy, drug safety, lactation, etc. Although there are some studies have shown that crohn's disease is associated with fertility, but they were based on number of pregnancy, first pregnancy. No study penetrates the systemic research of ovarian function.

Methods: This clinical study recruit 45 childbearing age (17–40) patients with Crohn's disease and 45 matching age healthy women in the sixth hospital affiliated to sun yat-sen university during May 2017 to December 2017. Collect patients' demographic, menstruation, birth, serological indexes, CDAI, pathological changes, biological characteristics, medical history, surgical history data. And testing oestrogen (oestrogen, E2), follicle stimulating FSH (follicle stimulating hormone, FSH), Anti Mullerian tube hormone (anti-Mullerian hormone, AMH), sinus follicle count (antral follicle count, AFC) on third menstrual period.

Results: The two group had no difference between age and height. But the weight and BMI were significantly lower in CD patients than healthy group. The AMH and AFC were significantly lower in CD patients than healthy group (2.28 ± 2.09 ng/ml vs. 4.68 ± 2.12 ng/ml, 12 ± 6 vs. 16 ± 5 , $p < 0.05$). Although the E2 were lower and the FSH were higher in CD patients, but there were no statistical differences. AMH were lower in patients with hypoproteinaemia than the patients with normal albumin levels (1.15 ± 1.19 ng/ml vs. 2.99 ± 2.14 ng/ml, $p < 0.05$). The patients treat with thalidomide had lower AMH than the patients with other drugs (1.09 ± 1.42 ng/ml vs. 2.64 ± 2.77 ng/ml , $p < 0.05$), but there were no relationship between AMH and lesion site, surgery.

Conclusions: The ovarian reserve function was significantly lower in childbearing age women with Crohn's disease than heathy people, especially in patients with hypoalbuminaemia and treated with thalidomide.

P755

Inflammatory bowel disease and risk of Type 2 diabetes: a nationwide Danish cohort study 1977–2014

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Background: The gut is a key regulator of glucose homeostasis, but the role of chronic intestinal inflammation in Type 2 diabetes (T2D) remains uncertain. We performed a Danish nationwide cohort study of the long-term risk of T2D in patients with inflammatory bowel disease (IBD).

Methods: A total of 6,028,844 individuals, of whom 65,180 were diagnosed with IBD, comprising Crohn's disease (CD) and ulcerative colitis (UC), during years 1977–2014, were followed until T2D, death, emigration, or December 31, 2014. The risk was presented as Standardised Incidence Ratios (SIR) with 95% confidence intervals (CI).

Results: During 736,072 person-years of follow-up, 3,436 IBD patients developed T2D vs. 2,224 expected (SIR, 1.54; 95% CI, 1.49-1.60). The risk was significantly increased both in patients with UC (SIR, 1.54; 95% CI, 1.48–1.60) and CD (SIR, 1.57; 95% CI, 1.47–1.67), and in women (SIR, 1.51; 95% CI, 1.44–1.59) and men (SIR, 1.57; 95% CI, 1.50–1.65). Although patients were most likely to receive a T2D diagnosis within the first year after IBD diagnosis (SIR, 4.48; 95% CI, 4.16–4.83), the risk remained elevated 20+ years following diagnosis (SIR, 1.26; 95% CI, 1.16–1.38) and was not explained by detection bias. Patients diagnosed with IBD during 2003–2014 (SIR, 1.79; 95% CI, 1.67–1.91) had significantly higher risk of T2D than patients diagnosed during 1977–1988 (SIR, 1.47; 95% CI, 1.39-1.56) and 1989–2002 (SIR, 1.48; 95% CI, 1.41–1.56) ($p < 0.01$).

Conclusions: This population-based cohort study shows an increased risk of T2D both in patients with UC and CD. Whether the significantly higher risk of T2D observed in recent years reflects an impact of current treatment options in IBD remains to be investigated.

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Assessment of metal exposures in deciduous teeth of patients with inflammatory bowel disease

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Background: Environmental factors are thought to play a major role in the pathogenesis of inflammatory bowel disease (IBD). Importantly, increasing epidemiological evidence suggests that exposures occurring during early life may be determinant of disease development. However, studying exposures occurring during this window of susceptibility is challenging, and very little has been elucidated about environmental exposures preceding disease onset. Teeth develop in an incremental manner, storing environmental information on compounds such as metals and organics as we age. The study of deciduous (baby) teeth-matrix biomarkers allows assessment of cumulative exposures, starting as early as the second trimester of prenatal development, and continuing into early childhood until teeth shedding. Herein, by studying deciduous teeth, we aimed to identify whether critical exposures during early development may be associated with IBD diagnosis later in life.

Methods: Adult IBD patients and healthy controls from a single-centre in Portugal were asked to donate their baby teeth; it is traditional for Portuguese families to keep naturally-shed deciduous teeth for years. Thirty teeth were obtained from 14 IBD patients (8 CD, 6 UC) and 16 from unaffected controls (3 from unaffected siblings of IBD patients). Laser ablation-inductively coupled mass spectrometry analysis was used to create temporal metal exposure profiles from the second trimester of pregnancy through the first 6 months of life. Data were analysed using distributed lag models by estimating the time-lagged association of exposures with IBD diagnosis while accounting for the correlated exposures.
Results: We found divergences in metal uptake in the teeth of individuals who eventually developed IBD when compared with controls in a time-dependent manner. Lead exposure, a known inflammatory toxicant that has been shown to predispose to murine colitis, as well as alter the gut microbiome and affect metabolic functions, was significantly higher during intra-uterine and the first 6 months of life ($p < 0.05$). Likewise, in IBD patients, copper (Cu) levels were significantly higher up to 15 weeks postnatally, and chromium (Cr) levels were also significantly elevated from 10 to 15 weeks before birth (both $p < 0.05$). While elevated copper levels have been shown in patients with UC, no link between chromium and IBD in humans has been previously established.
Conclusions: These data suggest that a deregulation in metal uptake during a critical window in early-life is a feature of IBD, prior to the emergence of any clinical symptoms.

P757

Prevalence of inflammatory bowel disease (IBD) in a colorectal cancer population screening program

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Background: in general, IBD are diagnosed in subjects with gastrointestinal symptoms, despite this a diagnostic delay is often observed. However IBD may also be present in asymptomatic subjects. In these cases, diagnosis may be further delayed, incidentally done or missed.
Methods: we analysed an electronic database of a regional colorectal cancer population screening program offered to subjects from 50 to 70 years old with faecal occult blood. From 1 September 2013 to 31 August 2018, among subjects who underwent colonoscopy in a single hospital, we identified subjects with endoscopic findings suggestive of IBD. Of these, we retrieved histological findings as well as information on other examinations and possible therapeutic decisions.
Results: 2062 subjects undergoing to colonoscopy were enrolled. In 33 (1.6%) subjects (18 men, mean age ± SD 60.8 ± 7.4 years) endoscopic findings suggestive of IBD were present: 23 of CD and 10 of UC; none of these subjects were taking oral anticoagulants or NSAIDs and reported gastrointestinal symptoms. After a median follow-up of 13 months (range 2–59), a definitive diagnosis of IBD was done in 10 subjects (0.5%). Of these, 3 already underwent to colonoscopy in the context of the same program and 1 showed familiarity for IBD. Seven were diagnosed with CD (6 men, 61.3 ± 7.1 years) and 3 with UC (2 men, 55.8 ± 3.0 years). In CD population, 4 patients showed colonic, 3 ileal and 1 ileo-colonic location; 1 was treated with steroids and then with vedolizumab, 1 with steroids and then with azathioprine, 1 with 5-ASA while 4 did not receive any therapy. In UC population, 2 patients showed extension limited to rectum and 1 to rectum and sigmoid colon; all patients started therapy with 5-ASA.
Conclusions: prevalence of IBD in a colorectal cancer population screening program is 0.5%. IBD diagnosis can be missed in asymptomatic subjects, but only 1 out of 3 subjects with endoscopic findings suggestive of IBD is eventually diagnosed as affected by CD or UC.

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Prevalence of moderate to vigorous physical activity and sedentary time in adolescents with inflammatory bowel disease: knowing and doing

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Background: The importance of physical activity in the prevention of chronic inflammatory diseases has been well established. In fact, it has been shown that higher levels of exercise were associated with reductions in inflammatory serum markers. Therefore, physical activity might be a protective factor against occurrence and progression of inflammatory bowel diseases (IBD). However, children with IBD tend to be less active than their healthy peers. The Canadian 24-H Movement Guidelines for Children and Youth recommend an average daily moderate-to-vigorous physical activity (MVPA) of at least 60 min 7 days a week.
Methods: The primary aim was to evaluate the prevalence of MVPA in Canadian children with IBD when compared with their healthy Canadian peers. The secondary aims were to assess the prevalence of sedentary behaviour in paediatric IBD and the knowledge about the Canadian MVPA guidelines. Between June and November 2018, children with IBD, age ≥12 years, were prospectively surveyed. Physical Activity was assessed using the Canadian Health Measure Survey Children-Physical Activity Questionnaire, filled out during outpatient visits. Responses were converted into metabolic equivalents of tasks (METS) by using validated tables. Activity with METS between 3 and 6 was classified as moderate intensity and above 6 as vigorous intensity. The proportion of children with at least 1 h daily of MVPA was measured and compared with Canadian data in healthy children.
Results: We included 121 patients (52 females; mean (SD) age 15.5 (1.6) years); 84 diagnosed(69.4%) with Crohn's disease(CD) and 29(24.0%) with ulcerative colitis(UC). Of these, 74.4% were in remission according to the Pediatric Crohn Disease Activity Index or Pediatric ulcerative colitis Activity Index(score ≤10). The prevalence of self-reported physically active patients was 83.5%. In addition, 78.5% claimed that physical activities in the previous week made them sweat and breathe harder. Yet, only 30.6% reached the Canadian physical activity target, which is close to the 35.0% MVPA among healthy Canadian children. The median (IQR) MVPA duration/day was 34.0 min(14.0 to 66.0) and the median (IQR) daily sedentary duration was 5.7 h (3.0 to 8.0). Furthermore, 45.7% of the patients claimed that they discussed the significance and benefits of MVPA with their teachers or doctors, but only 12% were aware of the national target and gave the correct time.
Conclusions: Our study showed a low prevalence of MVPA in Canadian children with IBD. The recommended target among this

population is far from being achieved. Likely explanations might be the excessive screen time of adolescents and limited promotion of MVPA potential benefits in this population with chronic diseases by healthcare providers.

P759

Incidence and clinical impact of perianal disease in patients with ulcerative colitis: a nationwide population-based study

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Background: The risk and clinical impact of perianal disease (PAD) in ulcerative colitis (UC) patients have not been fully evaluated. We investigated the incidence of PAD in UC patients and compared clinical characteristics and outcomes of UC according to the presence of PAD.

Methods: We performed a nationwide population-based cohort study and a hospital-based cohort study. Using the 2010–2014 data from the Korean national health insurance claims database, we calculated incidence rates and standardised incidence ratios (SIRs) of PAD in UC patients compared with the general population. We evaluated the clinical characteristics and outcomes of UC patients with PAD in both population-based and hospital-based cohorts. To reduce clinically meaningful confounding factors, we also conducted matched analyses.

Results: In the population-based cohort, the incidence rate and SIR of PAD in UC patients were 3.74/1000 person-years (95% confidence interval [CI], 3.25–4.31) and 2.88 (95% CI, 2.50–3.32), respectively. In the hospital-based cohort, the cumulative probabilities of PAD at 1, 5, 10, and 20 years after diagnosis were 1.0%, 2.3%, 4.0%, and 6.3%, respectively. In both population-based and hospital-based cohorts, UC patients with PAD showed higher proportions of corticosteroid use and extensive colitis at diagnosis. The requirements for anti-tumour necrosis factor agents and colectomy were significantly higher in UC patients with PAD before and after matched analysis.

Conclusions: The risk of PAD is higher in UC patients than in the general population. UC patients with PAD have distinct clinical features and poor outcomes, as indicated by the greater need for UC-related medications and colectomy.

P760

The risk of inflammatory bowel disease based on body mass index and waist circumference: a nationwide population-based study

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Background: The relationship between the occurrence of inflammatory bowel disease (IBD) and the indicators of obesity and underweight including body mass index (BMI) and waist circumference (WC) still remains unclear. The aims of this study was to determine the risk of developing IBD based on the baseline levels of BMI and WC, and changes in body weight.

Methods: We conducted a nationwide population-based cohort study using claims data from the National Health Insurance (NHI) database in Korea. A total of 19,356,194 individuals who attended a national health check-up program from 2011 to 2012. Among them, 10,699,693 (55.3%) individuals who had not undergone a national health check-up 2 years before the baseline, who had been diagnosed with IBD previously or had insufficient data were excluded in this study. Study endpoint was newly diagnosed IBD including Crohn's disease (CD) and ulcerative colitis (UC) during the follow-up to 2017. Obesity, overweight and underweight was defined based on the Asia-Pacific BMI classifications as follows: obesity, ≥25 kg/m^2; overweight, 23 to 24.9 kg/m^2; and underweight, < 18.5 kg/m^2.

Results: A total of 8,656,501 participants were enrolled in the study. Among them, obese, overweight and underweight individuals were 2,864,672 (33.1%), 2,197,148 (25.4%), and 289,580(3.3%), respectively. During the follow-up, IBD were newly detected in 267 (0.09%) of underweight, 2,365 (0.07%) of normal weight, 1,412 (0.06%) of overweight, 1,438 (0.06%) of class I obese, and 127 (0.04%) of class II obese groups. Compared with normal weight, the risks of developing CD was significantly higher in underweight (adjusted HR by age and sex, 1.73; 95% CI, 1.35–2.21), but lower in overweight (adjusted HR, 0.61; 95% CI, 0.52–0.72), class I (adjusted HR, 0.51; 95% CI, 0.43–0.60) and II obese groups (adjusted HR, 0.47; 95% CI, 0.32–0.71), respectively. The risk of developing UC was also significantly higher in underweight (adjusted HR, 1.31; 95% CI, 1.13–1.52), but lower in overweight (adjusted HR, 0.90; 95% CI, 0.83–0.97), class I (adjusted HR, 0.77; 95% CI, 0.72–0.83) and II obese groups (adjusted HR, 0.55; 95% CI, 0.45–0.67), respectively, compared with normal weight group. BMI and WC at baseline showed inverse linear associations of risk for developing IBD. Moreover, the interval decrease in body weight within 2 years significantly increased the risk for developing CD, but not UC, in proportion to the percentage of weight loss.

Conclusions: Underweight increased the risk for developing IBD, but overweight and obesity reduced the risk of IBD compared with normal weight. BMI and WC was inversely associated with risk of IBD. Physicians would be aware of the potential for developing CD in individuals experiencing unintentional weight loss.

P761

Healthcare quality assessment in inflammatory bowel disease Units in Spain under patient's perspective. IQCARO project

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Background: Measuring quality of care (QoC) received in inflammatory bowel disease (IBD) units from patient's perspective is becoming increasingly important. The aim of the IQCARO project was to assess the QoC of IBD units from Spain, by measuring the completion of a validated predefined decalogue of indicators by patients themselves.
Methods: A survey including patient's sociodemographic and clinical characteristics, as well as the previously validated Decalogue with the top 10 most relevant indicators of QoC selected by patients themselves, was developed. The survey was distributed online through the Confederation of Spanish Associations of Patients with Crohn's disease and ulcerative colitis (ACCU) webpage and on paper in 52 IBD units from all over Spain.
Results: Surveys from 940 patients were received (792 online, 148 on paper), of which 778 were valid for the current analysis. The population included patients from the 17 Spanish autonomous communities, and 183 sites. Mean age of patients was 43.4 years, and mean disease duration 13 years. 62.8% were women and 58.1% were diagnosed with Crohn's disease. Patients referred an average of 1.3 (0–21) flares, 1.1 (0–25) unplanned visits to the doctor and 0.4 (0–15) hospitalisations in the last year. The assessment of the QoC indicators that the patients perceived was 8.1 points out of 10, with a median of 9. The least fulfilled indicator was the one related to the recommendations for daily life management and the most fulfilled was the knowledge of the doctor in charge.

	Definition of the QoC Indicators	Percentage of compliance
1	My IBD care team has provided me with enough information about my illness.	82.4 %
2	My IBD care team participates in all phases of care (emergencies, outpatient consultation, hospitalization, endoscopy, etc.).	**74.2%**
3	My doctor pays me proper attention during my medical appointment.	88.8%
4	In case of an emergency, I can reach urgently my IBC care team when I have symptoms of an outbreak or complication.	80.1%
5	I am convinced that my IBD care team is capable to handle my illness correctly.	89.8%
6	My opinion, my personal and work situation has been taken into account when making decisions about the management of my illness.	80.1%
7	When I go to the outpatient clinic or hospital I have toilets nearby.	89.8%
8	Within my IBD care team, I know who is the physician in charge of my case.	90.2%
9	I have been offered recommendations to help me manage my illness in my daily life.	**64.3%**
10	I have received information about the benefits and risks before starting any treatment for my illness.	**74.8%**

Decalogue of the indicators selected by patients and the percentage of compliance.
Conclusions: The evaluation by the IBD patients revealed good fulfilment with the quality of care indicators in the IBD units from Spain. Despite the good general assessment, there are still some aspects that could be improved in the healthcare provided, mainly related to patient`s continuity of care and personal life.

P762

Onset of inflammatory bowel disease during treatment with secukinumab: Can anti-IL-17A be a trigger for inflammatory bowel disease?

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Background: Secukinumab is a monoclonal antibody that acts specifically on interleukin 17A (IL-17A), and is approved for the treatment of plaque psoriasis (PP), psoriatic arthritis (PA) and ankylosing spondylitis (AS). Although it is a pro-inflammatory cytokine raised to the level of intestinal mucosa in patients with inflammatory bowel disease (IBD), it is paradoxical that blocking the IL-17 pathway using secukinumab is not associated to a reduction in bowel inflammation, it even seems to make it worse. This is also due to the fact that IL-17 seems to act as protector against inflammation, contributing to the inhibition of the Th1 response and maintaining the integrity of the enterocyte's epithelial barrier and intestinal homeostasis. Although so far it has not been identified as a trigger of IBD. We describe several of the first cases (Table 1). In addition to this series of cases, only two other cases of onset of IBD during treatment with secukinumab have been reported, both during 2018.
Methods: Descriptive study of a series of cases with emergence of IBD during treatment with secukinumab due to PP, PA or AS in five hospitals in South of Spain.
Results: 353 patients started treatment with secukinumab by indication of rheumatology or dermatology. During treatment, five patients (1.4%) developed an IBD. A sixth case was detected in a hospital where we don´t know number of patients treated with secukinumab. Four of those six patients (66%) were women, with an average age of 41 years (IQR 26.5–47.2). Indications for treatment were 3 PA, 2 PP and 1 SA. Three patients (50%) had previously received anti-TNFα. Four patients were diagnosed with Crohn´s disease (66%) and two patients with ulcerative colitis (33%). The average time to develop IBD was 8.5 weeks from the start of the treatment (IQR 3.7–21.5). After the diagnosis of IBD, secukinumab was withdrawn in five patients and treatment was started with ustekinumab (two patients), infliximab (two patients) or golimumab (one patient). All patients reached a clinical improvement to IBD and rheumatological/dermatological pathology.

Patient	Gender	Age (years)	Underlying illness	Previous treatment	IBD	Montreal	Secukinumab dosage*	Time after first dose when illness appeared
1	Woman	19	Plaque psoriasis	Methotrexate	CD	A2 L3 B1	300 mg/week (induction) 300 mg/month (maintenance)	7-8 weeks
2	Man	60	Ankylosing spondylitis	Naproxen	UC	E2 S3	150 mg/week (induction) 150 mg/month (maintenance)	2-3 weeks
3	Woman	29	Psoriatic spondylitis	Adalimumab	CD	A2 L1 B1	300 mg/week (induction) 300 mg/month (maintenance)	16-17 weeks
4	Woman	43	Psoriatic arthritis	Adalimumab	CD	A3 L3 B3p	300 mg/week (induction) 300 mg/month (maintenance)	8-9 weeks
5	Woman	40	Plaque psoriasis	Etanercept	CD	A2 L1 B1	150 mg/month** (maintenance)	34-35 weeks
6	Man	42	Psoriatic arthritis	Methotrexate	UC	E2 S2	150 mg/week (induction) 150 mg/month (maintenance)	3-4 weeks

IBD, Inflammatory bowel disease; CD, Crohn´s disease; UC, ulcerative colitis.
*Induction was by administration of dosage according to pathology in weeks 0, 1, 2, 3 and 4 and then monthly during the maintenance phase.
**Patient 5 didn't receive induction dose

Secukinumab and onset of IBD. Cases in hospitals from Seville and Huelva.
Conclusions: This study documents the negative relationship between secukinumab and IBD. Thus, it could be that this drug, as well as possibly triggering an outbreak of activity, sets off cases of subclinical or latent disease, especially in genetically predisposed patients; therefore, in these cases, we should consider using other safer therapeutic options for the treatment of these rheumatological and dermatological entities (e.g. anti-TNFα or anti-IL12/23 drugs).

P763

Addiction in IBD patients: more than just smoke?

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Background: inflammatory bowel disease (IBD) represents a variety of chronic conditions, which may significantly impair the life of affected patients. Addictive behaviour of patients with IBD might significantly influence therapeutic outcome directly and indirectly. Hitherto, however, there exists no structured data about IBD and addiction. Objective of this study was to evaluate if patients with IBD are at higher risk for addictions. Moreover, to support the development of evidence-based tools aiming for improved medical assessment and hereby enable physicians to improve their therapeutic strategies.
Methods: In this prospective multi-centre cross-section analysis, patients with IBD at six specialised IBD departments in Germany were asked to fill out a paper based self-reported anonymous questionnaire with 87 questions covering validated screening tests for the six most common addictions in Germany (alcohol, nicotine, drugs and illegal drugs, gambling, food). Furthermore, current treatment and clinical disease activity, measured by PRO 3-Score, were documented as well.
Results: 191 patients (92 males, 99 females; mean age 39.0 years (SD 14.0), range 19–69 years) filled out the questionnaire between March and November 2018. Addictive behaviour could be determined at 61 of the 191 patients. The predominant share of these were regular smokers (27.7%), followed by high-risk drinkers (4.2%). 0.5% of the patients showed a severe level of drug abuse, 4.7% were classified as drug abusers on a moderate level. Another 0.5% of the patients were food dependent and 4.7% were at risk of food dependency. There have been no compulsive gamblers. Comparing these results with the general population, a significant higher proportion of IBD patients showed addictive behaviour for nicotine ($p = 0.049$).
IBD patients with addictive behaviour showed no significantly higher clinical disease activity based on calculation of the PRO 3-score compared with patients without any addictions. Patients with Crohn's disease were significantly more frequently smokers compared with patients with ulcerative colitis ($p = 0.004$; smoking in 35.7% of the patients with Crohn's disease vs. 12.3% of the patients with ulcerative colitis).
Conclusions: Addictive behaviour is not significantly more frequent in patients with IBD compared with the general population except of nicotine abuse. This addiction is significantly more prevalent among patients with Crohn's disease compared with patients with ulcerative colitis. Taking these results into account, qualified screening measures—particularly smoking assessment—should be implemented in daily practice, especially since addictions do not seem to be associated with higher self-reported disease activity.

P764

Prevalence of Autoimmune diseases among first- and second-degree relatives of patients with inflammatory bowel diseases. A case–control survey in Israel

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Background: Inflammatory bowel diseases (IBD) include Crohn's disease (CD) and ulcerative colitis (UC) and are chronic, relapsing, inflammatory diseases of the gastrointestinal tract with an unknown aetiology. They are complex, multi-factorial disorders, in which genetic factors play a major role, the so-called phenomenon of familial aggregation or clustering of IBD. A positive family history of IBD is generally reported among CD and UC probands, with percentages varying depending on the geographic context in which the studies are carried out. Israel is a complex and pluralistic society comprising of two major ethno-national groups and, as such, represents a unique living laboratory in which to test the role of genetic factors in the development of IBD as well as of other autoimmune disorders (ADs). More in detail, in Israel there reside 1.5 million Arab individuals representing up to 20% of the total population. Jews, and in particular Ashkenazi Jews, tend to exhibit a higher risk of CD as well as of other ADs. While studies have found a lower prevalence of ADs among Arabs when compared with Jews, few studies directly compare the two ethnicities
Methods: The present case–control study was designed to compare the rate of autoimmune disorders in first- and second-degree relatives of IBD patients, stratifying according to Jew and Arabic ethnicity
Results: We found that first-degree relatives of Jews patients had a higher risk of developing ADs (OR 1.89 [95% CI 1.18–3.03], $p = 0.0086$). Classifying ADs into systemic and local (endocrinological, gastrointestinal, dermatological, and neurological), first-degree relatives of Jews patients had a higher OR of developing local ADs (OR 2.12 [95% CI 1.25–3.62], $p = 0.0056$).
Conclusions: IBD are a complex, multi-factorial group of ADs. First-degree relatives of Israeli Jew IBD patients exhibit a statistically significant higher risk of developing ADs (in particular local ADs, such as gastrointestinal ones). General practitioners and physicians should be aware of this and explore carefully the familial pedigree when managing and treating Israeli Jew IBD patients

P765

A description of inflammatory bowel disease patients' beliefs in their medications, in comparison with patients with other chronic conditions

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Background: Patients' beliefs in their medications can influence intentional non-adherence. The objective of this work was to describe inflammatory bowel disease (IBD) patients' beliefs in their medicines, identify their main concerns and compare their beliefs with those of patients with other chronic conditions.
Methods: A survey was handed to consecutive patients with IBD, rheumatic diseases, Human Immunodeficiency Virus (HIV) infection or diabetes mellitus (DM). As part of it, patients completed the Beliefs

About Medicines Questionnaire (BMQ), obtaining their agreement with each statement through a Liker scale from 1 (strongly disagree) to 5 (strongly agree). Two partial scores (Necessity score and Concerns score, range 5 to 25) and an overall BMQ score (Necessity score minus Concerns score, range –20 to +20) were calculated.

Results: Of 2474 patients handed the survey, 1618 (65.4%) returned it (359 with rheumatic diseases, 341 with IBD, 467 with HIV infection, 451 with DM, mean age 56 years, 41% women). In general, the percentages of patients that 'agreed' or 'strongly agreed' with the Necessity statements were high (>70%) and were higher in patients with HIV infection and lower in patients with IBD (table). A meaningful percentage of patients 'agreed' or 'strongly agreed' with the Concerns statements: for example, 45% and 61% 'agreed' or 'strongly agreed' with the statements 'Having to take my medicines worries me' and 'I sometimes worry about the long-term effects of my medicines', percentages that were even higher in IBD and rheumatic patients. Patients with HIV infection showed higher Necessity and lower Concerns scores (table). The mean (SD) BMQ score was higher in patients with HIV infection (8.9 [6.4]) compared with patients with DM (6.4 [5.9]), IBD (5.4 [6.3]) or rheumatic diseases (5.2 [6.0], $p < 0.001$).

	Background disease					All patients
	IBD	Rheumatic diseases	HIV infection	Diabetes mellitus	p	
Necessity scale						
My health, at present, depends on my medicines	80.0%	83.8%	89.8%	85.6%	0.001	85.2%
My life would be impossible without my medicines	68.6%	73.8%	83.9%	75.2%	<0.001	76.0%
Without my medicines, I would be very ill	70.4%	76.9%	87.6%	78.6%	<0.001	79.1%
My health, in the future, will depend on my medicines	72.9%	80.3%	84.1%	86.5%	<0.001	81.6%
My medicines protect me from becoming worse	84.7%	84.3%	91.9%	88.1%	0.003	87.7%
Concerns scale						
Having to take my medicines worries me	46.7%	53.4%	36.5%	44.6%	<0.001	44.7%
I sometimes worry about the long-term effects of my medicines	69.3%	72.6%	57.0%	51.6%	<0.001	61.5%
My medicines are a mystery to me	25.7%	28.0%	22.5%	29.1%	0.125	26.2%
My medicines disrupt my life	15.9%	20.9%	16.2%	14.2%	0.088	16.6%
I sometimes worry about becoming too dependent on my medicines	32.4%	43.4%	28.1%	33.2%	<0.001	33.8%
BMQ Scores						
Necessity scale score, mean (SD)	20.2 (4.1)	20.8 (4.1)	22.2 (3.8)	20.7 (4.0)	<0.001	21.1 (4.0)
Concerns scale score, mean (SD)	14.7 (4.5)	15.5 (4.4)	13.3 (4.3)	14.3 (4.3)	<0.001	14.4 (4.3)
Overall BMQ score, mean (SD)	5.4 (6.3)	5.2 (6.0)	8.9 (6.4)	6.4 (5.9)	<0.001	6.6 (6.3)

Responses to the Beliefs About Medicines Questionnaire (percentage of patients who 'agreed' or 'strongly agreed' with the statements), and mean scores

Conclusions: Patients with chronic conditions describe strong beliefs in the necessity of their medications. However, they also express concerns. Patients with IBD or rheumatic diseases scored lower in the BMQ; this merits attention and implementation of actions aimed, especially, to reduce patients' concerns. The study was funded by Merck Sharp & Dohme of Spain and endorsed by 4 patients associations (ACCU: patients with Crohn's disease and ulcerative colitis; CONARTRITIS: patients with arthritis; SEISIDA: AIDS multi-discipline group, FEDE: patients with diabetes mellitus).

P766

Differences among disease pattern, medication use, surgery and hospitalisation rates in a low prevalence of ulcerative colitis population: A retrospective cohort from Bangkok, Thailand

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Background: The incidence of ulcerative colitis (UC) in Thailand is much lower than in the West. The burden of UC varies in different countries and populations. The aim of this study was to describe a temporal trend in disease characteristics, treatment pattern, disease outcomes after diagnosis in a low prevalence of UC population.

Methods: The medical records of 262 patients who were first diagnosed with UC from 2000 through 2017 in two University hospitals from Bangkok, Thailand were longitudinally reviewed for a total of 2100 person-years with a median follow-up duration of 7.7 years. The cumulative probability of thiopurine use, biologic use, developing IBD-related intestinal surgery and IBD-related hospitalisation was estimated using the 1-Kaplan Meier method. We stratified calendar period of UC diagnosis into 2000–2009 and 2010–2017.

Results: Demographic characteristics of the UC cohort are demonstrated in Table 1.

Characteristics	UC cohort (n=262)	
	2000-2009 (n=148)	2010-2017 (n=114)
Male sex (n, %)	64 (43%)	57 (50%)
Median age at diagnosis, years (IQR)	41 (32-53)	46 (34-60)
Median duration of symptom onset, years (IQR)	0.4 (0.1-1.2)	0.5(0.2-1.2)
Smoking status at diagnosis (n, %)		
• Current smoker	2 (1%)	0 (0%)
• Former smoker	12 (8%)	14 (12%)
• - Never smoker	134 (91%)	100 (88%)
UC location at diagnosis (n, %)		
• Proctitis	25 (17%)	28 (25%)
• Left-sided colitis	58 (39%)	35 (31%)
• Extensive colitis	65 (44%)	51 (45%)
UC medications‡ (n, %)		
• 5-Aminosalicylate	102 (69%)	89 (78%)
• Systemic corticosteroids	101 (68%)	162 (54%)*
• Thiopurine	85 (57%)	58 (51%)
• Biologics	2 (1%)	0 (0%)
UC-related surgery§ (n, %)	14 (9%)	1 (1%)*
UC-related hospitalization (n, %)	10 (7%)	2 (2%)

* p<0.05

Table 1. Baseline Characteristic of ulcerative colitis Cohorts, Between 2000 Through 2017.

Patients diagnosed in 2010–2017 were significantly older age at diagnosis and required systemic corticosteroid less than those of patients diagnosed in 2000–2009. The 5-year cumulative probability of thiopurine use of UC patients diagnosed in 2010–2017 were significantly higher than those of UC patients diagnosed in 2000–2009 (39% vs. 63%; $p < 0.01$, respectively). There were two biologic users in 2000–2009 and none of patient diagnosed in 2010–2017. For UC-related surgery, the cumulative probabilities of surgery after diagnosis among calendar period of 2000–2009 decreased from 5.8% to 1.3% when compared with calendar period of 2010–2017. For UC-related hospitalisation, the cumulative probability of hospitalisation was similar between two calendar periods (Figure 1).

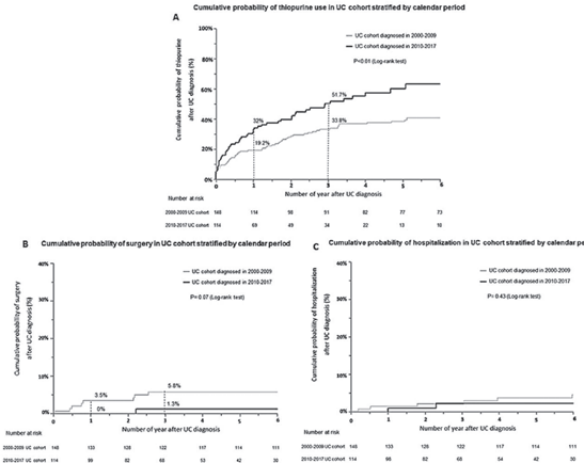

Figure 1. Cumulative probability of thiopurine use (A), surgery (B) and hospitalisation (C) in UC cohort

Conclusions: In this cohort shows the increase in thiopurine users paralleled with the decrease rates of systemic corticosteroid users and surgery. In Thailand, disease severity of UC was comparable to the West. However the rates of surgery and hospitalisation were relatively low as compared with the West.

P767

Non-adherence behaviours of patients with inflammatory bowel disease and other chronic conditions. Relationship with experience with healthcare and beliefs in medications

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Background: We describe the frequency of non-adherence behaviours of patients with four different chronic conditions, and the potential influence of their healthcare experience and beliefs in medications.

Methods: A survey was handed to patients with inflammatory bowel disease (IBD), rheumatic diseases (RD), Human Immunodeficiency Virus (HIV) infection or diabetes mellitus (DM). Five non-adherence behaviours were defined: 1) Forgiveness in taking medication; (2) Taking medication at unscheduled hours; (3) Leaving medication if feeling well; (4) Leaving medication if feeling sick and 5) Stopping medication after reading the patients' information leaflet. Experience with healthcare was assessed with IEXPAC ('Instrument to Evaluate the EXperience of PAtients with Chronic diseases'), scoring from 0 (worst) to 10 (best experience), and obtaining subscores for its 3 factors (productive interactions, new relational model, self-management). Beliefs in medicines was assessed with the Beliefs About Medicines Questionnaire (BMQ), obtaining necessity and concerns score, (range 5 to 25) and an overall BMQ score (–20 to +20). Variables associated to nonadherence were studied with multi-variate logistic regression models.

Results: Of 1530 patients (336 with RD, 332 with IBD, 442 with HIV infection, 430 with DM), 813 (53%) had at least one non-adherence behaviour. The frequency was higher in DM patients and lower in patients with HIV infection (RD: 56%, IBD: 56%, HIV infection: 43%, DM: 60%, $p < 0.001$). It was higher in patients with lower IEXPAC experience scores (Quartile [Q] 1: 62%, Q2: 55%, Q3: 48%, Q4: 47%, p-trend < 0.001) and with lower beliefs score (Q1: 66%, Q2: 63%, Q3: 50%, Q4: 37%, p-trend < 0.001), lower necessity scores or higher concerns score. In multi-variate models (table), non-adherence behaviour was associated to DM and to lower BMQ score. When factors and subscales were introduced, non-adherence was associated to DM, lower self-management IEXPAC score, lower necessity and higher concerns BMQ scores.

	Model 1 (IEXPAC and BMQ overall scores)		Model 2 (IEXPAC factors and BMQ sub-scores)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (1-year increment)	0.99 (0.98 – 1.00)	0.219	0.99 (0.98 – 1.01)	0.476
Gender (female versus male)	1.09 (0.83 – 1.43)	0.558	1.12 (0.84 – 1.49)	0.448
Chronic condition: DM (versus HIV infection)	2.17 (1.43 – 3.29)	<0.001	2.29 (1.47 – 3.56)	<0.001
Chronic condition: IBD (versus HIV infection)	1.26 (0.86 – 1.85)	0.244	1.19 (0.80 – 1.77)	0.398
Chronic condition: rheumatic disease (versus HIV infection)	1.21 (0.81 – 1.81)	0.349	1.16 (0.77 – 1.76)	0.485
Need of taking medication 3-4 times per day (versus 1-2 times per day)	1.34 (0.98 – 1.83)	0.069	1.29 (0.93 – 1.79)	0.135
Number of different medicines (1-unit increment)	0.95 (0.91 – 1.00)	0.071	0.96 (0.91 – 1.01)	0.095
IEXPAC overall score (1-unit increment)	0.98 (0.91 – 1.05)	0.516	-	-
IEXPAC productive interactions score (1-unit increment)	-	-	1.08 (0.98 – 1.18)	0.146
IEXPAC new relational model score (1-unit increment)	-	-	1.07 (1.00 – 1.14)	0.064
IEXPAC self-management score (1-unit increment)	-	-	0.87 (0.79 – 0.96)	0.007
BMQ overall score (1-unit increment)	0.93 (0.91 – 0.95)	<0.001	-	-
BMQ necessity score (1-unit increment)	-	-	0.93 (0.90 – 0.97)	<0.001
BMQ concerns score (1-unit increment)	-	-	1.08 (1.04 – 1.11)	<0.001

Multi-variate analysis. Factors associated to non-adherence behaviours

Conclusions: Non-adherence behaviours are frequent in chronic patients, more in patients with DM, and are associated to experience with healthcare (self-management) and, more significantly, to patients' beliefs in medications (lower necessity and higher concerns). These aspects must be addressed by clinical teams when dealing with chronic patients to increase medication adherence. The study was Funded by Merck Sharp & Dohme of Spain. Endorsed by patients' associations ACCU (IBD), CONARTRITIS (arthritis), SEISIDA (AIDS multi-discipline group) and FEDE (DM).

P768

Development and validation of Processed Foods Questionnaire (PFQ) in Israeli adult inflammatory bowel diseases patients

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Background: Western diet and its food components have been implicated in the pathogenesis of inflammatory bowel diseases (IBD). However, in the absence of a standard quality research that addresses the impact of processed foods on IBD, a validated processed foods questionnaire for IBD patients is essential. The goal of the current study was to develop a Processed Foods Questionnaire (PFQ) and to assess its reliability and validity.

Methods: A single-centre validation prospective study. Adult IBD patients, aged 18–65 years, were recruited. Reliability was assessed by comparing the PFQ of one patient at two-time points separated by at least 2 weeks. Validity was assessed by comparing the PFQ to a three to 7 days food diary. Validity was further tested by correlation of PFQ food consumption to urine sodium, which served as a biomarker for processed food consumption. Urine was analysed for sodium level from either the first morning urine or from a 24 h urine collection. Food intake was categorised to: unprocessed, processed and ultra-processed.

Results: Eighty-six IBD patients [57 (66.3%) Crohn's disease, 29 (34.7%) ulcerative colitis] at a mean age of 33.0 ± 10.7 years, were enrolled. Good test–retest reliability was indicated by intra-class correlation (ICC) of 0.75–0.88 for the different food processing levels. For validity, there were fair to good correlations for different levels of processed food intake between food diaries and the PFQ, ranging between 0.43 to 0.64 (Pearson r, $p < 0.001$). In addition, Kappa measure of agreement was fair- 0.28-0.4. Mean urine sodium levels were higher in patients with high processed-foods consumption compared with low consumption (104.57 ± 53.26 vs. 78.62 ± 39.08 mmol/l, $p = 0.011$). Furthermore, consumption of unprocessed foods negatively correlated with urine sodium levels (Pearson $r = -0.20$, $p = 0.034$).

Conclusions: The PFQ is a reliable and valid tool for the assessment of processed foods consumption in IBD patients and can be utilised for studying the association between processed food consumption and IBD etiopathogenesis.

P769

Seasonal variations in acute hospital admissions with inflammatory bowel disease

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Background: Several environmental factors have been reported to play a significant role in both the aetiology and exacerbation of inflammatory bowel disease (IBD). However, there is scarce and conflicting data assessing the role of seasonal variations on exacerbations of IBD. The aim of this study was to determine the relationship between seasonal variation and hospital admissions with IBD, and correlation between environmental factors (temperature and rainfall) and acute hospital admissions for IBD.
Methods: This single-centre retrospective cohort study included patients admitted acutely to our hospital with Crohn's disease (CD) or Ulcerative colitis (UC) between September 1st 2015 and August 31st 2018. Patient data were collected from Hospital In-Patients Enquiry (HIPE) system and temperature and rainfall data were accessed from the MET Èireann website.
Results: A total of 227 patients were included in the study. CD: 142 (M: 65, F: 77, Mean age: 42 ± 14.9 years), UC: 85 (M: 35, F: 50, Mean age: 51 ± 21 years). There were significantly more CD admissions in summer and spring (44, 44) compared with autumn and winter (28, 26), (p = 0.04 chi-square). By contrast, while there were low numbers of UC admissions in the summer (16) there was no significant seasonal variation when compared with spring (26), autumn (21) or winter (22); (p = 0.49). There was a significant negative correlation between CD admissions and mean monthly rainfall (p-value: 0.02) and a significant negative correlation between UC admissions and mean monthly temperature (p-value: 0.04). There was no significant correlation observed between temperature and CD admissions or between rainfall and UC admissions.
Conclusions: Our data indicate a high incidence of CD admissions in spring and summer with a low incidence of UC admissions in summer. Seasonal changes as well as changes in temperature and rainfall appear to have a dichotomous relationship with CD and UC. Seasonal factors may be responsible for triggering IBD exacerbations in addition to other environmental factors such as infections, smoking, NSAIDs and use of other medications.

P770

Epidemiology of inflammatory bowel diseases in French Polynesia

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Background: The prevalence of inflammatory bowel diseases (IBD) in Southeast Asia has been rapidly growing over the last 50 years. French Polynesia is an overseas territory located in South pacific which comprised in 2018, 275 918 inhabitants. No epidemiologic data on IBD are available in this population who has a single genetic and environmental background. The aim of this study was to describe the incidence, prevalence, characteristics and evolution of IBD patients in French Polynesia.
Methods: We performed a retrospective, multi-centre, cohort study including all patients with Crohn's disease (CD) or ulcerative colitis (UC) diagnosed and/or followed in general hospital or clinics in French Polynesia between January 2011 and April 2018. The diagnosis of IBD was based on clinical, biological, endoscopic and histological criteria. Three groups of patients were defined: Polynesians; Immigrants who developed IBD in Polynesia; and immigrants who developed IBD before their arrival in Polynesia.
Results: A total of 49 patients (25M, 24F) with IBD (27 CD, 30 UC) were identified in French Polynesia. The IBD overall prevalence in French Polynesia was 17 cases per 100 000 inhabitants (11/100 000 for UC and 6/100 000 for CD). Only five Polynesians were diagnosed with IBD (4 UC, 1 CD). Among immigrants, 12 (6 UC, 6 CD) IBD patients were diagnosed before their arrival in Polynesia and 21 (16 UC, 4 CD) developed their IBD in Polynesia. The prevalence of IBD in Polynesians was 1.2 cases/100 000 inhabitants (1.5/100 000 for UC and 0.4/100 000 for CD). The prevalence of IBD in immigrants who developed their IBD in Polynesia was 203 cases/100 000 inhabitants (154/100 000 for UC and 39/100 000 for CD). The mean overall incidence of IBD in Polynesians was 0.1 cases/100 000 inhabitants and 13 cases/100 000 inhabitants for immigrants. The median age at diagnosis of IBD was 43.4 (IQR: 34.1–51.2) years. The majority of IBD patients (72%) were Caucasian. No Polynesian with IBD required immunosuppressive therapy, biologic or surgery. Among immigrants who developed IBD in Polynesia, 19% of cases received immunosuppressive drugs, 14% received biologics and only one underwent surgery. Among immigrants with IBD before their arrival in Polynesia, 45% received immunosuppressive drugs and 66% biologics.
Conclusions: The results of our study demonstrate a very low prevalence of IBD among Polynesians as it was observed in Southeast Asia 50 years ago. The prevalence of IBD among immigrants who developed their disease in Polynesia is similar to IBD prevalence currently observed in European countries. The IBD developed in Polynesia seemed to require less immunosuppressive drugs, biologics or surgery.

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Predictors of health-related quality of life in patients with moderate to severely active ulcerative colitis receiving biological therapy

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Background: Patients with ulcerative colitis have reduced health-related quality of life compared with the general population. Current treatment strategy aims to reduce patients' symptoms and increase health-related quality of life. We aimed to investigate which symptoms of ulcerative colitis, correlate to decreased health-related quality of life.
Methods: Among 744 patients with moderate to severely active ulcerative colitis receiving biological therapy in a cross-sectional national study, we determined which disease-related symptoms, measured with Simple Clinical Colitis Activity Index, worsened health-related quality of life scores across the four Short Health Scale dimensions, while adjusting for treatment, age and clinical manifestation and stratifying for sex.
Results: Overall disease activity was associated with worsening of health-related quality of life. Both sexes had decreased health-related quality of life in all dimensions for the symptoms: bowel frequency during daytime, urgency of defaecation and blood in stool. Women were more often negatively affected by bowel frequency during night-time and arthritis than men, and being a woman was a

significant predictor of worse health-related quality of life in some dimensions.

Conclusions: Decreased health-related quality of life was most prominently associated to bowel frequency during daytime, urgency of defaecation and blood in stool. Other symptoms such as bowel frequency during night-time and arthritis were associated for some health-related quality of life dimensions, and appear to vary between the sexes. Furthermore, female sex was an independent predictor of worse health-related quality of life for some domains.

P772

Development and validation of tools to assess food additive intake: the ENIGMA study

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Background: Processed food additives are widely used to change food consistency, appearance and shelf life. In the Food Agriculture Organization/ WHO International Food Standards CODEX additives are deemed non-toxic or carcinogenic, but their functional impact is unknown. The global pandemics of metabolic and inflammatory bowel diseases have occurred in parallel with widespread additive use. Additives have been causally linked to microbiota changes and mucus layer destruction. A validated measure of food additive intake does not exist. We report the development and validation of 2 food additive measurement tools.

Methods: Questionnaire design: Two dietitians working in Australia and Hong Kong created a database of food additives (n = 10) implicated in IBD, the CODEX food-categories they are permitted in, and their maximum suggested permissible concentration (mg/kg). Food categories were condensed into 27 food lists, with examples. Intake in early life (part 1) and recently (part 2) were assessed. Part 1 comprised 39 dichotomous questions on breast-feeding, home and processed food consumption up to age 18. Part 2 assessed frequency of consumption for the 27 food lists in the preceding 12 months. Forward–backward translation into Hong Kong Chinese was undertaken. Pilot testing: 31 individuals assessed understandability. Validation: A new cohort of 26 individuals undertook the tool twice, 2 weeks apart, to assess reproducibility. Cohen's' Kappa-co-efficient was used to assess percent agreement for part 1 questions. Intra-class correlation coefficient (ICC) was used to assess the agreement between the total annual frequencies of the food lists.

Results: Pilot testing: Participants reported difficulty recalling food intake, estimating portions and confusion around certain terms. Instructions were therefore added for estimating food intake. Validation cohort: Respondents judged the questionnaires easy to understand and complete. The average kappa-coefficient for part 1 questions was 0.5. Eighteen per cent of questions had slight to fair correlations, 36% had moderate correlations, and 46% had substantial to almost perfect correlations. Researchers expect moderate correlations in measures of remote diet intake. For part 2 the ICC for total, annual frequency of the 27 food lists was 0.888 ($p < 0.001$), indicating good reliability.

Conclusions: Two tools (part 1 and 2) have been developed and validated, in two major languages and cultures, which reproducibly assess early-life and recent intake of food additives. These can be applied to individuals to assess this important emerging field of the relationship between food additive intake and disease.

P773

Sarcopenia is a new risk factor of non-alcoholic fatty liver disease in patients with inflammatory bowel disease.

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Background: Although there has been known high association between metabolic syndrome (MS), and non-alcoholic fatty liver disease (NAFLD) in general population, MS is less frequent in patients with inflammatory bowel disease (IBD). Recently, sarcopenia has been proposed as an additional risk factor in patients with NAFLD, no study has been reported in patients with IBD. We aimed to analyse the clinical association between sarcopenia and NAFLD, independently other risk factors of NAFLD in patients with IBD.

Methods: From January 2004 to December 2017, total 488 IBD patients with the result of computed tomography (CT) were included in the analysis. Among them, we classified into non-NAFLD vs. NAFLD group and compared the clinical characteristics. The volume of muscle was calculated by area of total psoas muscle (TPA) in third lumbar region on CT per patient's height^2 (m^2). Sarcopenia was defined as the cases in which the volume of muscle less than 545 mm^2/m^2 in men and less than 385 mm^2/m^2 in women.

Results: NAFLD was diagnosed in 49 patients (11.1%) from final 443 IBD patients. Patients in NAFLD group were older (45.1 vs. 38.6 years; p = 0.006), had higher level of body mass index (23.0 ± 2.7 vs. 20.8 ± 3.3 kg/m^2; $p < 0.001$), had higher proportions of ulcerative colitis (UC) (59.2% vs. 35.5%; p = 0.002), more metabolic syndrome (36.7% vs 7.4%; $p < 0.001$) than those in non-NAFLD group. Sarcopenia was more common in NAFLD group (51.0% vs. 33.0%; p = 0.019) than in non-NAFLD group. Sarcopenia was an independent risk factor for NAFLD in patients with IBD and the results was persistent after adjusting by age, gender, traditional metabolic risk factors, disease severity of IBD, and medication.

Conclusions: Our study showed that the prevalence of NAFLD in patients with IBD accounted for 11.1%. Along with other well-known, traditional risk factors, sarcopenia was also independent risk factor of NAFLD in patients with IBD. To prevent hepatic complication, physician need to consider carefully the nutrition, exercise and proper physical activity for maintaining sufficient muscle volume in patients with IBD.

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Higher plasma cotinine is associated with an increased risk for later developing IBD, especially among users of combusted tobacco

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Background: Smoking has previously been associated with inflammatory bowel disease (IBD), but no study has reported on cotinine, an objective measure of tobacco use. We aimed to test the hypothesis that cotinine is higher among healthy subjects who later develop IBD compared with matched controls. Also to adjust for use of combusted vs. non-combusted tobacco.
Methods: We analysed plasma cotinine and lifestyle questionnaires including tobacco habits in 96 subjects who later developed IBD (70 Ulcerative colitis (UC) and 26 Crohn´s disease (CD)) and in sex and age-matched controls.
Results: Patients who later developed IBD (median time to diagnosis 5.091 years) and UC had significant higher plasma cotinine levels compared with controls. Although plasma cotinine concentrations were higher in snuff users compared with smokers no increase in risk was seen for snuff users. In multi-variate analysis, higher log-cotinine was associated with higher risk for developing IBD (OR 1.338 (95% CI 1.099-1.630)). After stratifying for time to diagnosis, this confined to those with shorter time to diagnosis (OR 1.445 (1.087–1.920)). The findings were similar for UC but not for CD. For all IBD cases, snuff use was associated with a lower risk of developing IBD among subjects with shorter time to diagnosis in multivariate analysis.
Conclusions: Cotinine, an objective method for measuring tobacco use, is associated with later developing IBD and UC. The findings among snuff users indicate that components of combusted tobacco other than nicotine are involved in the genesis of IBD in smokers.

P775

Finger clubbing and Crohn's disease: higher frequency in patients with upper GI lesions in a prospective study

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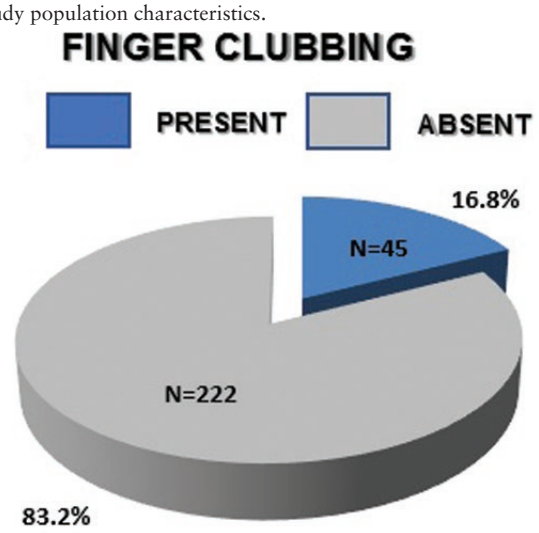
Background: Finger clubbing (FC) has been associated with Crohn's disease (CD). Clinical relevance of this finding is undefined. Primary aim was, in a prospective single-centre study, to assess if FC is associated with CD severity and behaviour.
Methods: From January to December 2016, patients with a diagnosis of CD and detailed clinical records were enrolled. Data expressed as median (range), Chi-squared or T-test as appropriate.
Results: FC was assessed in 267 CD patients. Population characteristics were: M 163 (60%), age 47.3 (17–83); age at diagnosis 33.2 (10–82); CD duration 13.3 (1–56). The disease involved ileum (I) in 160 (59.9%); Colon (C) in 12 (4.5%); ileum-colon (I-C) in 69 (25.8%), upper GI in 26 (9.8%) patients. Disease behaviour was non stricturing-non penetrating in 69 (25.8%), stricturing in 137 (51.3%); penetrating in 61 (22.9%) patients. Perianal disease (PA) was observed in 40 (14.9%) patients. Previous surgery in 143 (53.5%); thiopurines use in 113 (42.3%); anti-TNFα use in 99 (37.1%) patients. Smoking habits in CD were recorded (Yes, No, Ex: n = 82 [30.7%], n = 87 [32.5%], n = 98 [36.8%]. Chronic pulmonary diseases were observed in 19 (7.1%). FC was observed in 45/267 (16.8%) patients. In these patients with FC (n = 45) the lesions involved ileum in 25 (55.6%), colon in 1 (2.2%), I-C in 10 (22.2%), upper GI in 9 (20%). The frequency of upper GI lesions was significantly higher in CD patients with vs. without FC (9/45 [20%] vs. 17/222 [7.7%]; p = 0.01, OR 3.01, CI (95%): 1.2477 to 7.2841). FC was detected in 9/26 (34.6%) patients with upper CD. Other CD lesions were equally distributed in patients with vs. without FC (I: 25/45 [55.6%] vs. 135/222 [60.8%]; p = 0.511; C: 1/45 (2.2%) vs. 11/222 (4.9%); p = 0.419; I-C: 10/45 (22.2) vs. 59/222 (26.6%); p = 0.542. There was no difference between the two groups in terms of conventional immunosuppressive (ISS) nor Anti TNFa therapy (ISS: 21/45 [56.6%] vs. 92/222 [41.4%]; p = 0.58; Anti-TNFa: 20/45 [44.4%] vs. 79/222 [35.6%]; p = 0.26). The frequency of smokers, ex-, no-smokers did not differ between CD patients w/o FC (17/45 [37.8%] vs. 65/222 [29.3%]; p = 0.26; 17/45 [37.8%] vs. 81/222 [36.4%]; p = 0.87; 11/45 [24.4%] vs. 76/222 [34.2%]; p = 0.2. Pneumopaties were recorded in 3/45 (6.6%) with clubbing.

CD patients	TOTAL n=267	CLUBBING n=45 (16.8%)	P=
Age	47.3 (17-83)	50.4 (19-69)	p=n.s.
Age at diagnosis of CD	33 (10-82)	34.7 (12-68)	p=n.s.
CD duration	14 (1-56)	15.5 (1-38)	p=n.s.
CD site (n=)			
Ileum only	160 (59.9%)	25 (55.6%)	p=n.s
Colon only	12 (4.5%)	1 (2.2%)	p=n.s
Ileum-colon	69 (25.8%)	10 (22.2%)	p=n.s
Upper-GI	26 (9.8%)	9 (20%%)	p=0.01, OR 3.01
Perianal Disease	40 (20.1%)	8 (17.8%)	p=n.s.
Previous Surgery	143 (53.5%)	36 (80%)	p=n.s.
IS use	113 (42.3%)	21 (55.6%)	p=n.s.
Anti TNFα use	99 (37.1%)	20 (44.4%)	p=n.s.
Pulmunary diseases	19 (7.1%)	3 (6.6%)	p=n.s.

Study population characteristics.



Finger clubbing prevalence in study population.
Conclusions: The prevalence of FC was significantly higher in patients with upper GI lesions. FC in CD patients appeared not related to smoking habits nor to pulmonary diseases.

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Factors associated with quality of care perceived by patients in IBD units from Spain. Analysis from IQCARO project

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Background: Measuring patient's perceived quality of care (QoC) in inflammatory bowel disease (IBD) units is becoming increasingly important. The aim of this analysis was to assess the factors associated with QoC of IBD units from Spain, by measuring the fullfillment of a validated score of indicators by patients followed up by IBD specialists or general gastroenterologists (GG).

Methods: A survey was developed including patient's sociodemographic and clinical characteristics, as well as the final validated top 10 indicators of QoC. The survey was distributed online through the Spanish Association of Patients with Crohn's disease and ulcerative colitis (ACCU) webpage. In the multi-variate analysis the QoC index score was dichotomised (high quality/low quality) with a cut-off point of 9.5 to be used as a dependent variable in a binary logistic regression model to determine the factors that can influence the evaluation of QoC as high.

Results: Online-completed surveys from 640 patients were valid for analysis, with 451 patients (70%) being attended by IBD specialist and 138(30%) by GG. The population included patients from the 17 Spanish autonomous communities, and 183 sites. Mean age was 42.3 years, and mean disease duration 13 years. Sixty-six per cent were women and 60.7% were diagnosed with Crohn's disease. The QoC index mean was 7.8/10 being higher (meaning better QoC) in patients attended by IBD specialists vs. GG: 8.2 vs. 6.7, respectively, $p < 0.001$. We found no differences regarding disease activity ,number of flares, hospitalisations, emergency room visits in the last year or patients´ perception of disease control in the last 2 weeks, in patients attended by IBD specialist vs. GG, p = NS for all. When we analysed the QoC index score as a dichotomised variable, in the univariate analysis we found that older patients, longer disease duration, routine follow-up by IBD specialist, and better perception of controlled disease were all associated with high quality index score. Active disease, unscheduled visits in the last year, higher number of flares, and unemployed patients perceived low quality index score. The multi-variate analysis showed that employed patients, controlled disease, low number of unscheduled visits and being treated by an IBD specialist were all associated with a higher QoC index score.

	Coefficient	OR	IC_{95}	p
Employed	1.09	2.97	(1.51;5.85)	0.002
Controlled disease	1.08	2.69	(1.90;4.63)	< 0.001
Number of unscheduled visits	–0.20	0.81	(0.72;0.93)	0.003
IBD specialist	1.11	3.05	(1.88;4.95)	< 0.001
Constant	–2.89			< 0.001

Binary logistic regression analysis.

Conclusions: The evaluation of QoC by IBD patients from Spain is good but is higher when they are followed-up by IBD specialists. Personal and disease-related aspects may influence in the perceived QoC.

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The cancer incidence in paediatric onset inflammatory bowel disease: a population-based study from Denmark

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Background: The incidence of colorectal cancer (CRC) in IBD has been the subject of much debate over the last decades and seems to have decreased to a negligible [1].However, in most studies sub-analysis revealed young age at diagnosis to be a risk factor for CRC. A recent study from Sweden [2] reported an increased risk of cancer (all types) in paediatric onset IBD (pIBD) but the reproducibility of this in other countries is unknown. In this population-based study we aimed to estimate the incidence of cancer in the Danish pIBD population in a 23 years period.

Methods: The pIBD population was defined as individuals registered in the Danish Patient Register (LPR) with a diagnosis of Crohn's disease, ulcerative colitis or IBD-unclassified before their 18th birthday during the period 01 January 1992 to 31 December 2014. This cohort was cross referenced with the cancer register identifying all pIBD patients who subsequently developed cancer. Standardised incidence ratios (SIR) were calculated comparing observed numbers with expected numbers of cancers.

Results: 3.279 patients with pIBD were identified and followed through. Of these, 125 were registered in the cancer register. Using the Danish Pathology Register as gold standard, the cancer diagnosis could be confirmed in only 93 of these patients. The SIR of cancer in general was 4.6 (95% confidence interval (CI): 3.7-5.6). The cancer specific SIR was 7.2 (CI: 2.3–16.8) in CRC, 111 (CI: 41–243) in bile duct cancers, 3.6 (CI: 1.9–6.2) in skin cancers and 1.7 (CI: 0.5–4.3) in lymphoma.

Conclusions: Conclusion: In this population-based study, we found an increased risk of cancer in pIBD. By analysing the cancer specific SIR, we found a strikingly high increased risk of bile duct cancers in pIBD which consisted of cholangiocarcinomas only. These findings are in line with the existing Swedish study. However, the wide CI in our cancer specific analysis calls for larger international multi-centre studies.

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Risk of cancer in paediatric onset inflammatory bowel disease: a nationwide cohort study 1977–2014

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Background: The prognosis of paediatric onset inflammatory bowel disease (IBD) remains uncertain. We examined the overall and site-specific cancer risk among paediatric onset IBD patients when compared with non-IBD individuals from the general population.
Methods: Based on the Danish National Patient Register, we established a nationwide cohort (1977–2014) of all individuals recorded with IBD before the age of 18 (n = 4,221) and 42,210 randomly selected age- and sex-matched individuals from the general population. The risk of cancer was determined using Cox proportional hazard regression.
Results: During 59,563 person-years of follow-up, 126 of 4,221 paediatric onset IBD patients developed cancer (2.1 cases per 1000 person-years) when compared with 554 of 42,210 non-IBD individuals (1.0 case per 1000 person-years). Accordingly, the hazard ratio (HR) of any cancer was 2.16 (95% CI, 1.77–2.62) with a slightly higher risk in Crohn's disease (HR, 2.45; 95% CI, 1.82–3.30) than in ulcerative colitis (HR, 1.96; 95% CI, 1.51–2.55). Males with paediatric onset IBD (HR, 3.17; 95% CI, 2.33–4.29) had a significantly higher risk of cancer than females (HR, 1.71; 95% CI, 1.32–2.21). When examining site-specific cancers, the risk of liver, upper gastrointestinal, small bowel and colorectal cancer was significantly increased.
Conclusions: This nationwide cohort study showed a significantly increased relative risk of cancer in paediatric onset IBD. The risk was highest for liver, upper gastrointestinal, small bowel and colorectal cancer and was not influenced by medical treatment. Still, absolute numbers were low with only 1 additional cancer case per 1000 person-years of follow-up. This is important information to patients and clinicians.

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Extra intestinal manifestations and other comorbidities in Crohn's disease and Ulcerative colitis are equally likely to appear before IBD diagnosis: a Danish nationwide registry study from 2003 to 2015

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Background: Extraintestinal manifestations (EIM) in inflammatory bowel disease (IBD) may be frequent and can be a complication to the underlying abnormal immune response. EIMs may impact the quality of life for patients significantly, requiring specific treatment depending on the affected organ(s). This study investigated the occurrence and timing of EIMs in Crohn's disease (CD) and ulcerative colitis (UC) patients using population-based data in Denmark from 2003 to 2015.
Methods: In this register study using the Danish National Patient Register, incident CD and UC patients between 2003 and 2015 were assessed and matched on age and gender with one non-diseased control. The selected EIMs and comorbidities for this study included 51 different diagnoses divided into eight classes; musculoskeletal system, dermatologic and oral systems, hepatopancreatobiliary system, ocular system, metabolic system, renal system, nervous system and the respiratory system. Logistic regression analysis was applied to estimate odds ratios and test for significant differences in the timing and occurrence of EIMs and comorbidities between the patient groups and the control groups, and between the dates of IBD diagnosis.
Results: In total, 10 302 incident patients with CD and 22 144 incident patients with UC were identified and included in the analyses. The highest risk of patients experiencing EIM/comorbidities for the first time before their IBD diagnosis was in the dermatologic and oral systems, 6.0% of all CD patients and 4.1% of all UC patients. After IBD diagnosis, registered values were 9.5% and 4.6%, respectively. For CD, the odds ratio of having an EIM before or after IBD diagnosis, as compared with controls, was significant in the dermatologic, oral, hepatopancreatobiliary, musculoskeletal, ocular, renal and respiratory systems. For UC, the risks were similar before and after UC diagnosis, apart from the nervous system where the odds ratio was significantly higher before the diagnosis of UC, and after in the ocular system. Additionally, we observed that UC patients were significantly more likely to have a registered diagnosis of Parkinson's disease than controls. The odds ratio was 1.58 and comparable to that which has been reported in recent studies.
Conclusions: This study provides population-based evidence of EIMs in CD and UC patients that precede their IBD diagnosis at an equal risk of occurrence, after diagnosis. These findings may indicate a significant diagnostic delay of CD and UC, and the occurrence of known EIMs should prompt physicians to look for patients possibly having underlying IBD.

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Medical treatment and surgery in patients with elderly-onset inflammatory bowel disease: 3-year follow-up of Epi-IBD 2010–2011 cohorts

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Background: Previous reports have indicated that the treatment of patients with elderly-onset inflammatory bowel disease (IBD), defined as patients diagnosed ≥60 years, differs from that of younger patients. We aimed to assess the treatment of elderly-onset IBD during the first 3 years of follow-up, compared with IBD diagnosed in patients aged 15–39 and 40–59, in a European population-based inception cohort.

Methods: The EPI-IBD cohort is a prospective, population-based inception cohort of patients diagnosed 2010 and 2011 in 36 European and 1 Australian centres. For this study, data regarding disease characteristics and medical or surgical treatment during the first 3 years from diagnosis were analysed. All data were entered in a secure web-based database, www.epicom-ecco.eu. Patients were classified according to age at diagnosis into 15–39y, 40–59y and ≥60y. Medical treatment was assessed in each group and the time to biological and surgical treatment was analysed by Kaplan-Meyer curves. A Cox regression model was built to assess the influence of age at diagnosis in the need of biological treatment or surgery.

Results: In total, 2000 IBD patients (53.6% males) were included in the cohort, 747 (37.4%) CD, 1106 (55.3%) UC and 147 (7.4%) IBDU. Elderly-onset patients were more frequently diagnosed with UC compared with patients diagnosed at age 40–59y or 15–39y (62.9% vs. 56.3% vs. 52.6%, respectively, $p = 0.006$). In UC, the frequency of proctitis at diagnosis was lower, although non-statistically significant (16.2% vs. 24% vs. 23.2%, respectively, $p = 0.087$). In CD, elderly-onset patients more often had colonic location (38.1% vs. 29.0% vs. 22.6%, respectively, $p = 0.022$), while no differences were observed in disease behaviour. Elderly-onset patients were less frequently treated than the other age groups with immunomodulators (19.6% vs. 31.4% vs. 40.5%, respectively, $p < 0.001$) and biologicals (3.6% vs. 10.6% vs. 15.5%, respectively, $p < 0.01$). Biologicals were less prescribed in elderly-onset patients in both CD (7% vs. 20.9% vs. 25%, respectively, $p < 0.001$) and UC (2.4% vs. 5.1% vs. 9.5%, respectively, $p = 0.001$). No difference was found in the need of surgery among the age groups (7.7% vs. 9.7% vs. 9.1%, respectively, $p = 0.617$).

Conclusions: In this large population-based inception cohort, elderly-onset IBD patients were less aggressively treated than younger patients. This finding may reflect a less severe disease course in elderly-onset IBD.

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Defining the economic burden of venous thromboembolism after surgery for inflammatory bowel disease in the USA: a national inpatient sample study

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Background: The economic burden associated with VTE after surgery for IBD has not been reported. Therefore, we aimed to use a large national database to define the rate of post-operative VTE, and VTE-associated healthcare costs.

Methods: A retrospective, cross-sectional analysis was performed using National Inpatient Sample data from 2010 to 2014. The International Classification of Disease 9th ed. diagnostic and procedure codes were used to identify patients with primary diagnosis of Crohn's disease (CD) or ulcerative colitis (UC) who underwent major surgery. VTE included any extremity DVT, pulmonary embolism, portomesenteric venous thrombosis, and cerebral venous sinus thrombosis. The national VTE rate and VTE associated costs were estimated. Uni- and multi-variate logistic regression models were used to compare patient and hospital characteristics and outcomes between VTE and non-VTE groups. The total average direct costs in dollars were compared between groups using linear regression, in dollars, extrapolated to the national population.

Results: Any VTE was identified in 1,656 (5.3%) out of a total of 31,242 patients. On univariate analysis, older age, white race, higher Elixhauser comorbidity score, UC diagnosis, hospital transfer prior to surgery, larger bed size and urban teaching hospital were associated with VTE; conversely, elective surgery, laparoscopy and colectomy (compared with proctectomy and >1 type of resection) were associated with lower risk of VTE. On multi-variate analysis age, Elixhauser score, resection type, transfer status, hospital bed size, location and teaching status of hospital were independently associated with VTE. Proctectomy and >1 type of resection were independent factors associated with increased risk of VTE compared with colectomy alone (OR 1.5, 95% CI 1.3–1.9; OR 1.4, 95% CI 1.2–1.6, respectively; both $p < 0.001$). In terms of outcomes, patients who developed VTE had an increased length of stay (11.3 vs. 7.6 days; $p < 0.001$) and higher inpatient mortality (5.4% vs. 3.7%; OR 1.5, 95% CI 1.2–1.8; $p < 0.001$) compared with the non-VTE

cohort. Direct costs were significantly higher in the VTE group, with an addition cost of $14,939 (95% CI $12 369–$17 510, $p < 0.001$) per admission. After adjusting for clinically relevant covariates, the cost difference was $10,507 (95% CI $9649 – $11 365, $p < 0.001$). Nationwide, the additional cost of VTE was estimated at $17 031 847 annually.

Conclusions: VTE after abdominopelvic surgery for IBD occurred in >5% of patients, and was associated with additional costs of $10 000/patient, translating into >$17 million dollars in the USA annually. Novel screening and prophylactic regimens are sorely needed to reduce this morbid, costly, and potentially avoidable complication.

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Living with ulcerative colitis in Germany: quantifying the healthcare resource utilisation and direct healthcare costs associated with the treatment of moderate to severe ulcerative colitis in Germany

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Background: Biologic therapies are indicated for inducing and maintaining clinical remission in moderate to severe ulcerative colitis (UC). Whilst the safety and efficacy of biological therapies for the treatment of moderate to severe UC has been evaluated in clinical trials, there is limited data on real-world patient outcomes. Additionally, it is not known whether increased therapeutic drug monitoring and related dose escalations may be associated with high financial burden to patients and healthcare systems. We present data from the Living with UC Study in Germany with an aim to estimate the healthcare resource utilisation (HCRU) and direct healthcare costs among patients with moderate to severe UC initiated on biologic therapy.

Methods: A retrospective, longitudinal cohort design was employed utilising de-identified German statuary health insurance (SHI) claims data within the Health Risk Institute database. Adult patients (18+ years) with UC (ICD-10 K51) but without Crohn's disease (ICD-10 K50) were indexed between January 2013 and December 2015 on biologic therapy initiation (adalimumab [ADA], golimumab [GOL], infliximab [INF], vedolizumab [VED]). Patients had to be continuously insured by SHI and have no record of biologic therapy in the prior 12 months. All-cause HCRU (inpatient stays, emergency visits, outpatient visits, surgeries/procedures) and total direct healthcare costs were assessed in the 24 months following the index date. All outcomes were stratified by index biologic therapy. Descriptive analyses were reported. Statistical significance was assessed using analysis of variance.

Results: In total, 304 patients were identified (mean age 42.9, 56.3% male). The majority of patients were initiated on ADA (41.1%) and INF (37.5%), with 15.5% and 5.9% initiated on GOL and VED, respectively. HCRU and total direct healthcare costs following indexing are presented in Table 1. Across all patients, mean total direct healthcare costs were €58,574 with the highest and lowest costs observed for patients initiated on GOL (€75,464) and VED (€44,213), respectively. None of the outcomes assessed were significantly different across biologic therapies.

Conclusions: The total direct healthcare costs remain substantial for patients with moderate to severe UC using biologic therapies. These data suggest further advanced treatment options should be explored that are not only efficacious, but do not result in high financial burden to the patients and/or healthcare system.

Mean (SD)	UC (n=304)	Adalimumab (n=125)	Infliximab (n=114)	Golimumab (n=47)	Vedolizumab (n=18)
Inpatient stays*					
Number of stays	1.5 (2.2)	1.3 (1.7)	1.8 (2.5)	1.5 (2.6)	0.5 (0.7)
Length of stay (days)**	15.4 (38.0)	12.1 (25.1)	17.6 (34.6)	23.7 (68.4)	1.8 (4.6)
Emergency visits*					
Number of visits	0.6 (1.1)	0.5 (0.9)	0.7 (1.3)	0.6 (1.2)	0.2 (0.4)
Length of stay if admitted (days)**	7.2 (29.5)	4.1 (8.7)	7.6 (20.2)	16.9 (66.2)	0.2 (0.6)
Outpatient visits*					
Gastroenterologist	12.4 (12.6)	10.7 (12.9)	13.3 (12.0)	12.9 (10.2)	16.7 (17.5)
Visceral surgery	0.1 (0.4)	0.1 (0.6)	0.0 (0.2)	0.1 (0.3)	0
Psychology/Psychiatry	2.0 (8.6)	2.1 (8.6)	2.8 (10.2)	0.8 (5.1)	0.4 (1.9)
Surgeries/procedures*	1.1 (2.6)	0.9 (1.3)	1.2 (1.9)	1.5 (5.6)	0.7 (1.0)
Total direct healthcare costs (€)	58,574	56,702	55,930	75,464	44,213

**Includes patients who did not utilize any healthcare resources*
*** Includes patients who were not admitted to hospital and/or the emergency room*

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Long-term colectomy rate in acute severe ulcerative colitis. An observational multi-centre study on behalf of IG-IBD (Italian group for the study of inflammatory bowel disease)

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Background: Acute severe ulcerative colitis (ASUC) is a potentially life-threatening event affecting up to 25% of patients during disease course. Intensive intravenous glucocorticoid treatment (IIVT) and early colectomy have reduced mortality to less than 2% in the last four decades. Rescue therapies -Infliximab (IFX) or Cyclosporin (CyA)- may reduce early colectomy in IIVT refractory patients but their impact in the long-term is unclear. Aim of the present study was to evaluate the long-term colectomy rate in patients escaping early colectomy after a severe attack

Methods: From 2005 to 2016 all patients with ASUC meeting Truelove and Witts criteria modified by Chapman et al. referring to 14 Italian IBD referral centres were retrospectively reviewed. All patients received IIVT. IFX or CyA were used as rescue therapies. Primary outcome was long-term colectomy rate in patients escaping early colectomy (within 3 months). Secondary outcomes were overall need of escalation therapy (defined as need of anti-TNF agents or immunomodulators or steroids) or hospitalisation. Kaplan–Meier survival method was used to estimate the cumulative probability of a colectomy-free course and log-rank test to compare colectomy-free survival distributions in different subgroups. A stepwise regression model was used to look for predictive factors of long-term colectomy
Results: In total, 361 patients were enrolled. Of them, 15 (4.2%) underwent early colectomy and 346 avoided colectomy: due to of IIVT response (*n* = 223,64.5%) or rescue therapy response with IFX (*n* = 103, 29.7%) or CyA (*n* = 20, 5.8%).

	Overall n. 346	Steroid responders n 208	Rescue therapy responders n 138	P value
Gender n (%)				
- M	201 (58)	125 (60)	76 (55)	0.3
- F	145 (42)	83 (40)	62 (45)	
Age n (%)				
- < 40 yrs	186 (54)	107 (51)	79 (57)	0.3
- > 40 yrs	160 (46)	101 (49)	59 (43)	
Disease duration median (Range)	36 (0-456)	24 (0-336)	36 (0-456)	0.4
First attack n (%)	279 (80)	173 (83)	106 (77)	0.14
Recurrent attack n (%)	67 (20))	35 (17)	32 (23)	
Disease extension n (%)				
-left sided	90 (26)	53 (25)	38 (27)100 (73)	0.8
- extensive	256 (74)	155 (75)		
Endoscopic severity n (%)				
-Mayo 3	281(81)	166 (80)	115 (82)	
-Mayo ≤ 2	42 (12)	27 (13)	15 (11)	0.4
-not reported	23 (7)	15 (7)	8 (7)	
Smoking habits n (%)				
-no/former	214 (62)	125 (60)	89 (65)	0.6
- active	55 (16)	30 (15)	25 (18)	
-not reported	77 (22)	53 (25)	24 (17)	
Previous medications n (%)				
- steroids	222 (64)	119 (57)	103 (75)	
- immunomodulators	69 (20)	38 (18)	31 (22)	0.3
- anti TNF	33 (9.6)	23 (11)	10 (7)	
Maintenance after acute attack n (%)				
- mesalazine	118 (34)	105 (51)	13 (9)	
- immunomodulators	95 (28)	71 (34)	24 (18)	< 0.0001
- anti TNF (± IM)	120 (34)	26 (13)	94 (68)	
- not reported	13	6 (2)	7 (5)	

During a median follow-up of 43 months, 67 patients (19.4%) required colectomy

Clinical characteristics of patients.
During a median follow-up of 43 months (range 1–156),67 patients (19.4%) required colectomy. The cumulative probability of a colectomy-free course was 92.7, 87, 81.9 and 79.7% after 12, 24, 36 and 60 months, respectively. Colectomy risk was similar in IIVT responders and in rescue therapy responders. During follow-up, 135 (39%) and 109 (31.5%) patients required at least one escalation of therapy and hospitalisation, respectively. At multi-variate analysis none of the covariates considered (age, gender, first or recurrent attack, disease extension, C-Reactive Protein levels, endoscopic severity, steroid/rescue therapy responsiveness, maintenance treatment) was associated to long-term colectomy risk
Conclusions: The long-term colectomy risk after an acute severe attack is still relevant and do not seem to be influenced by the severity of the attack, resulting similar both in IIVT responders and in IIVT refractory patients responding to rescue therapies.

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Prevalence of cervical dysplasia in women with inflammatory bowel disease: data from the Parelsnoer Institute (PSI) and PALGA database (PAP-IBD study)

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Background: Women with inflammatory bowel disease (IBD) may be at higher risk for cervical intraepithelial neoplasia (CIN). Possible explanations for this elevated risk include increased persistence of high-risk human papillomavirus (hrHPV) and rapid progression of premalignant lesions in immunocompromised individuals. However, data on CIN in IBD are conflicting. The aim of this study was to assess the prevalence of CIN in a large cohort of female Dutch IBD patients when compared with the general cervical screening population.
Methods: We retrieved all cervical cytology and histology records from the nationwide Dutch Pathology Database (PALGA) for women with IBD in the Parelsnoer study; a large multi-centre cohort study (Parelsnoer Institute, Dutch IBD Biobank) in which clinical data are prospectively collected. Women in the IBD cohort were frequency matched 1:4 to a control group of women from the general cervical screening population from PALGA, based on age at first smear and year of screening.
Results: Cervical smears were available on 2,098 IBD patients (1,370 Crohn's disease (65.3%), 678 ulcerative colitis (32.3%), median age at IBD diagnosis 28.5 years). We found a significant difference in prevalence of CIN 2 or more severe (CIN 2+) lesions in IBD women (110/2,098, 5.2%) compared with the control group (324/8,439, 3.8%) with an odds ratio of 1.4 (95% confidence interval 1.1–1.7, p = 0.004). CIN 2 and CIN 3 were found more often in the IBD cohort (2.2% CIN 2, 2.9% CIN 3) than in the control group (1.4% CIN 2, 2.2% CIN 3, p = 0.002). Two cervical cancers occurred in our IBD cohort (2/2,098) compared with 20 cervical cancers in the control group (20/8,439) (p = 0.20). Possible risk factors associated with CIN, such as disease behaviour, smoking and immunosuppressive drugs are currently investigated in this study population.
Conclusions: Women with IBD are at increased risk for CIN2+ lesions compared with their age-matched controls. These results underline the current ECCO guideline on HPV vaccination in young IBD women, and the importance of adherence to screening guidelines. In addition, the benefits of more intensive cervical cancer screening, potentially starting at younger age, need to be assessed.

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The prevalence of inflammatory bowel disease doubled in the last decade in Israel: an epiIIRN national population-based study

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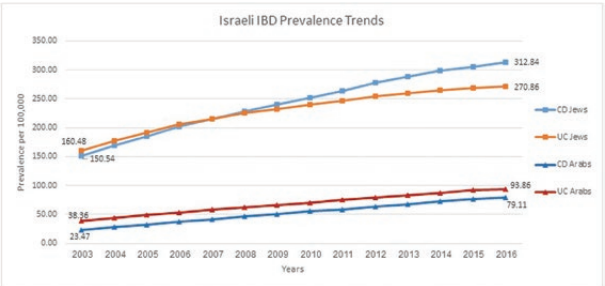
Background: Although inflammatory disease (IBD) prevalence is particularly high in Jews, the epidemiology of the disease in Israel is largely unknown. Following the validation of case-ascertainment algorithms for the epiIIRN registry, we retrieved IBD cases from all four Israeli HMOs' databases to calculate national epidemiology trends of IBD in Israel.
Methods: Basic demographics of IBD cases identified for the time period 1 January 2003–31 January 2017 were retrieved. Date of diagnosis and IBD type (Crohn's disease (CD) vs. ulcerative colitis (UC)) were determined by previously validated algorithms. Age- and sex-standardised rates were derived from the Israeli Central Bureau of Statistics; time trends were calculated by Kendall's Tau-b statistic.
Results: As of January 2017, a total of 42,022 IBD patients were residing in Israel (prevalence 0.5%), of whom, 37 770 (90%) were Jews, 3085 (7%) Arabs, and 1169 (3%) unknown. Of the 42 022 patients, 0.11% were 0–5 years of age, 0.26% were 6–9 years, 2.4% were 10–16 years, 38% were 17–39 years, 55% were 40–79 years and the others were >80 years. Since 2003, the Jewish prevalence doubled (0.31 to 0.59%) and the Arab prevalence increased threefold (0.06% to 0.17%). During 2006–2016, 19 378 patients were newly diagnosed with IBD, of whom 23 (0.11%) were diagnosed at the age of 0–1 years, 122 (0.63%) at 2–5 years, 280 (1.4%) at 6–9 years, 1907 (9.8%) at 10–16 years, 9820 (50.7%) at 17–39 years and 7226 (37.3%) ≥40 years. Adjusted prevalence of CD and UC per 100 000 were 313 and 271 among Jews, and 79 and 94 among Arabs, respectively, indicating that UC predominates only in the Arab population (Graph 1).



Israeli IBD prevalence trends.

While males slightly predominated in the entire cohort (50.4% vs. 49.6%; $p = 0.02$), there were more females in the Jewish UC population (51.5% vs. 48.5%, $p < 0.001$); CD patients were more likely to be males in both Jews and Arabs (51.8% vs. 48.4% in the combined population; $p < 0.001$). IBD incidence was 18.2/100 000 in 2016, and that did not change significantly since 2006. However, UC has decreased from 10.7/100,000 in 2006 to 7.5/100 000 in 2016 ($p = 0.003$). On the other hand, there was a significant increase of incidence in children 10–16 years both in CD (from 12.0/100 000 to 14.2/100 000, $p = 0.028$) and UC (from 3.9/100 000 to 7.2/100 000, $p = 0.001$).
Conclusions: IBD prevalence in Israel continues to increase, as does IBD incidence in children, and now affects 0.5% of the population. This study was supported by a grant from the Leona M. and Harry B. Helmsley Charitable Trust.

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Mode of delivery and risk of inflammatory bowel disease

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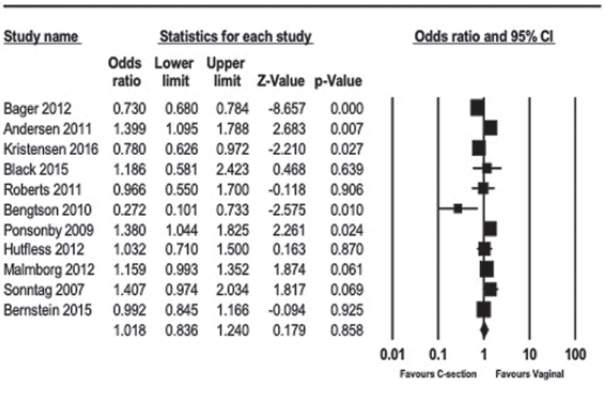
Background: Recent evidence suggests that early life exposures known to influence microbiome development (eg, breastfeeding, exposure to antibiotics, etc.) may also affect the risk of developing IBD. Mode of delivery is one of the major factors impacting the newborn's microbiome development, and specifically, Caesarean-section (C-section), which has been associated with altered colonisation of commensal gut flora, is thought to predispose to immune-mediated diseases later in life. The relation between C-section and IBD is not yet well characterised with different studies showing conflicting results. Therefore, we performed a meta-analysis to evaluate the risk of IBD, Crohn's disease (CD) and ulcerative colitis (UC) according to mode of delivery (C-section vs. vaginal delivery).
Methods: A systematic search was performed in PubMed and Scopus. Case–control and cohort studies were included. The primary outcome was the risk of IBD in individuals delivered vaginally compared with those born by C-section. Secondary outcomes were UC and CD risk according to mode of delivery and IBD risk in individuals born by emergent compared with elective C-section. Heterogeneity between the studies was assessed. Publication bias was evaluated by funnel plots and Egger's test. Study's quality was characterised using the Newcastle Ottawa Scale (NOS). Analysis was conducted using Comprehensive Meta-Analysis v2.
Results: 11 studies fulfilled the inclusion criteria, of which 6 were population-based. All the studies were from developed countries (UK, Denmark, Australia, USA, Germany, Canada, Scotland, Norway, Sweden) and 5 were limited to paediatric age. No publication bias was detected. Overall, the total number of IBD patients was 15,292 that were compared with 6,981,080 controls. When looking at all studies together, C-section was not associated with a higher risk of IBD (OR 1.02 [95% CI 0.84–1.24], $p = 0.86$).



Risk of IBD in individuals born by C-section and vaginal delivery.

We observed a trend towards an increased risk for CD in individuals born by C-section compared with those vaginally delivered, without significant results (OR 1.39 [95% CI 0.99–1.71], $p = 0.06$). No association was found between C-section and UC (OR 0.99 [95% CI 0.76–1.30], $p = 0.94$). No differences were found in IBD risk when comparing elective and emergent C-section (OR 1.05, [95% CI 0.59–1.87], $p = 0.87$).

Conclusions: Overall, the risk of developing IBD was not affected by mode of delivery. Likewise, the setting of C-section (emergent vs. elective) did not affect IBD risk. Individuals born by C-section may have a higher risk for CD.

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Vitamin D status and clinical outcomes in inflammatory bowel disease patients: a systematic review and meta-analysis

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Background: Vitamin D has been implicated to play a role in the pathogenesis of inflammatory bowel disease (IBD). Vitamin D deficiency occurs in up to 30–40% of patients with IBD, yet its association with IBD clinical outcomes is conflicting. We performed a systematic review and meta-analysis examine the impact of low vitamin D status on clinical outcomes in patients with IBD.

Methods: We searched Medline, Embase, Scopus, and Web of Science from inception to February 2018 for observational studies evaluating the impact of low 25(OH)D status on IBD clinical outcomes (disease activity, mucosal inflammation, clinical relapse, and quality of life). Odds ratios (ORs) were pooled and analysed using a random effects model.

Results: Twenty-seven observational studies comprising 8316 IBD patients (3115 ulcerative colitis, 5201 Crohn's disease) were included in our analysis. Quality of included studies per the Newcastle-Ottawa scale was high. Low vitamin D status was associated with increased odds of clinically active disease (pooled OR 1.53, 95% CI 1.32–1.77, $p < 0.00001$, $I^2 = 0\%$), mucosal inflammation (pooled OR 1.25, 95% CI 1.06–1.47, $p = 0.008$, $I^2 = 0\%$), low quality-of-life scores (pooled OR 1.30, 95% CI 1.06–1.60, $p = 0.01$, $I^2 = 0\%$), and clinical relapse (pooled OR 1.31, 95% CI 1.17–1.47, $p < 0.00001$, $I^2 = 0\%$).

Conclusions: Low serum vitamin D status among IBD patients is associated with adverse clinical outcomes. Interventional studies are needed to determine whether aiming for higher 25(OH)D concentrations may decrease the risk of poor outcomes associated with a low vitamin D status.

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Risks and predictors of osteoporosis in inflammatory bowel diseases: a nationwide Korean population-based cohort study

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Background: Risk of osteoporosis and pathologic fracture in patients with inflammatory bowel disease is higher than general population. Guidelines recommend screening for osteoporosis in IBD patient with conventional risk factors. However, little is known about the incidence and predictors of osteoporosis in IBD in Asian population. We estimated the incidence and risk factors of osteoporosis and pathological fracture in patients with inflammatory bowel disease.

Methods: Using the Korean National Health Insurance Research Database, we included 29,978 IBD patients and 185,566 age- and sex-matched controls. Cohort enrolled from January 2012 until December 2013 and followed up until December 2016. We calculated the hazard ratios (HRs) and 95% confidence intervals (CIs) of osteoporosis and pathological fracture in both cohorts by using Cox regression models.

Results: After adjusted with age, sex, comorbidity, the overall osteoporosis is higher in patients with inflammatory bowel disease [adjusted hazard ratio (aHR), 1.42; 95% CI, 1.36–1.49, $p < 0.001$]. Further analysis indicated that male (aHR, 1.92; 95% CI, 1.75–2.11, $p < 0.001$), young-aged patients (aHR, 5.13; 95% CI, 4.39–5.99, $p < 0.001$), patients with Crohn's disease (aHR, 2.01; 95% CI, 1.84–2.21, $p < 0.001$) and patients without comorbidities (aHR, 1.69; 95% CI, 1.57–1.81, $p < 0.001$) exhibited excessive risks of osteoporosis.

Conclusions: The incidence of osteoporosis and related fracture in patients with IBD was higher than that of non-IBD population. Understanding the increased risk of osteoporosis facilitates early diagnosis and may contribute to improvement in the quality of care of patients with IBD.

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Symptom burden and lack of remission among adult patients with ulcerative colitis (UC): retrospective analysis of cross-sectional survey data from the US and Germany

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Background: Patients with UC experience a wide range of debilitating symptoms covering bowel and abdominal manifestations with a significant impact on health-related quality of life. This study used data from the Adelphi Disease-specific Programme (DSP), a large, cross-sectional survey, to describe the burden of UC in a real-world setting in the US and Germany (DE).

Methods: This study is a retrospective, descriptive analysis of data collected from patients consulting for routine care in the US and Germany during Q4 2017. As part of the survey, patients and physicians were asked to report the symptoms currently experienced by the patient. Patient satisfaction with treatment, disease severity, and disease progression were captured along with current and prior treatment use.[1]

Results: Physician-reported symptoms data were collected from 1123 UC patients by 100 physicians across US and Germany. A voluntary subset of the sample provided patient-reported data which included 270 (US)/303 (DE) patients used for this analysis. In the overall sample, patients had a mean age: 42.7 (US)/35.2 (DE) and disease duration since diagnosis of 3.7 (US)/2.9 (DE) years. 30.3% (US)/22.3% (DE)of patients were receiving biologics at the time of the survey. At diagnosis, 88.3% (US)/91.5% (DE) of patients were considered to have moderate to severe disease per physician decreasing to 50.1% (US)/47.9 (DE) at the time of the survey. Patients reported the most common current and most bothersome symptoms to be abdominal cramps and pain, diarrhoea, tiredness/fatigue and rectal bleeding (Table 1).

Selected Symptoms, n (%):	US (n=270)		DE (n=303)	
	Most Common Current Symptoms	Most Bothersome Symptoms	Most Common Current Symptoms	Most Bothersome
n	247	234	299	303
Missing, n	23	36	4	0
Abdominal cramps	125 (50.61)	104 (44.44)	77 (25.75)	107 (36.39)
Rectal bleeding	74 (29.96)	70 (29.91)	28 (9.36)	38 (12.93)
Diarrhoea bloody	73 (29.55)	83 (35.47)	64 (21.40)	172 (58.50)
Diarrhoea non-bloody	66 (26.72)	50 (21.37)	110 (36.79)	88 (29.93)
Tiredness/fatigue	59 (23.89)	44 (18.80)	70 (23.41)	35 (11.90)
Abdominal pain	53 (21.46)	57 (24.36)	79 (26.42)	69 (23.47)

Despite improvements in disease severity, 50.9% (US)/39.6% (DE) of patients were not in remission with only 6.7% (US)/7.1% (DE) achieving clinical remission as reported by the physician. Interestingly, 87.2% (US) / 90.6% (DE) of patients expressed satisfaction at the extent to which their current treatment was able to manage the disease with 58.1% (US)/ 63.6% (DE) believing that this is the best control that can be achieved.

Conclusions: In a real-world setting, patients show a physician assessed improvement in disease severity from the time of diagnosis to present day with a relatively high patient-reported satisfaction rate. However, patients continue to experience numerous symptoms related to UC and have difficulty reaching remission, with only a small proportion of the patients achieving clinical remission as reported by physicians, suggesting that with currently available treatment patients do not expect to have complete resolution of symptoms.

Reference

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Epidemiology, clinical characteristics, evolution and treatments in newly diagnosed inflammatory bowel disease (IBD): results from the nationwide EpidemIBD study of GETECCU

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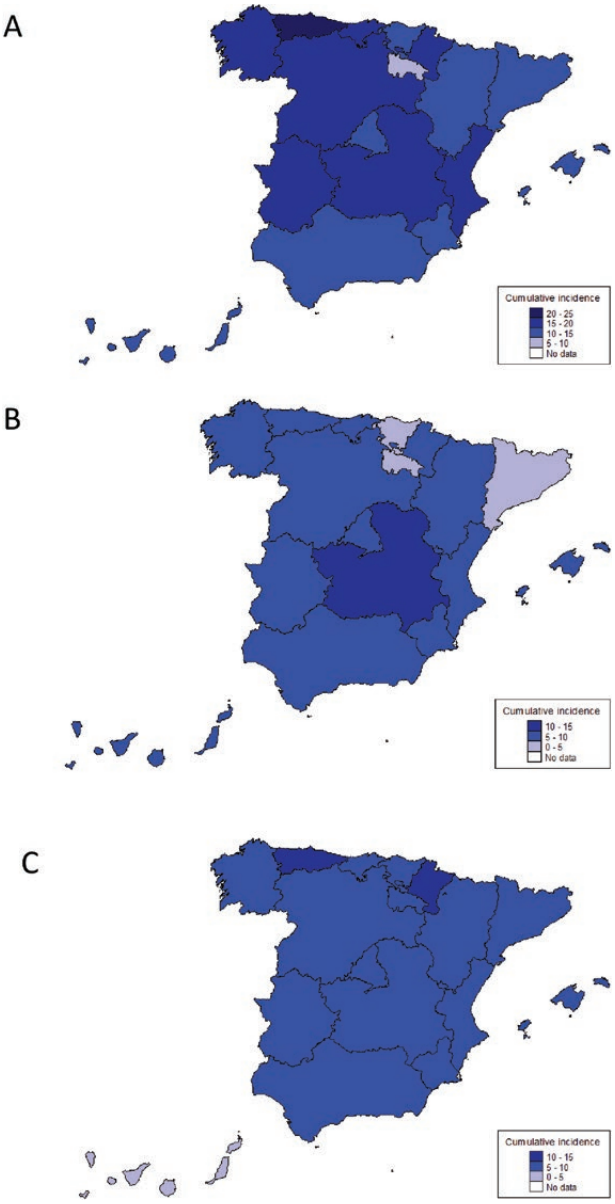

Figure 1. Incidence of inflammatory bowel disease (A), Crohn's disease (B) and ulcerative colitis (C) by Autonomous Communities in Spain in 2017 (cases/100000 person-years). Characteristics of the study cohort and by major categories (CD and UC) are summarised in Table 1.

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	Incident cases	PY	Incidence rate (/1000)	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Non-IBD	9074	542814.04	16.72	1			
IBD	2027	86793.46	23.35	1.40 (1.33–1.47)	< .0001	1.42 (1.36–1.49)	< .0001
UC	1536	59938.25	25.63	1.53 (1.45–1.62)	< .0001	1.30 (1.23–1.37)	< .0001
CD	488	26751.43	18.24	1.09 (0.99-1.20)	0.0604	2.01 (1.84–2.21)	< .0001

Incidence and adjusted hazard ratio of osteoporosis IBD patients with ulcerative colitis and Crohn's disease compared with controls.

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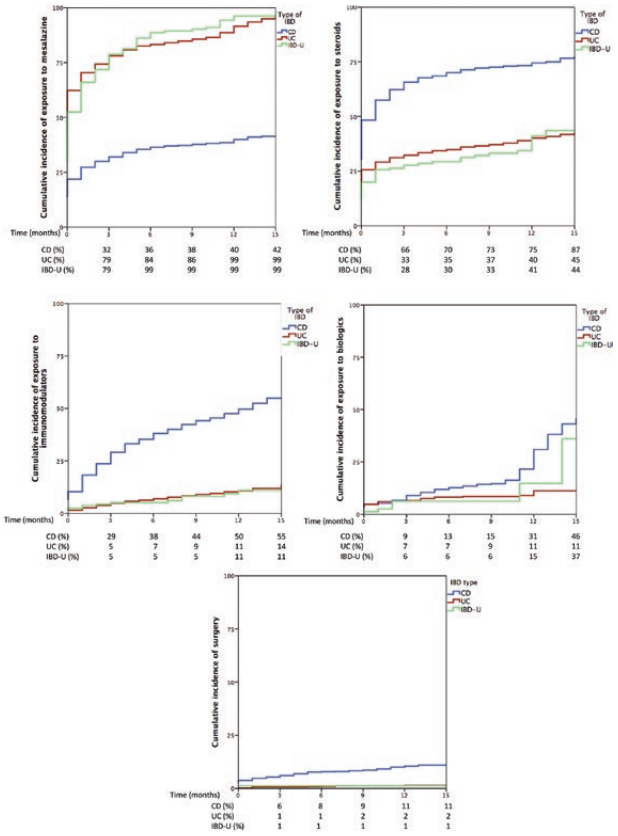

Figure 2. Cumulative incidence of exposure to treatments in Crohn's disease (CD), ulcerative colitis (UC) and inflammatory bowel disease unclassified (IBD-U) during follow-up.

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Background: Updated data on the incidence, evolution and treatment strategies used in IBD management in South Europe is needed. This is the largest study on the recent epidemiology of IBD in Spain. The aims of this study were (i) to assess the incidence of IBD in Spain; (ii) to describe the main epidemiological and clinical characteristics of patients at diagnosis and the evolution of the disease; and (iii) to explore the use of treatments in the biological era.

Methods: Prospective and population-based nationwide registry. Adult patients diagnosed with IBD Crohn's disease (CD), ulcerative colitis (UC) or IBD unclassified (IBD-U)- during 2017 in the 17 Spanish regions were included and will be followed-up for 5 years after diagnosis. Treatment was grouped into 5 categories: mesalazine (oral or topical), steroids (intravenous, oral or topical), immunomodulators (thiopurines, methotrexate or cyclosporine), biologics (anti-TNF, vedolizumab or ustekinumab) and surgery. Cumulative incidence of exposure to each of the studied treatments was estimated by Kaplan–Meier curves.

Results: In total, 3627 incident cases of IBD diagnosed during 2017 from 111 centres covering over 23 millions of adult inhabitants (about 50% of the Spanish population) comprise the study cohort. The overall incidence (per 100 000 person-years) of IBD was 14.3: 6.5 for CD, 7.1 for UC, and 0.7 for IBD-U (Figure 1).

Conclusions: The incidence of IBD in Spain is relatively high and similar to figures reported in Northern Europe. IBD patients require the use of substantial diagnostic and therapeutic resources, which are higher in CD than in CU. One third of patients are hospitalised in the first year after diagnosis and over 5% undergo surgery. Our results highlight the high burden of IBD as well as the important challenges faced by healthcare systems to manage this costly and complex disease.

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A.

Age, yr (IQR)	43 (31-56)
Male sex, n (%)	1,913 (53)
Median time of follow-up, months (IQR)	10 (3-12)
Diagnosis delay, months (IQR)	3 (1-9)
Symptoms at diagnosis, n (%)	3,293 (91.7)
Family history, n (%)	525 (14.5)
Extraintestinal manifestations, n (%)	327 (9)
Former smokers, n (%)	881 (24.4)
Crohn's disease, n (%)	1,656 (45.7)
Ileal, n (%)	908 (55)
Colonic, n (%)	317 (19)
Ileocolonic, n (%)	430 (26)
Upper gastrointestinal tract, n (%)	52 (3)
Inflammatory, n (%)	1,355 (82)
Stricturing, n (%)	183 (11)
Fistulizing, n (%)	118 (7)
Perianal disease, n (%)	186 (11)
Ulcerative colitis, n (%)	1,810 (49.9)
Pancolitis, n (%)	656 (33)
Left-sided colitis, n (%)	611 (31)
Proctitis, n (%)	696 (35)
IBD unclassified, n (%)	161 (4.4)
Mesalamine, n (%)	2,460 (67.8)
Steroids, n (%)	1,893 (52.2)
Immunomodulators, n (%)	862 (23.8)
Biologics, n (%)	488 (13.5)
Anti-TNF, n (%)	467 (13)
Vedolizumab, n (%)	29 (0.8)
Ustekinumab, n (%)	17 (0.5)
Hospitalizations, n (%)	995 (27.4)
IBD onset, n (%)	789 (79.2)
Disease flare up, n (%)	74 (7.4)
Obstruction, n (%)	42 (4.2)
Perianal disease, n (%)	25 (2.5)
Infections, n (%)	5 (0.6)
Adverse events, n (%)	24 (2.4)
Others, n (%)	36 (3)
Surgery, n (%)	195 (5.4)

B.

	Crohn's disease (N=1,656)	Ulcerative colitis (N=1,810)	p
Age, yr (IQR)	39 (25-53)	45 (33-56)	<0.01
Median time of follow-up, months (IQR)	11 (4-12)	10 (3-12)	>0.05
Diagnosis delay, months (IQR)	5 (1-15)	2 (1-5)	<0.01
Male sex, n (%)	827 (50)	1,000 (55)	<0.01
Symptoms at diagnosis, n (%)	1,472 (89.5)	1,677 (94)	<0.01
Family history, n (%)	287 (18)	227 (13)	<0.01
Former smokers, n (%)	630 (38)	218 (12)	<0.01
Extraintestinal manifestations, n (%)	206 (12.5)	112 (6)	<0.01
Mesalazine, n (%)	610 (37)	1,704 (94)	<0.01
Steroids, n (%)	1,168 (70.5)	668 (37)	<0.01
Immunomodulators, n (%)	698 (42)	151 (8)	<0.01
Biologics, n (%)	368 (22)	113 (6)	<0.01
Hospitalizations, n (%)	574 (35)	388 (22)	<0.01
Surgery, n (%)	171 (10)	21 (1.2)	<0.01

During a median follow-up of 10 months, 33 (2.4%) CD patients progressed to a more severe phenotype, and 2 (0.01%) UC patients to more extensive involvement. The cumulative incidences of the different treatments are shown in Figure 2.

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Influence of patients' preference in randomised controlled trials

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Background: Randomised controlled trials (RCT) are the gold standard to provide unbiased data. However, randomly allocating patients to treatments that do not accord with their preferences may influence participation and outcomes. As, in trials comparing treatments of significant different nature (e.g. surgery vs. medication), eligible patients could decline participation due to preference. This could limit the generalizability of results (reduced external validity). Furthermore, trials comparing experimental vs. standard treatment, are likely to include patients preferring experimental treatment, as trial participation is not needed for patients preferring standard treatment. Randomisation to the (non)-preferred strategy could influence adherence to treatment protocol or influence subjective outcomes (reduce internal validity). To preclude the influence of patients' preference on validity, a patient preference trial (PPT) has been designed. Patients with a preference for a treatment strategies will be treated accordingly, whereas only those patients without a distinct preference will be randomised in the usual way. The aim of this study was to assess the influence of patients' preference in RCTs.
Methods: In this systematic review and meta-analyses, we searched for PPTs published between January 1, 2005 and October 5, 2018. PPTs reporting on allocation of patients to random- and preference cohorts, while using the same study protocol for both cohorts were included. The main outcomes were external validity (participation and baseline characteristics) and internal validity (lost to follow-up, cross-over and the primary outcome), assessed by comparing standardised effect sizes of the random- and preference cohorts.
Results: In total 117 of 3734 identified articles met screening criteria and 44 were eligible (24873 patients). The participation rate in PPTs was >95% in 14 trials (range 48–100%) and acceptance of randomisation was < 50% in 26 trials (range's–81%). Higher education, female, older age, race and prior experience with one treatment-arm were characteristics of patients declining randomisation. Lost to follow-up and cross-over rate were significantly higher in the randomised cohort in comparison with the preference cohort. Following a meta-analysis the primary outcomes were comparable, mean difference 0·093(95% CI –0·178;0·364, p = 0·502).
Conclusions: Patients' preference led to a substantial proportion of a specific patient group refusing randomisation, while it did not influence the primary outcome within a PPT. Therefore, in the era of patients becoming more active participants in research, PPTs could increase participation without compromising the validity of the outcomes compared with RCTs.

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Phenotype and natural history of inflammatory bowel disease: results from the largest centre in Singapore

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Background: Data on the natural history of inflammatory bowel disease(IBD) in Asia are limited. We aimed to determine the clinical features and outcomes of IBD patients from the largest centre in Singapore.
Methods: We collected data on 581 patients with IBD (334 ulcerative colitis [UC], 245 Crohn's disease [CD], 2 IBD unclassified) from 1970 to 2017 using hospital administrative records. Disease phenotype, complications, use of medications, and surgery were analysed.
Results: The median age in 2017 of patients with CD and UC was 45 (interquartile range (IQR), 30–59) years and 56 (IQR, 45 -65) years, respectively. Median age at diagnosis was 30 (IQR, 20–46) years for CD and 40 (IQR, 30–50) years for UC. Median follow-up was 9 years (4–17) for CD and 12 years (6–20) for UC. At diagnosis, in CD, ileocolonic disease (58.7%) and inflammatory behaviour (62.3%) were the most frequent phenotype. Perianal disease developed in 17% of patients. At maximal follow-up disease location extension occurred in 3.8% and stricturing and penetrating (B2+B3) complications increased from 37.7% to 55.5% of patients. In UC, 21.5% of patients had proctitis, 44.8% left-sided and 33.6% extensive colitis. Proximal disease extension during follow-up occurred in 16.5%. A family history of IBD was reported in 5.5% of patients. Colorectal cancer developed in 0.5% of the cohort. In CD the cumulative probabilities of receiving corticosteroids (CS), immunosuppressive therapies (IS) and anti-tumour necrosis factor (anti-TNF) therapy were 78.7%, 73.7% and 35.5%, respectively, at maximal follow-up. In UC cumulative probabilities of receiving CS, IS and anti-TNF were 65.5%, 34.1%, and 9.3%, respectively, at maximal follow-up. Cumulative probabilities of surgery at 1 year and 10 years were 11.4% and 22.9%,, respectively, in CD and 1.8% and 4.5%, respectively, in UC (Figure 1 and Table 1).

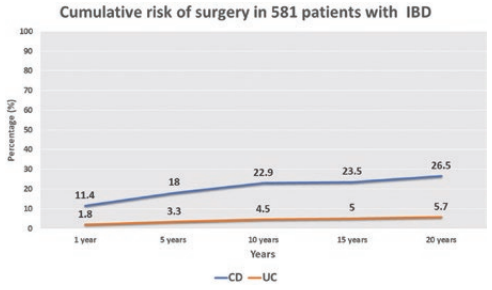

Figure 1.

	CD	UC	P value
Gender			
- Male	155 (63.3%)	205 (61.4%)	0.24
- Female	90 (36.7%)	129 (38.6%)	
Current Age (years old)	45(IQR 30-59)	56(IQR 45-65)	<0.01
Smoking			
- Current	18 (7.3%)	21 (6.3%)	0.26
- Ex-smoker	25 (10.2)	53(15.9%)	
- Non-smoker	191(78%)	236 (70.9%)	
Type of IBD			
UC			
- E1 (Proctitis)		71 (21.5%)	
- E2 (Left-side colitis)		148 (44.8%)	
- E3 (Extensive colitis)		111 (33.6%)	
Montreal location at CD diagnosis			
- L1 (ileal)	37 (15%)		
- L2 (colonic)	49 (19.8%)		
- L3 (ileocolonic)	145 (58.7%)		
- L4 (upper gastrointestinal tract)	0		
- L1+L4	1 (0.4%)		
- L2+L4	2 (0.8%)		
- L3+L4	13 (5.3%)		
Montreal behavior at CD diagnosis			
- B1 (inflammatory)	154 (62.3%)		
- B2 (stricturing)	53 (21.4%)		
- B3 (penetrating)	40 (16.2%)		
- B1+p	24 (9.7%)		
- B2+p	5 (2%)		
- B3+p	13 (5.3%)		
Age at diagnosis of IBD (years old)	30 (IQR 20-46)	40(IQR 30-50)	<0.01
Duration of IBD (years)	9(IQR 4-17)	12(IQR 6-20)	0.05
Current user of IM	127 (51.8%)	67 (20.1%)	<0.01
Current user of Anti-TNF	73 (29.8%)	15 (4.5%)	<0.01
Current user of vedolizumab	13 (5.3%)	12 (3.6%)	<0.01
Current user of Ustekinumab	13 (5.3%)	0	-
Prior surgery related to IBD	94 (38.5%)	23 (6.9%)	<0.01

CD, Crohn's disease; IBD, inflammatory bowel disease; IM, immunomodulators; UC, ulcerative colitis.

Table 1.

Conclusions: The disease phenotype and natural history of IBD in our cohort follow that of the western countries. CD is a disabling disease with higher surgical rates and requires more immunosuppressive therapies and biological therapies compared with UC.

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The cost burden of Crohn's disease and ulcerative colitis dependent on biologic treatment status – a register-based Danish population study from 2003 to 2015

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Background: Patients diagnosed with inflammatory bowel disease (IBD) may be put on biological treatment after diagnosis, depending on several medical and non-medical factors. This study investigated the average annual healthcare costs and production values of patients 10 years before and 8 years after diagnosis, and after initiating biologic treatment.

Methods: Incident CD and UC patients, aged 18 or more at diagnosis, in the period 2003–2015, were identified using the Danish National Patient Register. Average annual costs and production values of patients receiving biologic treatment after diagnosis were compared with patients who did not receive biologic treatment after diagnosis. Comparisons were also made between patients that initiated biologic treatment within the first year after diagnosis with those initiating treatment more than a year after diagnosis. Individual production values were estimated by multiplying the yearly employment rate with gender-specific gross average yearly wages, adjusted for the number of weekly working hours. Production values were estimated using 2016 wage indices. Linear regression models, adjusted for age and gender, accounted for differences in average annual costs and production value, per individual, between patients receiving or not receiving biologic treatment.

Results: A total of 9019 CD and 20 913 UC patients were included. Of these, 2351 (26.1%) CD and 2248 (10.7%) UC patients received biologic treatment at some point in the study period. The first year after diagnosis, 1091 CD patients initiated biologic treatment whereas 1260 initiated treatment more than a year after diagnosis. A total of 1022 UC patients started treatment within the first year after diagnosis and 1226 initiated treatment more than a year after diagnosis. Average annual production values of CD patients receiving biologic treatment the first year after diagnosis were lower before and after treatment initiation, compared with patients receiving treatment more than a year after diagnosis. UC patients receiving biologic treatment the first year after diagnosis had lower average annual production values the first year after treatment initiation compared with UC patients receiving treatment more than a year after diagnosis.

Conclusions: This study is not free from bias. It showed that patients receiving biologic treatment had higher average annual healthcare costs and lower average annual production values, compared with patients not receiving biologic treatment. This implies that patients treated with biologics are more severely affected compared with those not treated. Stratifying patients based on disease severity is warranted, however it was not undertaken in this analysis.

P794

Fatigue in inflammatory bowel disease

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Background: Fatigue is a common symptom of patients with chronic inflammatory diseases in general - and specifically in inflammatory bowel disease (IBD) - which results in huge impairment on quality of life of individuals. In spite of its frequency only few studies systematically investigated symptom burden and risk factors for fatigue in IBD. We aim to identify the prevalence of fatigue in a large IBD cohort and address physical risk factors, as well as psychological markers associated with fatigue.

Methods: We evaluated 1208 IBD patients from the Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS). Significant fatigue was defined as a visual analogue scale (VAS-F, range 0–10) ≥4 and severe fatigue as a VAS ≥8. Impact of fatigue on daily activities was assessed by the Fatigue Severity Scale with a score > 3 defining relevant impairment. IBD-related factors were assessed through patient and physician questionnaires.

Results: Overall, 672 IBD patients (55.6%) reported fatigue (VAS-F ≥4), whereas only 133 (11%) reported severe fatigue. Fatigue was associated with female gender (women 65.8% vs. men 43.9%, $p < 0.001$) and initial IBD diagnosis (Crohn's disease 59.1% vs. ulcerative colitis 51.5%, p = 0.008). Furthermore, patients with fatigue were of younger age (47.7 years vs. 51.4 years, $p < 0.001$), had a younger age at diagnosis (26.9 vs. 30.4 years, p = 0.001), lower educational level, higher disease activity indices and higher rates of complications, extraintestinal manifestation and intestinal surgery. Furthermore, patients suffering from fatigue had significantly higher indices for anxiety and depression in the Hospital Anxiety and Depression Scale and lower values in quality of life (IBD questionnaire). An impact of fatigue on daily activities was found in 49.5% of patients.

Conclusions: Fatigue is highly frequent in this large IBD cohort and impacts on daily activities. Patients at risk should be asked during outpatient visits about symptoms of fatigue and therapeutic strategies will need to be developed in the future.

P795

Increasing trends in prevalence and treatment patterns of paediatric ulcerative colitis patients in the USA

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Background: There has been much variation between epidemiological studies that report the prevalence of ulcerative colitis (UC) among children. This study aimed to analyse the annual diagnostic prevalence rates and treatment patterns of paediatric UC patients in the USA insured population from 2007 to 2017.
Methods: Trends in UC prevalence were calculated for the 11-year period covering January 1, 2007 to December 31, 2017. Paediatric (0–17 years old) UC patients were included in this retrospective analysis of medical and pharmacy claims data from the Truven Marketscan Commercial, Medicaid and Medicare-Supplemental Claims database. Prevalence was determined as having ≥1 UC diagnostic codes (ICD-9: 556.x; ICD-10:K51.x) within the calendar year. Patients with a Crohn's disease diagnosis (ICD9: 555.x; ICD-10: K50.x) were excluded. Prevalence rates in the database were determined and age- and gender-adjusted rates were projected to the U.S. Trends in treatment patterns were also analysed.
Results: The paediatric UC prevalence increased from 0.02% to 0.04% from 2007 to 2017. The mean age between 2007 and 2017 ranged from 12.29-13.86 years. Consistently throughout the years, approximately half of the paediatric UC patients were male. Rates of use of biologics and corticosteroids increased, while rates of immunomodulators, and opioids decreased. Rates of immunomodulators remained stable (Figure 1).

Variable	N=1,495
Gender	
Male	759 (50.8%)
Female	736 (49.2%)
Mean Age (SD)	13.18 (3.97)
0-7 years old	153 (10.2%)
8-11 years old	224 (15.0%)
12-17 years old	1,118 (74.8%)
Insurance	
Commercial	1,495 (100.0%)
Geographic Region	
Northeast	338 (22.6%)
North Central	305 (20.4%)
South	645 (43.1%)
West	197 (13.2%)
Unknown	10 (0.7%)
Comorbid Conditions	
Type 1 Diabetes	11 (0.7%)
Type 2 Diabetes	13 (0.9%)
Psoriasis	15 (1.0%)
Ankylosing Spondylitis	0 (0.0%)
Psoriatic Arthritis	2 (0.1%)
Uveitis	5 (0.3%)
Anthropathy	2 (0.1%)
Medications	
Biologics	335 (22.4%)
Immunomodulators	233 (15.6%)
5-ASA	897 (60.0%)
Corticosteroids	521 (34.8%)
Opioids	336 (22.5%)

Table 1. Characteristics of paediatric patients with ulcerative colitis (2017)

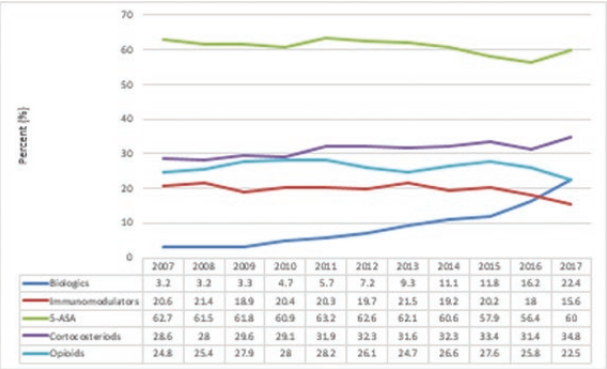

Figure 1. Trends in treatment patterns among paediatric UC patients, 2007–2017.

Conclusions: The prevalence of UC diagnosis codes among paediatric patients increased between 2007 and 2017, and is projected to affect nearly 29,500 U.S. children in 2017.

P796

Cardiovascular risk profile in Greek patients with inflammatory bowel disease

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Background: Inflammatory bowel diseases (IBD) are linked with a higher risk for cardiovascular diseases (CVD) due to the contribution of chronic systemic inflammation in the pathogenesis of atherosclerosis. However, the separate role of the traditional and non-traditional cardiovascular risk factors in this setting remains unclear. We aimed to investigate the prevalence of risk factors for cardiovascular diseases in Greek IBD patients in comparison to healthy controls.
Methods: Eligible were consecutive IBD patients aged 30–80 years without a prior CVD history followed in two tertiary referral centres. The cardiovascular risk profile was assessed by traditional risk factors [body composition measures (BMI), blood pressure, smoking status, plasma lipids and glucose] and non-traditional risk factors (inflammatory biomarkers) at a random point of time and compared with age-sex matched healthy controls from the ATTICA study. For the comparisons of proportions chi-square tests were used. Student's t-test and Mann–Whitney tests were used for the comparison of continuous variables between IBD patients and controls.
Results: Overall, 375 IBD patients [213 male, (199 CD, 176 UC), mean age 50.2 ± 12.8 years, mean age at IBD diagnosis 37.3 ± 13.6 years, 18.9% with a prior IBD-related surgery] were included and matched for age and sex with 750 healthy subjects from the ATTICA study. The proportion of obese subjects (BMI>30) was significantly higher in patients with IBD (19.6% vs. 1.9%, $p < 0.001$), whereas lower rates of hypertension were found in IBD patients (19.2% vs. 30.2%, $p < 0.001$) compared with healthy controls. Ever smokers were more in the IBD group (67.1% vs. 56.7%, $p = 0.001$), while the current smoker status was less common in the IBD group (31.9% vs. 41.5%, $p = 0.002$). Additionally, the rates of hypercholesterolemia were lower in those with IBD (12.5% vs. 43.7%, $p < 0.001$) whereas there was no statistical difference regarding the presence of diabetes ($p = 0.187$). Measurements at a random point of time showed significantly lower values of mean systolic and diastolic blood pressure, along with total cholesterol, low-density lipoprotein cholesterol and haemoglobin in IBD patients compared with healthy controls (all $p < 0.05$). Additionally, IBD patients had higher levels of high-density lipoprotein cholesterol, white blood cells, fibrinogen, platelets and C-reactive protein compared with controls (all $p < 0.05$).
Conclusions: Greek IBD patients have lower prevalence of traditional risk factors for CVD, except from obesity compared with healthy controls. Based on these results it could be suggested that systemic inflammation plays the most important role in the pathogenesis of CVD in IBD.

P797

Crohn's disease and ulcerative colitis was associated with different lipid profile disorders: a nationwide population-based study

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Background: The relationships between lipid profiles and the risk for developing inflammatory bowel disease (IBD) including Crohn's disease (CD) and ulcerative colitis (UC) still remains elusive. We conducted a nationwide population-based cohort study to investigate the relationship between lipid profiles and the risk for developing IBD.
Methods: We conducted a retrospective study using claims data from the National Healthcare Insurance (NHI) service in Korea. A total of 9,706,026 subjects who received medical check-ups arranged by NHI in 2009 were included and followed up until 2016. Serum lipid profiles, including total cholesterol, triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were collected. Individuals who developed CD and UC were identified during the follow-up.
Results: After a mean follow-up of 7.3 years, IBD was detected in 7,058 (0.073%) individuals. IBD group showed a significantly lower prevalence of hypertension, diabetes and dyslipidaemia, compared with non-IBD controls (p-value < 0.001 for each variable). IBD group was inversely associated with serum fasting glucose, serum total cholesterol, LDL-C, HDL-C and TG levels (p-value < 0.001 for each variable). Compared with the highest quartile (Q4) of serum total cholesterol, low serum total cholesterol was associated with higher risk of CD (adjusted hazard ratio [HR]: Q1, 2.52; Q2, 1.52; Q3, 1.27; p-value: Q1, < 0.001; Q2, < 0.001; Q3, 0.042), but not UC. Compared with the highest quartile (Q4) of LDL-C, low serum LDL-C was associated with higher risk of CD (adjusted HR: Q1, 1.92; Q2, 1.47; Q3, 1.22; p-value: Q1, < 0.001; Q2, < 0.001; Q3, 0.078), but not UC. Moreover, compared with the highest quartile (Q4) of HDL-C, low serum HDL-C was associated with higher rates of CD (adjusted HR: Q1, 2.49; Q2, 1.90; Q3 1.43; p-value: Q1, < 0.001; Q2, < 0.001; Q3, 0.002), but not UC. In contrast, low serum TG was associated with higher risk of UC (adjusted HR: Q1, 1.22; Q2, 1.19; Q3, 1.19; p-value < 0.001 for each quartile), but not CD.
Conclusions: Low serum total cholesterol, LDL-C and HDL-C were associated with the risk for developing CD, but low serum TG was related to the risk for developing UC.

P798

Quality of sexual life in patients with ulcerative colitis: a monocentric observational study. On behalf of IG-IBD

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Background: Inflammatory bowel diseases (IBD) are expected to have an adverse impact on sexual health. Depression and anxiety, common disorders in IBD, are known to be a risk factor for sexual dysfunction. Few data are available on the impact of IBD on relationships, body image and sexual function (SF). The aim of this study was to evaluate how ulcerative colitis (UC) may affected SF.
Methods: We enrolled 51 consecutive UC patients and 32 controls in current partnership referred to our centre. They were asked to fill in 6 validated questionnaires on quality of life (IBDQ), SF (FSFI or IIEF, ISS), psychological well-being (PGWBI), anxiety/depression (HADS) and couple functioning (DAS). Disease activity was assessed using Partial Mayo Score (PMS) and faecal calprotectin levels. Statistical analysis was performed by Pearson test, Shapiro test, Bartlett test, the Paired Sample T-Test. Partial Component Analysis and the analysis of variance (ANOVA)were evaluated to compare behaviours of patients and controls groups.
Results: Many SF indexes were significantly higher for controls than for patients (ISS $p = 0.018$, for women FSFI $p = 0.049$, for men IIEF-C $p = 0.0007$, IIEF-D $p = 0.001$, IIEF-E $p = 0.05$; Figure 1). Among patients, no significant correlation was found between disease severity and relationship quality (DAS). For those treated with topical therapy, an inverse correlation was found between sexual discomfort and relationship quality (ISS-DAS, $r = -0.68$,$p = 0.000006$); for patients treated with oral/parenteral therapy, the main factor influencing the relationship quality was depression (ISS-HADS Depression, $r = -0.5$, $p = 0.026$). In women, SF (FSFI) did not correlate with any of the analysed variables.
Conclusions: Our results confirm that UC patients have lower levels of sex life than controls. Well-being and couple cohesion was unaffected by the disease, even in case of topical therapy. Conversely, depression resulted to adversely impact the relationship quality In women, SF appears to be less affected by IBD-related factors

P799

Perinatal factors and development of IBD: a national case–control study with nearly 50 years of follow-up: report from the epiIIRN database

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Background: The changing epidemiology of IBD suggests that environmental factors have a major role in inducing or modifying disease expression. Nevertheless, identifying modifiable environmental factors is challenging. We aimed to determine the association of very early-life exposure with the subsequent development of IBD in a unique cohort with a follow-up of nearly 50 years, by merging data from the Jerusalem Perinatal Study (JPS) and the epidemiology Israeli IBD Research Network (epiIIRN).

Methods: We linked two relevant Israeli datasets: the epiIIRN and the JPS. The former is a validated registry of all IBD patients in the 4 national health maintenance organisations (HMOs), covering 98% of the population, and 1:3 age- and gender-matched non-IBD controls. The epiIIRN is updated to 01/2017. The JPS database recorded peri-natal information on a population-based cohort of 92,408 births in 1964–76 and their parents. The linkage of these two datasets allowed us to identify IBD and non-IBD subjects from the JPS cohort and to analyse very early-life events potentially associated with the development of IBD. Assessment of demographic features was performed, with multi-variate analysis of caesarean section delivery, mother's age and birth weight.

Results: A total of 465 individuals of the JPS cohort, born during 1964–1976, subsequently developed IBD (50.3% females, mean current age 47.9 ± 3.7 years, 53.5% with Crohn's disease (CD) and 46.5% with ulcerative colitis (UC). This translates into a prevalence rate of 5/1000 (or 0.5% of the population). The 1,279 subjects without IBD identified within the JPS cohort were broadly similar to the cases (42.7% females, mean current age 47.8 ± 3.7 years). Mother's age at the time of delivery (17–34 years vs. ≥35 years) was not associated with a higher risk of developing IBD (95% confidence interval [CI] 0.80–1.57; $p = 0.519$; Fisher exact test). Delivery through caesarean section did not prove to be a statistically significant predictor of IBD diagnosis (95% confidence interval; $p = 0.845$; Fisher exact test) and birth weight, whether low (< 1499 g) or high (≥4500 g) was not associated with the development of IBD later in life (95% confidence interval; $p = 0.779$, Pearson's χ^2 test).

Conclusions: The prevalence of IBD among the JPS cohort is comparable to the calculated national rate (0.5% of the population) which provides internal validity to this case–control study. We found that in this population very-early life factors such as mode of delivery (caesarean section), mother's age at birth and birth weight were not associated with a higher risk of developing IBD later in life, but further analysis using IBD subtype stratification (CD vs. UC) is warranted.

P800

Factors related to non-adherence behaviours of patients with inflammatory bowel disease

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Background: Non-adherence to medication leads to poorer outcomes and must be prevented. We describe the frequency of non-adherence behaviours in patients with inflammatory bowel disease (IBD) and its relationship to potentially modifiable variables.

Methods: Data were obtained through an anonymous survey. Five different non-adherence behaviours were defined, and co-variables analysed were patients' demographics, experience with healthcare (assessed with IEXPAC 'Instrument to Evaluate the EXperience of PAtients with Chronic diseases' scoring 0 [worst] to 10 [best experience]), beliefs in medicines (Beliefs About Medicines Questionnaire [BMQ], composed of a necessity and a concerns scale and scoring –20 [weaker] to +20 [stronger beliefs]) and medication characteristics. Variables associated to nonadherence were studied with a multivariate logistic regression model.

Results: Overall, 332 of 575 IBD patients (58%) returned the survey with the necessary data completed (mean age 47 [13] years, 48% women), of which 179 (56%) had at least one non-adherence behaviour. The frequency of the specific non-adherence behaviours was: (1) Forgiveness in taking medication: 36%; (2) Taking medication at unscheduled hours: 6%; (3) Leaving medication when feeling well: 10%; Leaving medication when feeling sick: 28% and 5) Stopping medication after reading the patients' information leaflet: 8%. The frequency of at least one non-adherence behaviour was similar by age, gender, educational level, working status, number of medicines taken or doses per day needed. Non-adherence behaviours were more frequent in patients with lower (worse experience) IEXPAC scores (Quartile [Q] 1: 64%, Q2: 62%, Q3: 44%, Q4: 47%, p-trend: 0.005) or lower (low-necessity / high concerns) BMQ score (Q1: 65%, Q2: 61%, Q3: 52%, Q4: 39%, *p*-trend < 0.001). The multivariate model (table) confirmed the relationship of non-adherence behaviours with worse experience and lower BMQ beliefs scores.

	OR (95% CI)	p-value
Age (1-year increment)	0.98 (0.96 – 1.01)	0.163
Gender (female versus male)	0.65 (0.37 – 1.16)	0.558
Need of taking medication 3-4 times per day (versus 1-2 times per day)	1.75 (0.90 – 3.43)	0.101
Number of different medicines (1-unit increment)	0.94 (0.81 – 1.01)	0.390
IEXPAC overall score (1-unit increment)	0.84 (0.72 – 0.98)	0.025
BMQ overall score (1-unit increment)	0.93 (0.88 – 0.98)	0.004

Multi-variate analysis. Factors associated to non-adherence behaviours of IBD patients

Conclusions: Non-adherence behaviours are frequent in IBD patients and are mainly associated to two aspects with potential to be addressed in daily clinical practice to prevent non-adherence: their experience with healthcare (measured with IEXPAC) and their beliefs in medications (assessed with BMQ). The study was funded by Merck Sharp & Dohme of Spain and endorsed by 4 patients associations (ACCU: patients with Crohn's disease and ulcerative colitis; CONARTRITIS: patients with arthritis; SEISIDA: AIDS multi-discipline group, FEDE: patients with diabetes mellitus).

P801

Physicians' knowledge and application of immunisation strategies in patients with inflammatory bowel disease: a survey by the Italian Group for the study of inflammatory bowel disease (IG-IBD)

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Background: No data on European countries about knowledge and application of immunisation strategies in patients with inflammatory bowel disease (IBD) are available. We designed a questionnaire aimed at exploring these issues among Italian gastroenterologists dealing with adult and paediatric IBD.

Methods: An anonymous, 24-item, questionnaire was sent via e-mail to all members of the Italian Group for the study of inflammatory bowel disease (IG-IBD). Three sets of questions were formulated: 1. Characteristics of respondents; 2: General opinions on the role of vaccines in IBD patients; 3: Immunisations of IBD patients in clinical practice.
Results: Of the 455 total surveys sent, there were 198 respondents (response rate: 43.5%). The great majority of respondents (82.9%) reputed as 'very important' to perform the vaccinations recommended by the guidelines in patients with IBD. Data on vaccines status of IBD patients are 'always' collected by 23.3% of the respondents and 'most of the times' by 63.9% of them, while the indication to perform the vaccinations recommended by the guidelines is 'always' given by 55.9% of the surveyed IG-IBD members. The indication to immunisation is given at the diagnosis of the disease by 55.6% of the respondents. The most frequently recommended vaccine in IBD patients is the annual flu vaccine, while the recommendation rates for the other vaccines is variable depending on the different pathogens.
Conclusions: Efforts carried out by the scientific societies are required to increase the awareness of this relevant topic among physicians.

P802

Perforating Crohn's Disease and pancolitis as risk factors for incident cancer: a prospective multi-centre nested case–control IG-IBD study at 6 years

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Background: In a prospective, multi-centre, nested case–control study at 6 years (years), we aimed to characterise incident cases of cancer in inflammatory bowel disease (IBD). Secondary end point was to evaluate risk factors for cancerc in IBD.
Methods: From 31 December 2011 to 31 December 2017, all incident cases of cancer in IBD patients referring to 16 IG-IBD Units (≥2 visits/year) were recorded. Each IBD patient with incident cancer was matched with 2 IBD patients with no cancer for: IBD type (Crohn's disease, CD; ulcerative colitis, UC), gender, age (±5 years). Data expressed as median (range). Wilcoxon, χ^2, Fisher exact test, multi-variate logistic regression analysis (OR [95% CI]).
Results: Incident cancer occurred in 403 IBD patients: 204 CD (CD-K),199 UC (UC-K). Overall, 1209 IBD patients were considered (403 IBD-K; 806 IBD-C). In IBD, cancer (n = 403) involved (n = [%]): digestive system (129 [32%]), skin (60 [14.9%]: 27 NMSC, 31 melanoma, 2 others),urinary tract (39 [9.7%]), lung (28 [6.9%]), breast (22 [5.5%]), genital tract (26 [6.5%]), thyroid (8 [1.98%]), lymphoma (11 [2.72%] all in CD), small bowel cancers (16 [3.9%];15 CD [7.3%], 1 UC ileal pouch [0.5%]), others (64[15.9%]). Cancer frequency was comparable between CD and UC considering (n = [%]):digestive system (61[30%] vs. 6 [34%]);skin (33[16%] vs. 27[13.5%]);lung (14[6.8%] vs. 14 [7.0%]);breast (22[10.7%] vs. 24[12.1%]);genital tract (15[7.3%] vs. 11 [5.5%];p>0.05). Colorectal and urinary tract cancers were more frequent in UC vs. CD (58[29%] vs. 35[17%],p < 0.005;26[13%] vs. 13[6.3%], p = 0.039). Extracolonic cancers were more frequent in CD vs. UC (35/204 [17%] vs. 58/199 [29%]; p < 0.005). Risk factors considered: age (<40 vs. ≥40 years), IBD duration (< 10 vs. ≥10 years), smoking (Yes/No), ISS and/or anti-TNFα (Y/N),IBD-related surgery, UC extent, CD pattern, perianal CD risk factors for any cancer identified in UC: UC-related surgery (4.63 [2.62–8.42]), extensive vs. distal UC (1.73 [1.10–2.75]). The other risk factors were not significant (OR 1.30 [0.74–2.39]; 0.92 [0.63–1.35]; 0.92 [0.55–1.52]; 0.84 [0.51–1.38]; 1.54 [0.95–2.51], respectively). In CD, perforating pattern was the only significant risk factor (OR 2.33 [1.33–4.11]) (other risk factors: OR 0.93 [0.59–1.48]; 0.98 [0.67–1.43]; 0.74 [0.51–1.07]; 1.31 [0.90–1.92]; 0.97 [0.62–1.51]; 1.25 [0.79–2.01]; 1.02 [0.65–1.60]).In CD, the frequency of B3 pattern was higher in CD-K vs. CD-C (26% [54/204] vs. 15% [63/408]; p = 0.0033).The frequency of extensive UC was higher in UC-K vs. UC-C (51% [101/199] vs. 38% [152/398]; p = 0.0045).
Conclusions: In a prospective, multi-centre, nested-case–control study at 6 years, penetrating CD, extensive UC and UC-related surgery were significant risk factors for any incident cancer. Clinical characteristics of severity of IBD may increase the overall cancer risk. Lymphoma and SBC were associated with CD.

P803

A single-centre study on the uptake of cervical cancer screening in patients with inflammatory bowel disease

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Background: Researchers have found a higher risk of cervical neoplasia in patients with inflammatory bowel disease, especially those

treated with azathioprine. In Ireland, cervical cancer is the second most common cancer in women aged 25–39 years. Screening in Ireland is co-ordinated by CervicalCheck, the national cervical screening programme. ECCO guidelines and several others strongly recommend regular cervical screening for women with IBD, especially if treated with immunomodualtors. Several studies across different populations looking into the IBD population have showed a low-adherence to the recommendation regarding cervical cancer screening. The uptake rates of this screening programme in Irish IBD patients is largely unknown. The aim of this study was to assess the uptake and adherence of IBD patients to the national cervical screening programme(CSP).

Methods: This cross-sectional study was conducted from August to November 2018 in the outpatient department at University Hospital Galway. Female patients of cervical screening age (25–60 years) with a known diagnosis of inflammatory bowel disease attending the IBD clinics were recruited. Patients who agreed to participate and gave written consent were given a questionnaire to complete. The questionnaire included demographic data, name of drug therapy, questions regarding cervical smear test uptake, compliance to follow-up, and smear results if known. Ethical approval was granted for this study. Data were analysed using SPSS.

Results: 64 patients provided complete information regarding their cervical screening history. These women were relatively young (Mean =41 years, SD= 9.7) 58 (91%) reported enrolment in the CSP. Twenty-one (33%) of these patients had at one time had an irregular smear. Four(6.4%) women had high grade smear changes requiring LETZ procedure. All the women with high-grade changes were in receipt of immunomodulator therapy. The survey identified 48 (75%) women who reported regular follow-up with the CSP.

Conclusions: This cross-sectional study showed that our cohort of women participated in the screening programme at satisfactory levels. However, this number drops in terms of follow-up with the CSP. Patients need ongoing education and encouragement to maintain participation in the CSP. Although this is a single-centre study, and the numbers studied are smaller than that reported in other similar studies, the results provide a glimpse into the prevalence of the uptake of cervical screening among Irish women with IBD.

P804
Prevalence of fybromialgia in IBD patients: a single-centre observational prospective study

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Background: Joint pain is frequently reported by IBD patients and can be associated to extraintestinal manifestations of diseases, comorbidity or adverse events associated to anti-TNF or vedolizumab therapy. An appropriate rheumatological referral is crucial to drive an appropriate therapeutic strategy in case of concomitant spondyloarthritis. Fybromyalgia (FM) is a frequent cause of chronic pain that need to be identify in order to not overestimate the prevalence of SpA in IBD patients. Aim of the study was to assess the prevalence of FM in a cohort of IBD outpatients.

Methods: Consecutive patients of the IBD Unit coming for a routine visit were screened by a rheumatologist in order to identify cases presenting the 2010 ACR criteria for FM or ASAS criteria for SpA. Patients affected by other rheumatic conditions such as rheumatoid arthritis and microcrystalline arthritis were excluded from the study. The rheumatological assessment included a joint cunt of 66 SJ and 68 TJ, MASEI, LEI and the fibromyalgia tender points examination. The patient completed BASDAI and BANSFI in the day of clinical evaluation. Imaging exams (MSK ultrasound, MRI) and HLAB27 determination were requested if needed for diagnostic purpose.

Results: Between January to May 2018 210 patients were enrolled in the study and 181 complete the clinical-imaging examination. . Thirty-four patients (18.8%) presented the criteria for primary FM, 58 patients presented ASAS criteria for SpA (32%).In the group of SpA patients 10 patients presented a concomitant FM. A total of 44 patients (24.3%) in our IBD cohort presented the ACR 2010 criteria for FM. Of note FM patients presented LEI; BASDAI and BANSFI scores higher than SpA patients.

Conclusions: FM is a common comorbidity in IBD patients and can be associated to SpA. An appropriate rheumatological referral is crucial to exclude a concomitant SpA and to manage FM.

P805
Fertility, conception and delivery in patients with IBD, a retrospective study in two centres in Greece

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Background: Patients with IBD are concern about fertility, conception and relapse of disease during pregnancy. Birth weight and pregnancy outcome seems to be related with surgical procedures and medical treatment.

Methods: We evaluated these parameters in a retrospective analysis of Greek IBD patients.

Results: In total 430 patients were registered, 212 men (49.3%) of median age 33 ± 14 and 218 women (50.7%) of median age 33.1 ± 14.5. The majority of them (54.9%) had Crohn's disease (CD). No children have been reported by 173 (41.2%) patients: 99 males (46.7%) and 74 females (33.9%), p = 0.005. The rest 257 patients (59.8%) had at least one child (average 1.92 kids per patient). Patients with children are statistically older than these without (39 ± 13.8 vs. 24.3 ± 9.7, p < 0.001). Caesarean section was performed in 34% of deliveries (168/494). Median age of the first conception was 27.6 ± 6 years old in both sexes. For the women, median age of first, second and third conception was 25.7 ± 5.4, 27.7 ± 5 and 28.4 ± 7 year olds, respectively. One third of patient had their first child after the IBD diagnosis (n = 75, 29.2%), while 182 (70.8%) before.https://planner.smart-abstract.com/ecco2019/submission/en/abstract/13286/content#. Women with active disease at conception had clinical relapse during pregnancy more often than these with quiescent disease (37.5% vs. 4.8%, p = 0.005). Moreover, active disease in conception increased the risk of clinical relapse during pregnancy 12 times (OR = 12, 95% CI = 1.6–90). Relapse during pregnancy increased the risk of preterm delivery from 1.5% to 28.6% (p < 0.001). Infant's weight was, as expected, statistically lower in preterm deliveries (p < 0.001) as well as in pregnancies with relapse of IBD (2934 vs. 3227.5 g, p = 0.16). Infant's weight from parents with serious disease (surgery) was lower than these from parents without surgeries or parents that had children before IBD

diagnosis (2754 ± 1089 vs. 3183.8 ± 521 vs. 3317 ± 571 g, respectively, p = 0.043). Additionally, infant's weight from parents that conceived after IBD diagnosis was lower compared with the infants that were before IBD diagnosis (3076 ± 490 vs. 3293.5 ± 567 g, p = 0.017).

Conclusions: Fertility, conception, birth weight and outcome of pregnancies in Greek IBD patients do not differ from these published in other populations.

P806

Impact of patient age, gender and season of admission on length of stay in hospital for acute inflammatory bowel disease admissions

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Background: There has been increased emphasis on predicting Estimated Date of Discharge (EDD) for patients admitted to acute Irish public hospitals. Several factors including age and gender has been associated with prolonged hospital admissions. Environmental factors also play a role in exacerbations of inflammatory bowel disease. To the best our knowledge there has been no such study that assessed the role of age, gender and seasons in predicting length of stay (LOS) in patients admitted with acute exacerbations of IBD. The aim of this study was to determine whether age, gender or season of admission could be used as predictor for Length of stay for patients admitted to acute hospital with exacerbations of IBD.

Methods: This single-centre retrospective cohort study included patients admitted acutely to our hospital with exacerbation of Crohn's disease (CD) and Ulcerative colitis (UC) between January 1st 2015 and August 31st 2018. Patient data were accessed from Hospital In-Patients Enquiry (HIPE) system. The mean length of stay was correlated with gender, month of admission and different age groups. The data were analysed using IBM-SPSS software.

Results: A total of 266 patients were included in the study. CD: 168 (M: 81, F: 87, Mean age: 41 ± 15.3 years), UC: 98 (M: 39, F: 59, Mean age: 51.14 ± 21.07 years). For CD, the mean LOS for males and females was 6.70 days and 5.86 days, respectively (p = 0.180, t-test). For UC, the mean LOS for males and females was 6.82 days and 5.51 days, respectively (p = 0.778, t-test). In CD, the mean LOS for age groups < 35 years, 35–55 years and >55 years was 6.1 days, 6.4 days, and 6.5 days, respectively (p = 0.91, one-way Innova test). In UC, the mean LOS for age groups < 35 years, 35–55 years and >55 years was 6.1 days, 4.7 days, and 6.5 days, respectively (p = 0.36, one-way Innova test). In CD, the mean LOS for seasons spring, summer, autumn and winter was 5.6 days, 6.3 days, 6.1 days and 6.9 days, respectively (p = 0.78, one-way Innova test). In UC, the mean LOS for seasons spring, summer, autumn and winter was 6.4 days, 5.5 days, 6.9 days and 5.4 days, respectively (p = 0.65, one-way Innova test).

Conclusions: Our data indicate that there is no significant correlation between age, gender and season of admission when compared with mean length of stay. Elderly population has higher co-morbidities, which lengthens their hospital stay; however, younger patients with IBD may have more aggressive disease and this results in almost similar length of stay in both patient groups.

P807

Burden of disease in patients with Crohn's disease: retrospective analysis of cross-sectional survey data from the USA and Germany

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Background: Individuals with Crohn's disease (CD) experience a wide range of debilitating symptoms covering bowel, abdominal and systemic manifestations[1] with a significant impact on health-related quality of life (HRQoL). This study utilised data from the Adelphi Disease-specific Programme (DSP), a large, cross-sectional survey, to describe the burden of CD in a real-world clinical setting in both the USA and Germany.[2]

Methods: This study is a retrospective, descriptive analysis of Adelphi DSP data collected from patients consulting for routine care in the USA and Germany (DE) during Q4 2017 (GSK sponsored analysis; study HO-18-19282). As part of the survey, physicians and patients reported the symptoms currently experienced by the patient. Measures of HRQoL included the short-form Inflammatory Bowel Disease Questionnaire (SIBDQ). Current and prior treatment use was captured. Data were evaluated for the overall population and separately for patients with physician-perceived mild or moderate to severe disease.

Results: The total number of participating physicians was 100 (US)/60 (DE), with physician-reported data for 803 (USA)/480 (DE) patients. 328 (USA)/350 (DE) patients provided voluntary patient-reported data. In the overall sample, patients had a mean disease duration since diagnosis of 4.1 (USA)/2.9 (DE) years. At the time of the survey, 52% (USA)/73% (DE) were biologic naïve and 44% (USA)/26% (DE) receiving biologic treatment. Approximately half (50% USA; 55% DE) of the patients were perceived by their physicians to have mild disease, and the remaining moderate or severe. The most common current symptoms were abdominal cramps/pain, non-bloody diarrhoea, rectal urgency and fatigue (Table 1). Notably, physicians reported fatigue severity to be at least moderate in almost a third of mild patients and over three quarters of moderate/severe patients, with similar findings for pain severity. SIBDQ data indicate that QoL was impaired in the overall sample with greatest impairment in the moderate/severe group (Table 1).

	US		DE	
Most common symptoms, n (%):	**Physician-reported (n=799)**	**Patient-reported (n=304)**	**Physician-reported (n=479)**	**Patient-reported (n=345)**
Abdominal cramps	375 (46.93)	153 (50.33)	145 (30.27)	93 (26.96)
Non-bloody diarrhoea	313 (39.17)	99 (32.57)	221 (46.14)	153 (44.35)
Abdominal pain	255 (31.91)	89 (29.28)	201 (41.96)	131 (37.97)
Rectal urgency	89 (11.14)	57 (18.75)	172 (35.91)	94 (27.25)
Fatigue	Not collected	85 (27.96)	Not collected	82 (23.77)
SIBDQ total score (mean)	**Patient reported score (scale 1 = worst, 7 = best) mean (SD), n**			
Overall population	5.5 (1.0), n=156		5.3 (1.1), n=350	
Mild disease	5.7 (0.86), n=120		5.8 (0.87), n=202	
Moderate/severe disease	4.8 (1.18), n=36		4.6 (1.03), n=148	

Conclusions: The symptom burden of CD is high, commonly including bowel, abdominal and systemic symptoms (e.g. fatigue); HRQoL is also impaired. These findings highlight the need for more effective treatments for patients with Crohn's disease.

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P808

Prevalence and risk factors of cholelithiasis in patients with Crohn's disease

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Background: In thus far published literature, the cholelithiasis in patients with Crohn's disease (CD) is twice more frequent than in the general population. The reason for this difference has not been satisfactorily explained. The aim of our study was to determine the prevalence of cholelithiasis in CD patients, to compare prevalence with a control group and to analyse the risk factors of cholelithiasis.
Methods: The study was a monocentric retrospective case–control and was conducted at the IBD Center of the 5th Department of Internal Medicine in Bratislava. The CD patients who underwent abdominal ultrasound from January 2007 to January 2018 were involved into the study. The control group consisted of non-CD patients paired in 1: 1 ratio based by age and gender. The statistical analysis was performed in SPPS software.
Results: The study included 238 CD patients and 238 controls. The prevalence of cholelithiasis in CD group was 12.6% and 9.2% in control group (RR 1.36, p = 0.24). In the univariate analysis, we observed cholelithiasis association with multiple risk factors such as - age, age at CD diagnosis, inflammatory vs. aggressive disease behaviour, duration of disease, abdominal resection, number of intestinal resections, length of ileal resection, number of corticosteroid treatments, hospitalisations and total parenteral nutritions. The age (OR 1,077, 95% CI 1,043–1,112, $p < 0.001$) and the number of total parenteral nutrition (OR 1,812 95% CI 1,131–2,903, p = 0.013) were determined as independent risk factors for cholelithiasis in CD patients by multi-variate analysis.
Conclusions: The prevalence of cholelithiasis in our CD patient population reached 12.6%, which was not significantly higher than in the control group. We identified 2 independent risk factors of cholelithiasis in CD patients - age and number of parenteral nutrition.

P809

Quality of care through the eyes of the patients in a Spanish inflammatory bowel disease Unit

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Background: The aim of the present study was to evaluate the quality of healthcare from a point of view of the patients in an inflammatory bowel disease (IBD) Unit.
Methods: Observational, prospective, unicentre study. Patients diagnosed with Crohn's disease (CD) or ulcerative colitis (UC) attending at the IBD Unit of Hospital Universitario de La Princesa, were invited to anonymously fill the 'quality of care through the eyes of patients with IBD' (QUOTE-IBD) questionnaire. The same questionnaire was applied to patients from other Spanish IBD Units, as a control group. QUOTE-IBD is a validated 23-items questionnaire on healthcare which explores the Importance that patients give to care aspects, and the Performance of medical practices and healthcare workers. Each item assesses 8 care dimensions: competence, autonomy, courtesy, accessibility, information, costs, continuity of care, and accommodation. The combined effect of Importance and Performance is defined as Quality Impact (QI). The QI of total care was calculated as the average of the QI's from each dimension, and for every care dimension a QI score ≥9 was considered as patient satisfaction.
Results: 100 patients (51% women, median age 49 years, 54% CD) from our IBD Unit and 100 controls completed the QUOTE-IBD. A QI score lower than 9 was reported for all the dimensions of care. In our patients, the QI of total care score was higher than in controls (7.70 ± 0.2 vs. 7.05 ± 0.19, $p = 0.007$). In terms of dimensions, patients gave the highest Importance score to aspects related to Information (8.24), followed by Competence in IBD care (7.86). In the subanalysis, Competence was more relevant for patients with a disease duration >10 years vs. < 10 years (8.24 vs. 7.57, $p = 0.037$). Women vs. men (7.23 vs. 7.84, $p = 0.045$) and patients with surgical interventions vs. non-surgical patients (7.06 vs. 7.70, $p = 0.045$) gave less importance to Courtesy. Accommodation was more important to UC vs. CD (7.51 vs. 6.64, $p = 0.022$). The scores of Performance ranged from 0.4 ± 0.29 for Continuity of care to 0.01 ± 0.1 for Cost. In terms of dimensions of healthcare, the scores of QI ranged from 6.78 ± 2.9 for Information to 9.9 ± 1 for Costs. Compared with control group, all dimensions except Accommodation had a higher QI in our patients. Differences in Competence (7.21 ± 0.25 vs. 8.05 ± 0.26 $p = 0.027$) and Continuity of Care (6.17 ± 0.27 vs. 7.27 ± 0.27) were statistically significant.
Conclusions: According to QUOTE-IBD, the quality of care of our IBD Unit has room for improvement. Patients gave more Importance to Information about IBD and they considered that we had our best Performance in Continuity of care. The QI total care score and the QI in almost all dimensions of care were higher in our Unit than in controls.

P810

Clinical features of ulcerative colitis patients in Sardinia, Italy – First results from a multi-centre study

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Background: There are few data on epidemiological and clinical features of adult ulcerative colitis (UC) patients in Sardinia (Italy), mainly derived from administrative sources such as Hospital Discharge Register. The aim of this study was to assess the main clinical and epidemiological features of adult patients diagnosed with ulcerative colitis (UC) in Sardinia, Italy.
Methods: We evaluated the main clinical features of UC patients followed-up in 7 Gastroenterology/Endoscopy Units in Sardinia, Italy. Data were obtained from medical patients' records and from a questionnaire administered at inclusion visit.
Results: 374 patients with UC were included: 52.9% were female, with a female-to-male ratio of 1.125. Eleven per cent of patients were active smokers and 36.4% were former smokers. Mean age at diagnosis was 39.2 years (SD 15.4). Only 4.3% of patients were < 16 years old at diagnosis; 53.2% were diagnosed at age ranging from 17 to 40 and 42.5% at age >40. About three quarters of patients were diagnosed between 17 and 49 years old (23.7% between 17 and 29, 25.8% between 30 and 39 and 22.8% between 40 and 49). Disease extent at diagnosis was proctitis in 18.2% of patients, left-sided colitis in 38.8% and extensive colitis in 41.2% (missing data in 1.9% of patients). After a median disease duration of 9 years (IQR 13.8), proximal extension of proctitis or left-sided colitis (from E1 to E2/E3 or from E2 to E3) occurred in 12% of patients. 17.9% of patients developed extraintestinal manifestations, the most frequent being articular (11.8%). There were six patients (1.6%) with concomitant primary sclerosing cholangitis. Two patients developed colorectal cancer.
Conclusions: This multi-centre study provides important preliminary clinical data on UC in Sardinia.

P811

Trends in the cost of medical care for inflammatory bowel disease in Korea over the last 5 years

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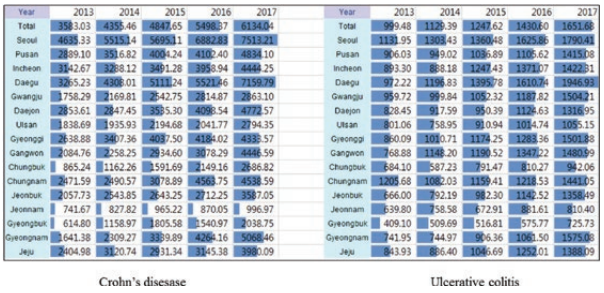
Background: As the incidence of IBD has increased, the overall cost of medical care also has been increasing. However, It is not clear whether the per-capita cost is increasing or not in the era of biologics. We aimed to estimate annual per-capita healthcare expenditures for IBD and analyse the trends by region and age in Korea overall the last 5 years
Methods: We estimated IBD patient data and reimbursement information from the Korean Health Insurance Review & Assessment Service between 2013 and 2017. The data converted into the annual per capita healthcare expenditures were analysed by region and age. For analysis of the results, the currency unit is KRW1000. (KRW1000 = USD0.9).
Results: The overall number of IBD patient has increased steadily (CD;16 138 and UC; 31 026 in 2013 vs. CD; 20 231 and UC; 40 939 in 2017), and the overall cost of medical care has also increased significantly. The annual per capita healthcare costs for CD and UC have also increased steadily since 2013 and nearly doubled in 2017(CD; 3583.03 and UC; 999.48 in 2013 vs. CD; 6134.04 and UC; 1651.68 in 2017). The annual per capita healthcare costs for CD and UC in major cities including Seoul, where Tertiary referred hospitals are located, was higher than that for other regions (Figure 1).

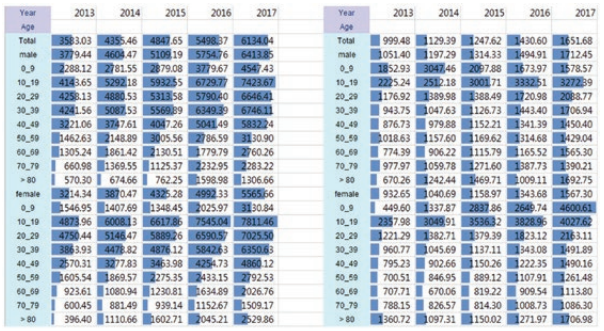


Year	2013	2014	2015	2016	2017
Total	3583.03	4355.46	4847.65	5498.37	6134.04
Seoul	4635.33	5515.14	5695.11	6882.83	7513.21
Pusan	2889.10	3516.82	4004.24	4102.40	4834.10
Incheon	3142.67	3828.12	3491.28	3958.94	4448.25
Daegu	3265.23	4308.01	5111.24	5521.86	7159.79
Gwangju	1758.29	2169.81	2542.75	2814.87	2863.10
Daejon	2853.61	2847.45	3585.30	4098.54	4772.57
Ulsan	1838.69	1935.93	2194.68	2041.77	2794.35
Gyeonggi	2638.88	3407.36	4037.50	4184.02	4333.57
Gangwon	2084.76	2258.25	2934.60	3078.29	4446.59
Chungbuk	865.24	1162.26	1591.69	2149.16	2886.82
Chungnam	2471.59	2490.57	3078.89	4563.75	4538.59
Jeonbuk	2057.73	2643.85	2643.25	2712.25	3587.05
Jeonnam	741.67	827.82	965.22	870.05	996.97
Gyeongbuk	614.80	1158.97	1805.58	1540.97	2038.75
Gyeongnam	1641.38	2309.27	3339.89	4264.16	5068.46
Jeju	2404.98	3120.74	2931.34	3145.38	3980.09

Year	2013	2014	2015	2016	2017
Total	999.48	1129.39	1247.62	1430.60	1651.68
Seoul	1131.95	1308.43	1360.48	1625.89	1790.41
Pusan	906.03	949.02	1036.89	1105.62	1415.08
Incheon	893.30	888.18	1247.43	1371.07	1422.31
Daegu	972.22	1196.83	1395.78	1610.74	1946.93
Gwangju	859.72	999.84	1052.32	1187.82	1504.21
Daejon	828.45	917.59	950.39	1124.63	1316.95
Ulsan	801.06	758.95	910.94	1014.74	1055.15
Gyeonggi	860.09	1010.71	1174.25	1283.36	1501.88
Gangwon	768.88	1148.20	1198.52	1347.22	1480.99
Chungbuk	684.10	587.23	791.47	810.27	992.06
Chungnam	1205.68	1082.03	1159.41	1218.53	1441.05
Jeonbuk	866.00	792.19	982.30	1142.52	1358.49
Jeonnam	639.80	758.58	672.91	881.61	810.40
Gyeongbuk	409.10	509.69	516.81	575.77	725.73
Gyeongnam	741.95	744.97	906.36	1081.50	1575.08
Jeju	843.93	886.40	1046.69	1252.01	1388.09

Crohn's disease Ulcerative colitis

The annual per capita healthcare costs for CD in teens, 20s, and 30s was higher than other decades and then decreased sharply, and that for UC in teens and 20s was high and then gradually decreased (Figure 2).



Year / Age	2013	2014	2015	2016	2017
Total	3583.03	4355.46	4847.65	5498.37	6134.04
male	3779.44	4604.47	5108.19	5754.76	6413.85
0_9	2288.12	2781.55	2879.08	3279.67	4547.43
10_19	4143.65	5282.18	5932.55	6728.77	7423.67
20_29	4255.13	4880.53	5313.58	5790.80	6646.41
30_39	4241.56	5087.53	5569.89	6349.39	6746.11
40_49	3221.06	3747.61	4047.26	5041.49	5832.24
50_59	1462.63	1748.89	2005.56	2786.59	3130.90
60_69	1305.24	1861.42	2130.51	2779.79	2760.26
70_79	660.98	1369.55	1125.37	2232.95	2283.22
> 80	570.30	674.66	762.25	1598.98	1306.66
female	3214.34	3870.47	4325.28	4992.33	5565.66
0_9	2546.95	3407.69	3348.45	4025.97	4130.84
10_19	4873.96	6008.13	6617.86	7545.04	7811.46
20_29	4750.44	5146.47	5889.26	6590.57	7025.50
30_39	3863.93	4473.82	4876.12	5842.83	6350.63
40_49	2670.31	3277.83	3463.98	4254.73	4860.12
50_59	1605.54	1869.57	2275.35	2433.15	2792.53
60_69	923.61	1080.94	1230.81	1634.89	2026.76
70_79	600.45	881.49	939.14	1152.67	1509.17
> 80	396.40	1110.66	1602.71	2045.21	2529.86

Year / Age	2013	2014	2015	2016	2017
Total	999.48	1129.39	1247.62	1430.60	1651.68
male	1051.40	1197.29	1314.33	1494.91	1712.45
0_9	1852.93	3047.46	2697.88	1673.97	1578.57
10_19	2225.24	2512.18	3001.71	3332.51	3272.89
20_29	1176.92	1389.98	1388.49	1720.98	2038.77
30_39	943.75	1047.63	1126.73	1443.40	1706.94
40_49	876.73	979.88	1152.21	1341.39	1450.40
50_59	1018.63	1157.60	1169.62	1314.68	1429.04
60_69	774.39	906.22	1115.79	1165.52	1565.30
70_79	977.97	1059.78	1271.60	1387.73	1390.21
> 80	670.26	1242.44	1469.71	1009.11	1892.75
female	932.65	1040.69	1158.97	1343.68	1567.30
0_9	449.60	1337.87	2837.86	2649.74	4600.61
10_19	2257.98	3049.91	3536.32	3828.96	4027.62
20_29	1221.29	1382.71	1379.39	1823.12	2183.11
30_39	960.77	1045.69	1137.11	1343.08	1491.89
40_49	795.23	902.66	1150.26	1222.35	1490.16
50_59	700.51	846.95	889.12	1107.91	1261.48
60_69	707.71	670.06	819.22	909.54	1113.80
70_79	788.15	826.57	814.30	1008.73	1086.30
> 80	1360.72	1097.31	1150.02	1271.97	1706.98

Crohn's disease Ulcerative colitis

Interestingly, the annual per capita healthcare costs for women under 10 years in UC has increased dramatically.
Conclusions: The healthcare cost in IBD has been increasing not only on a whole scale but also on a per capita healthcare costs in Korea over the last 5 years. Consuming more medical costs at younger ages means that they are suffering from moderate-to-severe disease, which means that there is a large socio-economic loss. Given the increasing trend, government measures are needed to support medical expenses in the future, and it is thought that a sustained trend analysis is needed.

P812

Anaemia during Crohn's disease: Does its mechanism predict the extent of the disease?

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Background: Anaemia is the most common extraintestinal complication during Crohn's disease (CD). Several studies have looked at possible mechanisms and its treatment but few have tried to link it to a specific localisation of the disease. The aim of our study is to determine the prevalence, mechanisms of anaemia during CD and seek for a locational value by type.
Methods: A retrospective descriptive and analytical study, spread out over 5 years, including patients diagnosed with a CD at the department of gastroenterology of Sousse. Anaemia was defined as haemoglobin < 13 g/dl in men and < 12 g/dl in women.

Results: We collected 166 patients of mean age 42.9 years [15–73 years] and sex ratio 0.55. Two thirds of the patients were anaemic (75.3%) with an average haemoglobin level of 10.4 g / dl [6.7–11.8 g/dl]. Iron deficiency anaemia was found in 62.4% of cases (N = 78). Normocytosis was found in 37.6% of cases (N = 47). In this case, it was associated with inflammatory anaemia in 51.06% of cases (ferritin blood level average : 157 ng/ml [102–406 ng/ml]), an haematologic toxicity of azathioprine in 14.9% and combined vitamin B12 and iron deficiency anaemia in 34.04% of cases. A statistically significant correlation was found between iron deficiency anaemia and ileocolic localisation of the disease (p = 0.05). In addition, combined normocytic anaemia was more common in cases of extensive ileal localisation without significant correlation (p = 0.06). Inflammatory anaemia had no locating value.
Conclusions: In our study, anaemia was predominantly iron-deficient and was associated with ileocolic localisation, unlike inflammatory anaemia, which had no locating value. More large studies are needed to confirm our hypotheses.

P813

Pregnancy, postpartum and health of newborn in patients with inflammatory bowel disease: experience at a single-centre

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Background: Inflammatory bowel disease (IBD) affects young women. According to the evidence, IBD does not affect fertility. It is advisable to plan conception in quiescent phase.
Aim: development of pregnancy, postpartum and activity of the disease. Effect of maternal disease in the health of the newborns.
Methods: Retrospective descriptive study. Database from patients of the Hospital Universitario San Cecilio of Granada (Spain). Electronic clinical records between 2012 and 2017 have been reviewed.
Results: There were 68 pregnancies. Description of the population in Table 1. Mean age from diagnosis to pregnancy is 8.83 years.

Variable	Frequency
Number of pregnancies: 1; ≥2	37 women; 13 women
Maternal age (years old): < 35; ≥35	39 (57.35%); 29 (42.65%)
Smoking mothers	13%
Type of disease: Ulcerative colitis (UC) (Pancolitis; Recto sigmoiditis; Proctitis, Unknown extension), Crohn's disease (CD) (Ileocolitis; Ileal; Colitis; Antroduodenal and ileocolitis; Unknown extension; Perianal disease)	32 patients (47.06%) (16.65%; 37.49%; 28.12%; 18.74%), 36 patients (52.94%) (55.56%; 25%; 13.88%; 2.78%; 2.78%; 22.22%)
Treatment: mesalazine; thiopurines; anti-TNF; without treatment	46.87%; 23.44%; 18.75%; 10.94%

Characteristics of the population.Of the 68 pregnancies, 10 women (14.71%) had history of surgery due to IBD, all of them with Crohn's disease (CD). In conception, 8/10 were in quiescent phase. During pregnancy, 17.65% of patients stopped their treatment on own initiative or indication of the general practitioner. In all patients anti-TNF could be suspended in the third trimester.
There were seven flare-up (10.29%), and all of them were controlled with corticosteroids. 10.29% women had other complications during pregnancy, but only one was due to IBD (severe thrombocytopenia in a patient in treatment with azatioprine which needed caesarean section). There were two induced abortion and six early miscarriage, being 75% in CD patients.
Most were full-term newborns, there were only three late preterm infants in women with CD. The labour was vaginal delivery in 53 cases and caesarean section in 15 (22.06%), three of them due to perianal disease, and the rest for obstetric reasons. Only one newborn (1.47%) was small for gestational age, they was one of the twins of a multiple gestation. 69.12% mothers were breastfeeding, more frequent in ulcerative colitis (UC) (81,25%) than CD (41,67%).
Any newborn from mothers with UC had any relevant disease, but there were a case of hip dysplasia, one of Rubinstein–Taybi syndrome and another of enterovirus meningitis in infants from mothers with CD.
14.71% of women had flare-up in the year after delivery, being 90% in the six first months.
Conclusions: (1) The frequency of obstetric complications in IBD was similar to general population. Only a case of severe thrombocytopenia and three out of five caesarean sections were due to IBD. (2) Miscarriages and complications in newborns were more frequent in CD. (3) IBD affects young women in reproductive age. In our series, 18% of women stopped treatment during pregnancy. It is required medical advice to avoid suspension of treatment. Most IBD treatments are safe during pregnancy and breastfeeding.

P814

Vitamin D levels and correlations in inflammatory bowel diseases

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Background: Vitamin D (vitD) deficiency occurs more commonly in the inflammatory bowel disease (IBD) than in general population and it has been associated with IBD pathogenesis, disease activity, severity and outcome. VitD also exerts immunomodulatory actions that could be beneficial for IBD. The aim of our study was to determine the prevalence of vitD deficiency among IBD patients and assess for correlations with disease and patients' characteristics, drug treatment, steroid exposure and bone density status.
Methods: Patients that have recently undergone colonoscopy were included in the study and their serum 25-hydroxy vitD levels were measured. The patients' endoscopic activity was recorded as no- or mucosal healing, which was defined as Mayo sub-score=0, SES-CD score=0 or Rutgeerts score=0 for Ulcerative colitis (UC), Crohn's disease (CD) and CD patients with ileocolonic resection, respectively. The patients' age, disease type and duration, location, previous surgery, current medical treatment, steroid exposure and bone density status were also recorded. Statistical analysis (linear regression analysis) of the data was then performed to assess for statistically significant differences.
Results: In total, 68 patients (66.2% with CD and the rest with UC), with a mean age of 45.9 years old, were enrolled in the study. 24.4% of CD patients had ileal disease, 6.6% had colitis, 50% had ileocolitis

while 14.6% had undergone surgery. 30.4% of UC patients had left-sided, 69.5% had extensive disease while none had proctitis. 51.5% had mucosal healing on endoscopy with the rest exhibiting a degree of endoscopic abnormality. The patients' current medical treatment, prior exposure to steroids and bone density status were as follows:

5-ASA	Azathioprine	Adalimumab	Infliximab	Vedolizumab	No treatment
N=23	N=4	N=16	N=17	N=2	N=6
Prior steroid exposure					
Any Exposure		Topical steroids		Systemic Steroids	
N=29		N=10		N=29	
Bone density (measured in 44 patients)					
Normal N=22		Osteopenia N=17		Osteoporosis N=5	

Only 8 patients had normal vitD levels (>30 ng/ml) while 32% had insufficient (20–30 ng/ml) and 55.9% had deficient (< 20 ng/ml) levels. The overall mean vitD level was 21.24 ng/ml. On multivariable analysis, none of the studied variables was found to be independently associated with vitD levels.

Conclusions: The percentage of patients with low-vitD levels was as high as 88.2% while 50% were suffering from osteopenia/osteoporosis. The vitD levels were not correlated with any disease characteristic or previous ileocolonic resection and were independent of patients' age and sex. No correlation of endoscopic disease activity and vitD levels was also found. Finally, it could be suggested that vitD levels should be included in the biochemical exams' panel during monitoring of IBD patients irrespectively of their disease characteristics.

Genetics

P815

Clinical and endoscopic features of XIAP deficiency mimicking refractory Crohn's disease in paediatric patients

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Background: X-linked inhibitor of apoptosis protein (XIAP) deficiency is a rare immunodeficiency that is characterised by recurrent haemophagocytic lymphohistiocytosis (HLH) and splenomegaly and often associated with refractory inflammatory bowel disease (IBD). We report on four patients with childhood-onset XIAP deficiency who were initially diagnosed with Crohn's disease (CD) and had been treated with frequent relapse.

Methods: We aimed to investigate clinical characteristics and endoscopic features of paediatric patients diagnosed with XIAP deficiency at Sapporo Kosei General Hospital, Sapporo, Japan. Symptoms, complications, endoscopic images and genetic data were reviewed.

Results: At onset four male patients were between the age of 8 and 11 years. They were then histopathologically diagnosed with CD and underwent treatment with prednisolone, several immunosuppressants, and thereafter with infliximab. All of them responded to treatment partially and relapsed frequently. Three of the four patients were complicated with HLH. Serum interleukin (IL)-18 levels (normal range: 0–300 pg/ml) of three patients were elevated. western blot analysis demonstrated absent XIAP expressions and genetic analyses definitely confirmed XIAP deficiency in all the four patients. Three patients underwent haematopoietic stem cell transplantation (HSCT) and the fourth one is planning to undergo HSCT.

	P 1	P 2	P 3	P 4
Age of onset (yrs)	8	11	8	11
Sex	Male	Male	Male	Male
Chief complaint at onset	Fever, diarrhea, anal fistula	Fever, diarrhea, anal fistula, splenomegaly	Fever, diarrhea, anal fistula, splenomegaly	Fever, diarrhea, anal fistula
Features of histopathology	CD Granuloma(–)	CD Granuloma(+)	CD Granuloma(+)	CD Granuloma(–)
HLH (times)	2	4	3	2
Effect of therapy	Resistant	Resistant	Resistant	Resistant
IL-18 (pg/ml)	2,110	4,640	18,800	N.D.
Mutation in *XIAP*	c.1141C>T (p.Arg381X)	c.340C>T (p.Gln114X)	2199bps defect in exon 1	c.73G>T (p.Glu25X)
Treatment	HSCT	HSCT	HSCT	planning to HSCT

Table. Summary of patients with XIAP deficiency.

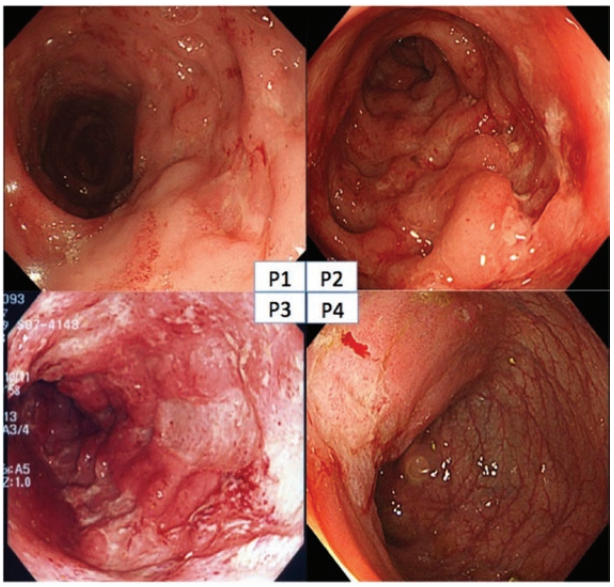

Figure. Endoscopic images of the wide and longitudinal ulcers with scooped-out appearance in the colon.

Conclusions: CD like inflammatory bowel disease associated with recurrent HLH, splenomegaly and anal fistula is a characteristic clinical feature of patients with XIAP deficiency. We presented here a characteristic endoscopic finding of wide and 'scooped-out' multiple longitudinal ulcer lesions in all the four XIAP deficiency patients. We propose that XIAP deficiency should be suspected for those with characteristic clinical features and unique endoscopic findings as described above. We recommend flow-cytometric analysis or western blot of XIAP expression followed by whole-exome sequencing analysis as soon as possible. CD-like inflammatory bowel disease in our three cases was improved remarkably after HSCT and has been maintained remission without any further treatments. We should not postpone the timing of performing genetic analysis because HSCT is the only curative treatment for XIAP deficiency patients.

P816

Functional rare variants influence the clinical response to anti-TNF therapy in Crohn's disease

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Background: Loss-of-function (LoF) variants are one of the most interesting forms of rare functional genetic variations as they impair the function of a gene and are more likely to lead to extreme phenotypes. Our aim was to know the impact of functional rare variants in clinical response to anti-TNF therapy in Crohn's disease (CD).

Methods: CD anti-TNF naïve patients starting anti-TNF treatment due to active disease (CDAI>150) were included. The whole genome was sequenced using the Illumina Hiseq4000 platform. Clinical response was defined as a CDAI score < 150 at Week 14 of anti-TNF treatment. Low-frequency variants were annotated and classified according to their damaging potential. The whole genome of CD patients was screened to identify homozygous LoF variants. The TNF signalling pathway was tested for overabundance of damaging variants using the SKAT-O method. Functional implication of the associated rare variation was evaluated using cell-type epigenetic enrichment analyses.

Results: 41 CD patients were included -61% had remission and 24% were primary non-responders (Table 1); 3,250 functional rare variants (2,682 damaging and 568 LoF variants) associated with response to anti-TNF therapy were identified (Table 2). The strongest damaging impact was detected in 10 LoF SNPs (Table 3). Two homozygous LoF mutations were found in HLA-B and HLA-DRB1 genes associated with lack of response and remission, respectively. Genome-wide LoF variants were enriched in epigenetic marks specific for the gastrointestinal tissue (colon, $p = 4.11e{-}4$; duodenum, $p = 0.011$). The burden of damaging variation in the TNF signalling pathway was associated with response to anti-TNF drugs ($p = 0.018$); damaging variants were enriched in epigenetic marks from CD8+ ($p = 6.01e{-}4$) and CD4+ ($p = 0.032$) T cells.

Conclusions: Functional rare variants are involved in the response to anti-TNF therapy in CD. Cell-type enrichment analysis suggests that the gut mucosa and CD8+ T cells are the main mediators of this response. These findings provide new insights into the underlying heterogeneity of CD, revealing the basis of TNF-dependent biological mechanisms.

Men (%)	22 (53.7)
Location (%)	
Ileal	14 (34)
Colonic	6 (14.6)
Ileocolonic	17 (41.5)
Behavior (%)	
Inflammatory	21 (51.2)
Stricturing	5 (12)
Fistulizing	11 (26.8)
Perianal disease (%)	8 (19.5)
Extraintestinal manifestations (%)	14 (34)
Previous surgery (%)	17 (41.5)
Smoking habit (%)	16 (39)
Steroids	7 (17)
Immunomodulators (%)	
Thiopurines	30 (73)
Methotrexate	3 (7.3)
Anti-TNF type (%)	
Adalimumab	16 (39)
Infliximab	25 (61)

VARIANT ANNOTATION	VARIANTS*
Start lost	8
Stop gained	2
Stop lost	2
Synonymous	30
Missense	2,590
Splice donor	2
Splice region	89
Structural interaction	50
Long intergenic non-coding RNA	56
Sense intronic	17
Small nuclear RNA	12
3' UTR	479
5' UTR	86
Nonsense-mediated decay	1
Nonstop decay	9

*Number of low-frequency damaging variants showing the indicated annotation. Given that a single genetic variant can impact different genes, the annotated variants outnumber those predicted as damaging

SNP	CHR	COORD	A1	A2	GENE	VARIANT TYPE	ANNOTATION	CD (%)	RESP	NRESP
rs150581659	1	16447908	G	A	*NECAP2*	exonic	stop gained	1 (2.4)	1	0
rs761330653	1	39639623	C	T	*HEYL*	exonic	start lost	1 (2.4)	1	0
rs764641613	1	39639624	A	C	*HEYL*	exonic	start lost	1 (2.4)	1	0
chr2:88173152	2	88173152	T	C	*THNSL2*	exonic	start lost	1 (2.4)	0	1
rs41272317	3	132618633	C	A	*NPHP3-ACAD11*	intronic	splice donor	1 (2.4)	0	1
rs138856042	3	137998869	A	G	*CLDN18*	exonic	start lost	1 (2.4)	1	0
rs151314696	6	31719303	C	T	*LY6G6C*	exonic	start lost	1 (2.4)	1	0
rs61732354	6	42890786	C	T	*C6orf226*	exonic	start lost	2 (4.8)	1	1
rs192561318	11	61920191	A	G	*RAB3IL1*	intronic	start lost	1 (2.4)	1	0
rs79556405	17	29941799	G	A	*EFCAB5*	intronic	start lost	4 (9.7)	2	2

Abbreviations: A1, reference allele; A2, alternative allele that causes the LoF of the protein encoded by the indicated gene; CD, number of CD patients carrying the LoF variant; Chr, chromosome; Coord, SNP coordinates in GRCh38/hg38, Nresp, number of patients that carry the LoF variant and did not show a significant clinical response to anti-TNF therapy; Resp, number of patients that carry the LoF variant and responded to anti-TNF therapy; SNP, single nucleotide polymorphism.

P817

Profiles of somatic mutations in tissue of IBD and IBD-associated carcinomas revealed by a targeted next-generation sequencing (NGS) tumour panel confirm notable differences from sporadic colorectal carcinomas

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Background: Inflammatory bowel diseases (IBD) present an increased risk of developing colorectal carcinoma. Neutrophil-released chemicals in the immune response to inflammation causes mutagenesis, and its long-term effects may result in the development of tumour-specific DNA mutations that are the initiators of malignant conversion of intestinal tissue cells. The subsequent molecular changes within the affected gastrointestinal mucosa induce focal changes of the tissue morphology. The molecular mechanisms of this malignant conversion show specific differences from similar mechanisms leading to other types of colorectal carcinoma. The aim of the project is to trace tissue-specific somatic DNA mutations by massively parallel next-generation sequencing using an extensive panel of 50 carcinoma-associated genes (oncogenes and tumour suppressors). Furthermore, the purposes was to compare the resulting profiles obtained from IBD (Crohn's disease, Ulcerative colitis) and IBD-associated carcinomas to those obtained from tissue of sporadic colorectal tumours.
Methods: The group consisted of 25 patients with IBD and 5 patients with sporadic colorectal cancer covering samples from primary tumour, metastases with both MSI and MSS status. For each tumour DNA was extracted from either a biopsy or resected tissue (native or FFPE) and subjected to NGS performed on Illumina MiSeq sequencer using SureSeq™ Solid tumour hybridisation-based enrichment panel (Oxford Gene Technology, Oxfordshire, UK). NGS data were processed by NextGENe sequence analysis suite (Softgenetics, State College, PA).
Results: We mapped the incidence and frequency of major control oncogenic mutations in tissue samples of IBD patients. In general, a difference was observed when comparing mutational spectra among IBD, IBD-associated carcinomas and sporadic carcinomas. As expected, we have confirmed an inverse succession of mutations affecting oncogenes and tumour-suppressors from traditional sporadic pathway. Furthermore, we have revealed a high incidence of somatic mutations of the NOTCH1 and EPAS1 genes, which have previously been shown to be related to their activation and inflammatory processes in the tissue.
Conclusions: Investigation of the presence of specific mutations in inflammatory tissue of IBD patients represents a qualitatively new approach to disease characterisation, including the prediction of the risk of malignant conversion. The study was supported by Czech Ministry of Defense research project MO1012.

P818

Polymorphisms in C1orf106, IL1RN, IL10 are associated with postinduction infliximab trough level in Crohn's disease patients

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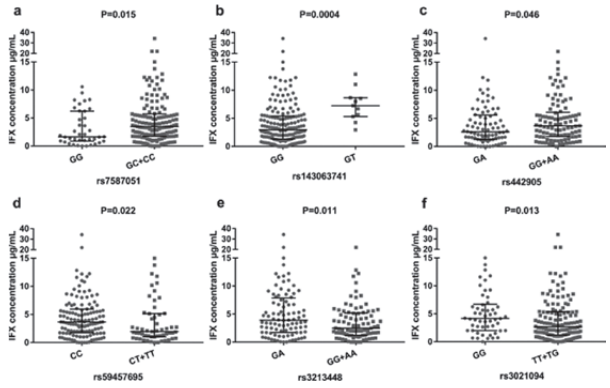
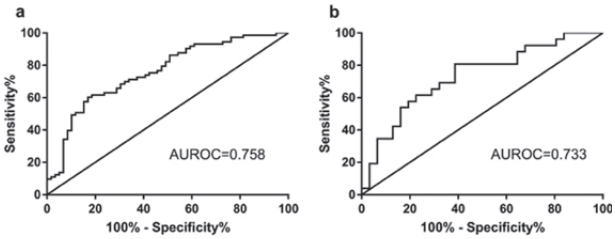
Background: The post induction serum infliximab trough concentration was associated with short-term and long-term response to infliximab (IFX), but it has large interindividual difference.
Methods: The present study investigated the effects of genetic (polymorphisms within FCGR3A, ATG16L1, C1orf106, OSM, OSMR, NF-κB1, IL1RN, IL10) and nongenetic (sex, weight, baseline albumin and combination therapy) factors on IFX therapeutic threshold (3 μg/ml) after 14 weeks-induction therapy.

Results: We found that rs7587051, rs143063741, rs442905, rs59457695, rs3213448 and rs3021094 were found to be significantly associated with the post induction IFX trough level ($p < 0.05$).



Genotype in response to infliximab level in patients. Results of 6 SNPs as showed (a) to (f). Mann–Whitney U-test.

Using multi-variate logistic regression analysis, baseline albumin and SNPs within C1orf106, IL1RN, IL10 were included in the multivariate prediction model (AUROC = 0.758) with p values of 0.002, 0.025, 0.049, 0.056 and 0.047 for baseline albumin, rs442905, rs59457695, rs3213448 and rs3021094, respectively. The sensitivity and specificity of this prediction model was 60.27% and 83.05%, respectively. This result was verified in a testing dataset with AUROC of 0.733.



ROC curve analysis the performance of multi-variate Logistic regression model on training datasets and testing datasets.

Conclusions: Serum albumin level and polymorphisms in C1orf106, IL1RN, IL10 play important role in the variability of IFX post induction level and should be measured before IFX administration. Through the prediction model, the patients who might fail to achieve IFX therapeutic threshold could be found in advance and dose intensification in the future might be needed for them.

P819

Whole-exome sequencing in early-onset primary sclerosing cholangitis: first results of the WHELP study

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Background: Primary sclerosing cholangitis (PSC) is a severe liver disease leading to fibrotic destruction of the bile ducts and ultimately to the need for liver transplantation. In children the connection with inflammatory bowel disease (IBD) is close to 100%. Genome-wide association studies (GWAS) in adults have identified many risk loci for both IBD and PSC, but a large part of the heritability remains unexplained. We hypothesise that we can identify rare, but disease-causing variants in patients with an extreme PSC phenotype, such as children with early-onset PSC.

Methods: In this multi-centre parent-offspring study, we collected DNA from 31 children who were diagnosed with PSC before the age of 13, and their biological parents. Whole-exome sequencing (WES) was performed on all 93 DNA samples. We first performed parents-child trio analyses and prioritised rare coding and splice variants matching recessive (homozygous and compound heterozygous variants) and dominant (*de novo*) inheritance in the children. Pathogenicity of the variants was predicted with an in-house developed algorithm (GAVIN). Secondly, we performed a cohort analysis in which we prioritised genes that carried a rare pathogenic variant in 3 or more cases, but were not found in population controls.

Results: We identified compound heterozygous variants in three trios in genes *ABCB6*, *DACT1* and *JMJDC1*, and in 13 other trios we identified a total of 16 *de novo* variants in 16 genes with predicted pathogenic effects on protein functions. The same *de novo CNOT2* variant was shared between two families, as well as the *de novo TNRC18* variant. Most identified genes have roles in bile salt transport and the immune system.

Conclusions: So far, 19 candidate disease-causing variants with large effects on protein function were found in children with early-onset PSC involving immunological or bile salt pathways. Network analysis is currently being performed to assess the relation between these genes and signalling pathways associated with PSC and or IBD.

P820

Molecular changes in non-inflamed terminal ileum in patients with ulcerative colitis

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Background: Ulcerative colitis (UC) is a chronic inflammatory disease of the intestine, typically confined to the mucosal layer of the colon. Small intestinal dysfunction has, however, been described in patients

with UC, although the underlying mechanisms of these alterations in apparently intact ileum are currently unknown. We here evaluated molecular changes and biological networks in non-inflamed terminal ileum in UC, and their association with colonic inflammation.

Methods: Terminal ileum biopsies were obtained during endoscopy from 36 patients with UC (7 active (Mayo endoscopic subscore ≥2) and 29 inactive) and 16 healthy controls. Subjects with endoscopic or histological (backwash) ileitis were not included. Single-end RNA sequencing was performed using Illumina HiSeq4000. Gene expression differences were analysed using DESeq2, and corrected for age and gender. Weighted gene co-expression network analysis (WGCNA) was performed to find biological networks of genes that correlate with UC activity. Pathways and upstream regulators were identified using IPA.

Results: When we compared ileal expression levels of active UC (71% male, median age 52 years) with controls (44% male, median age 57 years), we found 20 differentially expressed (adj. $p \leq 0.05$ and fold change (FC)≥2) genes, with *DUOXA2* being the most significant (FC=4.9, adj. $p = 0.009$). The 20 genes were involved in free radical scavenging, molecular transport, cell-to-cell signalling, and cellular proliferation. Cytokines IL1A, IFNG, and TNF were predicted as upstream regulators. Comparison of inactive UC (59% male, median age 52 years) with controls only found 2 dysregulated genes (*CEBPD* and *REG1B*). *REG1B* was also one of the 20 dysregulated genes in active UC (active UC: FC=4.1, adj. $p = 0.02$; inactive UC: FC=2.7, adj. $p = 0.04$). WGCNA analysis found 38 co-expression modules, 3 of which were positively correlated (adj. $p \leq 0.2$) with active UC, and with the enclosed genes mainly involved in immune functions (e.g. interferon and cytokine signalling, and antigen presentation). One module was positively correlated with inactive UC (enriched for genes involved in mitochondrial translation), and one was negatively correlated (enriched in signal regulatory protein (SIRP) family interactions and NF-kB activation genes).

Conclusions: Our transcriptome analysis identified significant alterations in non-inflamed ileum of UC patients, depending on colonic inflammation. Ileal changes in active UC are mainly related to immune function, but the causal and temporal relationship with colonic inflammation is unclear. Ileal changes in inactive UC on the other hand seem to be functioning to maintain the intestinal barrier with increased mitochondrial functions and dampened immune functions.

P821

Distinct and common gene expression profiles between inflamed ileum and colon of newly diagnosed CD patients

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Background: The origin of the heterogeneous clinical presentation of Crohn's disease (CD) is poorly understood. We therefore aimed to characterise the molecular networks in inflamed tissue of CD patients with ileal and/or colonic disease location, and how they relate to control colon and ileum.

Methods: Inflamed colonic ($n = 31$, 8 L2 + 23 L3) and ileal ($n = 31$; 17 L1 + 14 L3) biopsies were collected from newly diagnosed CD patients across three Belgian IBD centres (PANTHER study B322201627472/S57662). Patients naïve for biologicals and immunosuppressives, and without previous IBD-related surgery were included within 6 months after diagnosis. Thirty-six colonic and 14 ileal biopsies from non-IBD were used as controls. All biopsies underwent single-end RNA sequencing, and downstream data were corrected for age and gender. Co-expression networks (correlation ≥ 0.55, adj. $p \leq 0.05$) were found with weighted gene co-expression network analysis (WGCNA), and pathways with IPA.

Results: WGCNA identified 10 co-expression clusters. The number of genes in these clusters ranged from 180 to 1611. Six clusters were significantly correlated with our clinical traits (colonic CD or ileal CD compared with controls) (Figure 1, left).

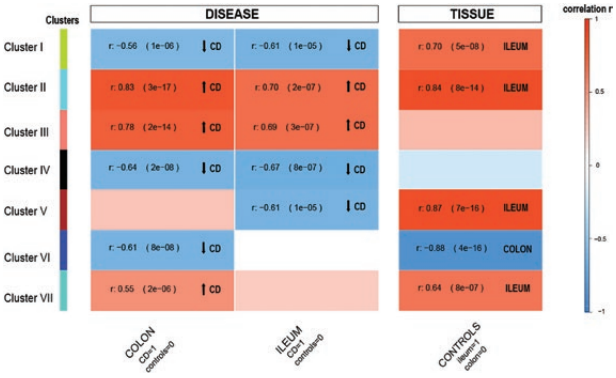

Figure 1. Co-expression cluster trait correlations: Weighted Gene Co-expression Network Analysis (WGCNA) was performed on inflamed colonic and ilea(lakpsies of newly diagnosed CD patients and normal biopsies from non-IBD controls_ First, an unsupervised approach clustered similarly expressed genes info groups (termed 'clusters?, which were then tested for correlation with traits of interest (colonic CD vs. normal colon; deal CD vs. normal ileum; control ileum vs. control colon). Only significant (correlation r N155, adip 0.05) are represented (correlation strengths r with adjusted p-values in brackets). Positive correlations represent an up-regulation of the tested trail =1, while negative correlations represent a down-regulation of the tested trait =1). CD, Crohn's disease; r, correlation

Figure 1. Co-expression cluster - trait correlations_2.

More specifically, clusters I and IV were down-regulated in both traits, while clusters II and III were up-regulated in both. Cluster V was down-regulated in ileal CD, and clusters VI and VII were, respectively, down- and up-regulated in colonic CD. IPA analyses showed that cluster I was enriched in xenobiotic metabolism, cluster II in antigen presentation, cluster III in (a)granulocyte adhesion/diapedesis, cluster IV in AMPK signalling, cluster V in melatonin degradation, cluster VI in ERK5 signalling, and cluster VII in Th1 and Th2 activation. Interestingly, clusters I, II, V and VII were up-regulated in ileal vs. colonic location in controls, meaning that in controls, these clusters are more specific to the ileum than to the colon (Fig. 1, right). Cluster VI was down-regulated in colonic vs. ileal location in controls, meaning that these clusters are more specific to colon than to ileum in controls.

Conclusions: In this study, we identified both common and distinct gene expression profiles between inflamed ileum and inflamed colon of CD patients. While some gene networks were in general disease-related (eg. (a)granulocyte adhesion/diapedesis), others reflected an up- or down-regulation of a location-specific signature in disease (eg. melatonin degradation), or even showed a loss of location-specific signatures in disease (eg. xenobiotic metabolism).

P822

Genome-wide association study (GWAS) of a Maltese inflammatory bowel disease cohort

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Background: Whilst most of the early inflammatory bowel disease (IBD) genetic studies were performed on Caucasian subjects, it is now increasingly recognised that different genes might be involved in different populations, especially from different ethnic backgrounds. Prior research in Maltese IBD patients had in fact determined that prevalence of NOD2 polymorphisms was very low, in stark contrast to IBD patients from mainland Europe. Hence, the aim of this study was to genotypically characterise a discovery cohort consisting of Maltese IBD patients.

Methods: We conducted a case–control genetic association study using a hypothesis-free approach. Genotyping was carried out on the Illumina Immunochip platform.

Results: After strict quality control 93 ulcerative colitis (UC), 160 Crohn's (CD) patients and 188 healthy controls remained. Figure 1 demonstrates no significant population stratification with evidence of several disease associated loci.

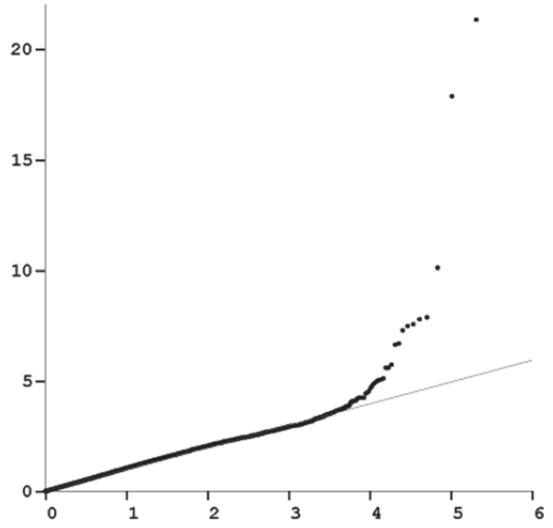

Figure 1. QQ-plot of the entire QCed IBD study population. The graph is linear, in keeping with no significant population stratification. Compelling evidence for an excess of disease associations is represented by the tail end.

Separate analyses were carried out for CD and UC and these are reported in Tables 1 and 2, respectively. Disease association with CD were larger in number and strength, compared with UC.

Chromosome:SNP	*P* value	Odds ratio (OR)	Confidence Interval L95%	U95%	Rsid	Candidate Gene	Position / Mutation
Shared							
chr1:197423973	4.2E-05	2.479	1.59	3.864	rs12089070	CRB1	Intron variant
chr10:82648824	5.4E-06	3.206	1.901	5.407	rs145303161		Deep intergenic
CD only							
chr14:69000348	1.3E-14	4.566	3.045	6.847	rs2525520	RAD51B	Intron variant
chr16:68773912	2.8E-14	4.272	2.892	6.31	rs7196661	CDH1	Intron variant
chr16:68773860	7.2E-14	4.209	2.844	6.23	rs7196495	CDH1	Intron variant
chr11:60219235	9.9E-12	4.722	2.935	7.597	rs61900760	MS4A5	Intron variant
chr2:204661621	1.6E-10	4.652	2.815	7.687	rs16840128	NPM1P33	Regulatory downstream variant
chr8:11082224	9.5E-10	3.055	2.118	4.404	rs4141829	RPL19P13	Upstream gene variant
chr1:207653395	3.6E-08	2.629	1.854	3.728	rs17617	CR2	Exonic missense variant
chr20:1642861	2.8E-06	3.526	2.028	6.131	rs6080013	SIRPG	Intron variant
chr12:58437375	1.5E-05	2.593	1.668	4.03	rs77374104		Intergenic
chr6:160699116	2E-05	2.032	1.463	2.822	rs17589858	SLC22A2	Upstream gene variant
chr6:29938025	2.7E-05	0.3932	0.2519	0.6138	rs6457116	MICD	Upstream gene variant
chr10:124740727	2.8E-05	1.975	1.433	2.722	rs9423239	PSTK	Intron variant
chr9:139366653	4.7E-05	2.397	1.561	3.68	rs117237371	SEC16A	Intron variant
chr7:31652328	6.6E-05	0.4999	0.3546	0.7048	rs38332	CCDC129	Intron variant
chr4:189338814	6.8E-05	2.1	1.452	3.037	rs10008710	LINC01060	Intron variant
chr9:13071072	7.7E-05	1.859	1.365	2.532	rs10809894		Intergenic
chr10:125275458	8.8E-05	0.4308	0.2807	0.6612	rs11248566	LOC105378531	Intron variant
chr4:66389701	8.9E-05	1.904	1.377	2.632	rs7684022	EPHA5	Intron variant
chr4:85995856	9.8E-05	1.914	1.378	2.659	rs11097031		Deep Intergenic
chr4:86130990	9.9E-05	1.917	1.379	2.665	rs7673737		Deep intergenic

Table 1. Genome-wide association results from a cohort of Maltese CD patients in descending order of significance. Two SNPs on chromosome 16 (CDH1 gene) demonstrate strong linkage disequilibrium.

Chromosome:SNP	*P* value	Odds ratio (OR)	Confidence Interval L95%	U95%	Rsid	Candidate Gene	Position / Mutation
Shared							
chr1:197423973	9.8E-07	3.225	1.986	5.236	rs12089070	CRB1	Intron variant
chr10:82648824	4.5E-06	3.571	2.02	6.314	rs145303161		Deep intergenic
UC only							
chr17:26082787	2.3E-06	0.2877	0.1678	0.4932	rs4796029	NOS2	Downstream gene variant
chr4:131941333	1.8E-05	2.183	1.524	3.127	rs10006329		Deep intergenic
chr9:88122937	2.6E-05	2.613	1.654	4.127	rs7043100	AGTPBP1	Downstream gene variant
chr9:88233659	5.8E-05	2.082	1.452	2.984	rs2814724	AGTPBP1	Intron variant
chr2:100912394	8.9E-05	2.104	1.445	3.062	rs13409545	LONRF2	Intron variant
chr8:10990816	9.8E-05	3.283	1.757	6.135	rs79710897	XKR6	Intron variant

Table 2. Genome-wide association results from a cohort of Maltese UC patients in descending order of significance. Weaker associations have emerged from this analysis possibly related to the smaller sample size.

Furthermore, whilst some loci contributed to both types of IBD, most demonstrated preferential association with either CD or UC (Figure 2).

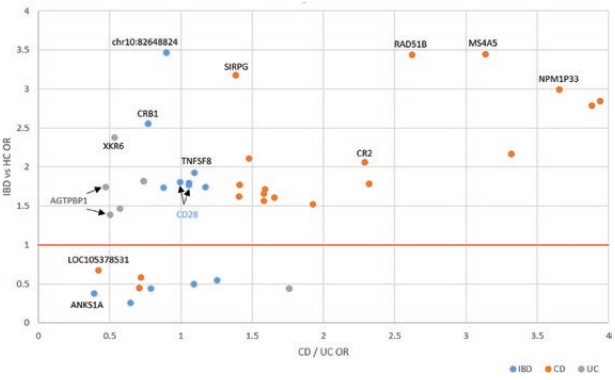

Figure 2. Odds ratio (OR) plot showing IBD-type specificity for typed SNPs. The 53 independent signals, plotted by total IBD OR and phenotype specificity (measured by the OR of CD relative to UC), have been coloured according to IBD phenotype.

Conclusions: This study is the first genotype-association study in the Maltese IBD population and despite the relatively small sample size and lack of a replication cohort we recruited approximately one fourth of the country's entire IBD population. RAD51B, CDH1, HLA-DPB2 and MS4A5 represented the most significant polymorphisms and whilst several loci in our cohort are amongst the 231 known IBD risk loci, several others have never been associated with IBD. The previously reported low-prevalence of NOD2 polymorphisms in Maltese patients has been confirmed in our cohort, further validating our findings and highlighting the importance of biomedical research in small populations and under-represented communities.

P823

Study launch: Investigating genetic and environmental factors in the faroese IBD cohort—the INCEPTION study

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Background: The Faroe Islands constitute a unique genetically and geographically isolated population located in the North Atlantic Ocean. Previous epidemiological studies have found the worldwide highest

incidence of inflammatory bowel disease (IBD) on the Faroe Islands[1] as well as high familial aggregation and influence of environmental factors on disease risk.[2] Therefore, the Faroe Islands present a unique opportunity for studying the genetic risk for IBD, environmental modifiers of disease penetrance, and their joint contribution. The INCEPTION study aims to investigate this using the Faroese IBD cohort—a nationwide cohort of all IBD patients diagnosed with ulcerative colitis, Crohn's disease, and IBD Unclassified since 1960. The foundation of the cohort is a PROGENY and a Epi-IBD database of clinical, epidemiological, and genealogical information. We now report on the initial recruitment stages and experimental pipeline for the INCEPTION study – the first clinical study involving the Faroese IBD cohort.

Methods: We are recruiting a cross-sectional cohort of ulcerative colitis patients matched with healthy controls. Samples are being collected for whole-exome-sequencing, 16S rRNA bacterial sequencing, environmental exposures and nutritional status, along with questionnaires addressing environmental factors, disease activity and food recall. All human and bacterial sequencing is being performed on-site at Research Park iNOVA, Tórshavn, Faroe Islands.

Results: We have identified 559 living ulcerative colitis patients in the Faroese IBD cohort, 327 with age of onset between 18–40. To ensure genetic associations identified during analysis are due to disease and not inter-relatedness, all identified patients and healthy controls are being sorted to exclude first degree relatives. Following sorting, 158 patients were sent an invitation to participate in the study. Since the project launch meeting on October 24, 2018, informed consent has been received for 32 patients and over 300 matched-control individuals have been identified through the FarGen project. Blood samples from 32 patients and 300 controls are currently in the routine whole-exome sequencing pipeline. DNA from 17 stool samples has been extracted and is biobanked awaiting 16S rRNA library prep and sequencing. Ethical permission to recruit prospectively has been granted. We are now working out the logistics of recruitment and collection of biopsies at the National Hospital of the Faroe Islands.

Conclusions: The first project to focus on the genetic and environmental factors driving the high incidence of IBD with ulcerative colitis as the prominent disease phenotype within the Faroese population has been successfully launched.

References

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2. Hammer T, Lophaven SN, Nielsen KR, *et al.* Inflammatory bowel diseases in Faroese-born Danish residents and their offspring: further evidence of the dominant role of environmental factors in IBD development. *Aliment Pharmacol Ther* 2017.

P824

Phenotypic and genetic markers of disease severity in a Maltese IBD cohort

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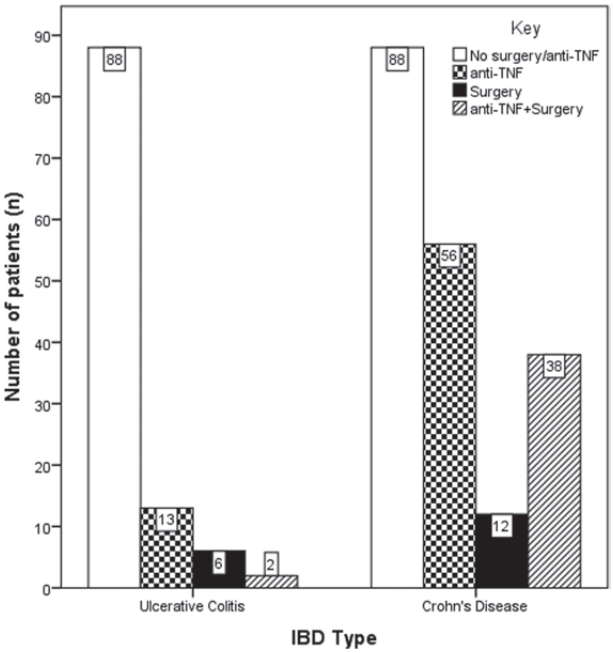
Background: Whilst most inflammatory bowel disease (IBD) treatment algorithms depend on disease severity classification, no formal validated definitions exist on what constitutes mild, moderate and severe ulcerative colitis (UC) and Crohn's disease (CD). Furthermore, the genetic architecture of disease severity may be distinct from that of disease susceptibility.

Methods: IBD patients were compared with eachother on the basis of disease severity. For the purpose of this study severe IBD was defined as current or previous use of anti-TNF agents or surgery. Genotyping was carried out on the Illumina Immunochip platform. Patients were characterised using the Montreal classification.

Results: Using our definition for disease severity resulted in more CD patients being classified as severe.



Bar graph showing proportion of non-severe (white bars) to severe patients in both UC and CD.

Tables 1 and 2 summarise disease characteristics for UC (n = 109) and CD (n = 194) patients in our cohort. Mean illness durations for UC and CD were 11.9 years and 11.1 years.

		% Non-severe (n)	% Severe (n)	Statistic	*P* value
Gender	Male	51.1% (45)	42.9% (9)	χ2	.628
	Female	48.9% (43)	57.1% (12)		
Age (Montreal)	<17	6.8% (6)	9.5% (2)		
	17-40	58.0% (51)	61.9% (13)	χ2	.804
	>40	35.2% (31)	28.6% (6)		
Location (Montreal)	Proctitis	42.0% (37)	4.8% (1)		
	Left-sided	29.5% (26)	23.8% (5)	χ2	<.001
	Pancolitis	28.4% (25)	71.4% (15)		
Family History		15.9% (14)	9.5% (2)	χ2	.732
Hospitalisation		20.5% (18)	95.2% (20)	χ2	<.001
Inflammatory Markers		54.5% (48)	95.2% (20)	χ2	<.001
Extra-Inestinal Manifestations		9.1% (8)	19.0% (4)	χ2	.241
Smoking	Ex- / Current	21.6% (19)	28.6% (6)	χ2	.565
	Non-	78.4% (69)	71.4% (15)		
Thiopurines (AZA, 6MP)	Current	33.0% (29)	52.4% (11)		
	Stopped	5.7% (5)	23.8% (5)	χ2	.002
	Never	61.4% (54)	23.8% (5)		
Steroid use	Multiple Courses	37.5% (33)	71.4% (15)		
	On diagnosis	28.4% (25)	23.8% (5)	χ2	.008
	Never	34.1% (30)	4.8% (1)		

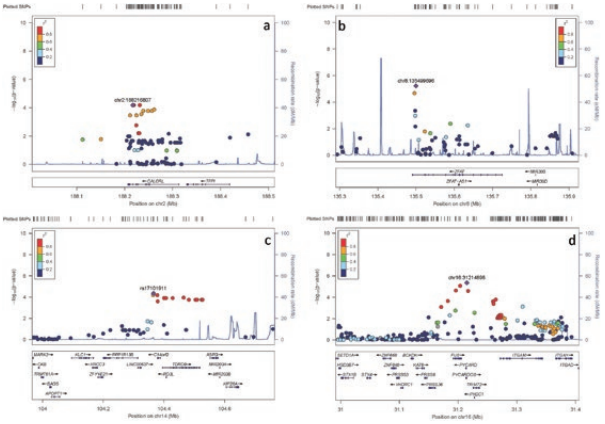
Table 1. UC clinical characteristics and associations with disease severity.

		% Non-severe (n)	% Severe (n)	Statistic	*P* value
Gender	Male	46.6% (41)	53.4% (56)	χ2	.471
	Female	53.4% (47)	47.2% (50)		
Age (Montreal)	A1	2.3% (2)	18.9% (20)		
	A2	68.2% (60)	56.6% (60)	χ2	.001
	A3	29.5% (26)	24.5% (26)		
Location (Montreal)	L1	21.6% (19)	18.9% (20)		
	L2	46.6% (41)	20.8% (22)	χ2	<.001
	L3	31.8% (28)	60.4% (64)		
Behaviour (Montreal)	B1	88.6% (78)	45.3% (48)		
	B2	9.1% (8)	34.0% (36)	χ2	<.001
	B3	2.3% (2)	20.8% (22)		
Perianal disease		1.1% (1)	7.5% (8)	χ2	.042
Upper GI disease		2.3% (2)	6.7% (7)	χ2	.185
Smoking	Current	13.8% (12)	21.3% (20)		
	Ex-	6.9% (6)	7.4% (7)	χ2	.399
	Non-	79.3% (69)	71.3% (67)		
Immunosuppressants (AZA, 6-MP, MTX)	Current	58.0% (51)	67.9% (72)		
	Stopped	0.0% (0)	13.2% (14)	χ2	<.001
	Never	42.0% (37)	18.9% (20)		

Table 2. CD clinical characteristics and associations with disease severity.

Amongst these variables only disease duration (OR = 1.1) and hospitalisation (OR = 13) in UC and young age at diagnosis (OR = 1.1), disease behaviour (B2 OR = 6; B3 OR = 22) and location (L3 OR = 2) in CD remained significant after performing binary logistic regression.

Whilst several SNPs reached borderline association significance, 4 separate loci on chromosomes 2, 8, 14 and 16 are of special interest since they exhibit strong linkage disequilibrium between each other. Furthermore, these loci were different from the IBD susceptibility loci that emerged from another case–control association analysis comparing the same IBD patients to healthy controls.



Regional association plot for (a) CALCRL, (b) ZFAT, (c) C14orf2 and (d) PYCARD / FUS. 8d shows the strong linkage that exists between our typed SNPs and several polymorphisms occurring in integrin genes ITGAM, ITGAX and ITGAD.

Conclusions: IBD severity and susceptibility seem to be under the influence of different genetic factors and biological pathways. Whilst history of hospitalisation was the strongest determinant for severe UC, all domains of the Montreal classification contributed to CD severity. Further research on this subject requires international collaboration and agreement on what defines severe IBD.

P825

Low-prevalence of NOD2 polymorphisms in a Maltese IBD cohort

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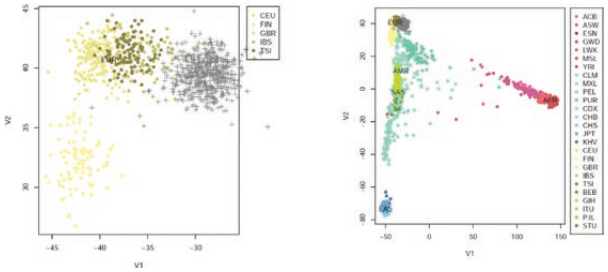
Background: NOD2 was the first IBD susceptibility gene to be discovered, back in 2001. Despite the discovery of many other susceptibility loci, NOD2 remains of interest as it is one of the few risk loci that is not shared between Ulcerative colitis (UC) and Crohn's disease (CD), as it only contributes to the latter. Whilst NOD2 polymorphisms are very common in European CD patients, prior study on 83 Maltese CD patients showed low prevalence of the 3 main NOD2 polymorphisms: p.Arg702Trp, p.Gly908Arg and p.Leu1007fsinsC.

Methods: We conducted a case–control discovery genetic association study using the Illumina Immunochip (v2) as a genotyping platform. 517 individuals were recruited, however, after strict quality control (QC), 160 CD, 93 UC and 188 healthy controls (HC) remained.

Results: Gender distribution was approximately equal between all groups. Table 1 is a summary of baseline characteristics and demographic data of our study cohort.

		UC	CD	Controls
Gender	Male (%)	54 (49.5%)	97 (50.0%)	108 (50.0%)
	Female (%)	55 (50.5%)	97 (50.0%)	108 (50.0%)
Mean age	(years)	47.4 ± 3.0	43.5 ± 2.4	52.4 ± 2.6

Baseline characteristics of case and control subjects.



Principal component plot showing clustering of Maltese individuals (crosses) close to other European populations.

This was the first genome-wide association study ever conducted in a Maltese population. Principal component analysis shows clustering of Maltese individuals (crosses) close to other European ethnicities from the 1000 genomes project, the TSI (Toscani from Italy) group being closest.

Table 1 summarises minor allele frequencies (MAF) for the 3 common NOD2 polymorphisms in our population.

Conclusions: Prevalence of NOD2 polymorphisms was similar between CD, UC and HC individuals hence it is unlikely for this gene to be contributing significantly towards IBD susceptibility in our population. Despite the relatively small sample size, we have validated findings from prior research that have used low-throughput genotyping techniques. Furthermore,the studied population represents approximately one fourth of the entire current Maltese IBD population. Whilst low prevalence of NOD2 polymorphisms has been documented in other populations.[1] To the best our knowledge this is the first such finding in a population demonstrating European ancestry.

Reference

1. Liu JZ *et al*. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat Genet* 2015;47:979–986.

Abstract P825

Table 2. Allele frequencies of common NOD2 polymorphisms in Maltese patients. *Rs2066845/Gly908Arg polymorphism not included on the Illumina Immunochip.

	p.Arg702Trp	(Homo / Hetero)	p.Gly908Arg	(Homo / Hetero)	p.Leu1007fsinsC	(Homo / Hetero)
	Cases	Controls	Cases	Controls	Cases	Controls
Immunochip results (CD)	0 / 0.07	0 / 0.08	NA*	NA*	0 / 0.02	0 / 0.02
Immunochip results (UC)	0 / 0.07		NA*		0 / 0	
P. Ellul et al. (CD only)	0.024 / 0.012	NA	0.012 / 0.024	NA	0.024 / 0.024	NA

P826

Unexplained higher frequency of mutant thiopurine S-methyltransferase genotypes in inflammatory bowel disease patients of Latvia population.

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Background: The most common variant alleles, TPMT*2, TPMT*3A, and TPMT*3C, account for 95% of TPMT deficiency. This leads to an accumulation of higher levels of cytotoxic thiopurine nucleotides in patients carrying defective TPMT alleles and subsequent severe haematological toxicity with standard doses of the parent drugs (Robert D. Nerenz, 2018). TPMT single-nucleotide polymorphisms can prospectively identify patients at higher risk for thiopurines toxicity [Paugh et al., 2011]. The frequencies of TPMT polymorphisms in the Europe population are in average 4% (*3A), 0.4% (*3C) and 0.2% (*2). TPMT*1/*3B allele is not common to be found in Europe population and reaches not more than 0.3% [Milek et al., 2006; Schaeffeler et al., 2004].

Methods: Blood samples were collected from IBD patients in Genome Database of the Latvia Population. TPMT genotyping with real-time qPCR (TaqMan Drug Metabolism Genotyping Assays) for the detection of rs1800462, rs1800460, rs1142345, respectively, TPMT*2, *3B, *3C polymorphisms, was used. Three TPMT alleles were obtained in 244 adults, 51% (n = 124) women and 59% (n = 120) men. TPMT*2, *3A, *3B, *3C polymorphisms found we have checked and approved with RFLP (restriction fragment length polymorphism) method. Categorical data were analysed by the Pearson's χ^2 test; Fisher exact test was used if the number in any expected cell < 5 (SPSS®23).

Results: Prospective study includes 244 adults, 78% (n = 190) of patients with ulcerative colitis, median age 41 years (Q1-Q3=29.8–54.3) and 22% (n = 54) of patients with Crohn's disease, median age 43 years (Q1-Q3=30.8–55.0), p = 0.5. 93.9% were wild-type homozygous TPMT*1/*1 genotype, 6.1% heterozygous and had polymorphisms and 4.9% of them were ulcerative colitis patients. The most frequent polymorphisms were: 5.3% TPMT*1/*3A genotype, this allele contains two variants TPMT*3B and TPMT*3C. 0.4% patients had TPMT*1/*3C genotype and 0.4% had TPMT*1/*2 genotype. In our study, no carriers of the TPMT*3B polymorphism were identified. No patients were homozygous for any mutation.

Conclusions: The homozygous wild-type TPMT*1/*1 genotype was the most frequent genotype in both groups of IBD patients. Distributions of TPMT genotype and allele frequency in Latvian population are different from Europe population. We have identified TPMT*3A as the most prevalent polymorphisms in Latvian population, but also the exceptional presence of TPMT*2 polymorphism and the absence of TPMT*3B polymorphism. TPMT*2, *3A, *3B, *3C polymorphisms were approved with both real-time qPCR and RFLP methods.

P827

Up-regulation of IL17-related pathways in affected colon from ulcerative colitis compared with Crohn's disease

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Background: Crohn's disease (CD) and ulcerative colitis (UC) can both affect the large intestine but harbour key differences in the type of inflammation. The underlying molecular differences might be important for guidance of therapeutic decisions. We aimed to elucidate the molecular networks in inflamed colonic biopsies from newly diagnosed CD and UC patients.

Methods: Patients naïve for biologicals and immunosuppressives, and without previous IBD-related surgery were prospectively included within 6 months after diagnosis, across three Belgian IBD centres (PANTHER study B322201627472/S57662). We collected serum and inflamed colonic biopsies from 52 patients: 31 CD (median age 25 (16–63) years; 65% male) and 21 UC (age 29 (17–77) years; 43% male). All biopsies underwent single-end RNA sequencing. Differential gene expression (fold change>2, adj. p < 0.05) and co-expression networks (adj. $p \leq 0.1$) were analysed using DESeq2 and WGCNA (R). A panel of 91 serological inflammatory proteins (OLINK) was tested for correlation with co-expression clusters.

Results: We found 336 (223 up, 113 down) differentially expressed genes between UC and CD, and 21 co-expression clusters. Four clusters were up-regulated in UC, 3 in CD, the others did not show a difference between CD and UC (Figure 1).

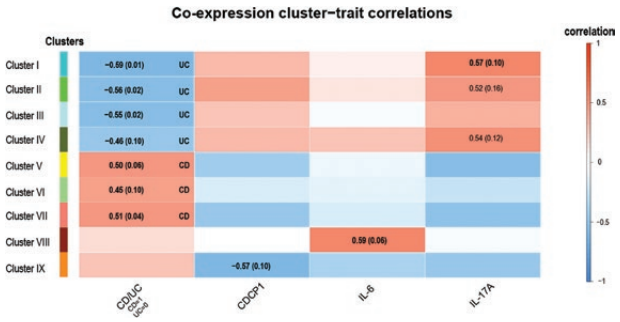

Figure 1: Co-expression cluster - trait correlations: Weighted Gene Co-expression Network Analysis (WGCNA) was performed on inflamed colonic biopsies of newly diagnosed CD and UC patients. First, an unsupervised approach clustered similarly expressed genes into groups (termed 'clusters), which were then tested for correlation with trails of interest (CO/UC, normalised protein values of serological inflammatory markers having passed QC ($n = 85$)). Only significant (adjusted $p = 50$. i) or borderline significant correlations are represented (correlation strengths r with adjusted p-values in brackets). CO, Crohn's disease; UC, ulcerative colitis.

Figure 1_Co-expression cluster - trait correlations.

Genes within UC-up-regulated clusters (I to IV) were mainly involved in (a)granulocyte adhesion/diapedesis, and in the role of IL-17 in psoriasis. CD-up-regulated clusters were enriched for mitochondrial dysfunction and sirtuin signalling. Three clusters significantly correlated with serological marker levels: IL-6 with CD/UC cluster VIII, CDCP1 with CD/UC cluster IX, and IL-17A with UC cluster I (Figure 1). The latter cluster was enriched for protein ubiquitination, known to be regulated by IL-17A. Of note, IL-17A serum levels were higher in UC than in CD ($p < 0.001$), while IL-6 and CDCP1 were similar. Moreover, IL-17A tended to positively correlate with UC clusters II and III (Figure 1), of which cluster II contained IL-17A and IL-23A, both significantly increased in UC compared with CD.

Conclusions: In treatment-naïve newly diagnosed CD and UC patients, we found both common and distinct gene expression profiles, such as an up-regulation of IL-17-related pathways specifically in UC. Higher expression of these IL-17 pathways at mucosal level correlated with higher serological IL-17A. These differences potentially affect novel drug target identification and therapeutic decision-making, and emphasise the need for additional studies on the role and potential blockade of IL-23/IL-17 pathways in UC.

P828

Network analysis of GWAS reveals differential top-ranked risk loci and proteins associated with the inflammatory bowel disease phenotypes

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Background: Crohn's disease (CD) and Ulcerative colitis (UC) are the two main entities of inflammatory bowel disease (IBD). Genome-wide association studies (GWAS) identified more than 200 risk loci in populations of predominantly European ancestry.

Methods: Here we report the GWAS study of IBD data from an extended cohort of 573 Greek IBD patients (364 C and 209 UC) and 445 controls. We implicate 89 loci in IBD risk. Additionally, through pathway-based analysis we identified distinct functional pathways associated with each of the two IBD forms and their phenotypes.

Results: For the majority of the IBD susceptibility loci, the direction and magnitude of effect are consistent in IBD cohorts. Pathway analysis to detect functional interactions was performed using the KEGG and Reactome databases via the Enrichr gene list enrichment analysis tool. Protein associations were subsequently analysed using the STRING functional enrichment association network platform, to create extended protein networks enriched with additions from various experimental, bibliographical and gene interaction databases. These phenotype-specific functional interaction networks, through centrality analysis, reveal well known IBD-related genes and their interactors.

Conclusions: We introduce a novel approach that ranks the associated proteins and signalling pathways by disease implication and provides new insights into IBD's molecular background, highlighting targets of potential diagnostic and therapeutic value.

Microbiology

P829

Mucosal 5-ASA concentration is associated with changes in mucosal bacterial microbiome diversity and composition in patients with quiescent ulcerative colitis

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Background: 5-aminosalicylic acid (5-ASA) is the mainstay of ulcerative colitis (UC) treatment and acts locally in the colonic mucosa by a variety of purposed mechanisms. Recent in vitro studies suggest that 5-ASA may affect intestinal bacteria's ability to adhere to and infiltrate to the intestinal mucosa, which may be important in the pathogenesis of UC.

Methods: Mucosal 5-ASA concentration and bacterial microbiome in colon biopsies and faeces were analysed in patients with quiescent UC using mesalazine monotherapy 4.0–4.8 g/day. 5-ASA concentrations were measured in mucosal biopsies (sampled 10, 25 and 40 cm from the anal verge) by ultra-high-performance liquid chromatography. Bacterial microbiome was sequenced from one faecal sample and one biopsy sample (taken 25 cm from the anal verge) by 16S rRNA sequencing on Illumina MiSeq platform. Disease activity

was assessed with Mayo score, Geboes histological score and faecal calprotectin. Regression analyses were performed to relate 5-ASA concentrations to bacterial abundances.
Results: Forty-two patients with UC were included. The disease activity was low with a median (IQR) total Mayo score of 1.0 (2.0), Geboes score of 1.1 (1.1) and a calprotectin concentration of 66 (211) mg/kg. Geometric mean (95% CI) 5-ASA mucosal concentration was 1.43 ng/mg (0.84–2.44). Mucosal 5-ASA concentration was positively associated with mucosal bacterial diversity ($p = 0.0005$), but not with faecal bacterial diversity ($p = 0.66$). The mucosal 5-ASA concentration was significantly associated with mucosal bacterial abundance on all taxonomic levels; high 5-ASA concentrations were associated with reduced abundance of Proteobacteria ($p = 1.2{\cdot}10{-}15$) and increased abundance of Firmicutes ($2.6{\cdot}10{-}6$) and Bacteroidetes ($p = 3.1{\cdot}10{-}4$) on phylum-level. Furthermore, mucosal 5-ASA concentration was associated with abundances of 16 bacterial families and 19 bacterial genera; positive associations between mucosal 5-ASA concentration and Lachnospiraceae and Ruminococcaceae families, Faecalibacterium, Roseburia and Bifidobacterium genera and *F. prausnitzii* species were found. Mucosal 5-ASA concentration was negatively associated with the faecal abundance of Prevotella and Sutterella genera, for the former the association was also seen on family, order and class level. Mucosal 5-ASA concentration was not associated with disease activity.
Conclusions: For the first time, we demonstrate that a high mucosal 5-ASA concentration is associated with high mucosal bacterial diversity and a mucosal bacterial composition which is perceived favourable in UC. 5-ASA may have beneficial effects on the mucosal microbiome, which in turn may affect disease course.

P830

Adherent-invasive *Escherichia coli* in inflammatory bowel disease impacts faecal microbiota transplantation efficacy by hindering engraftment of beneficial bacteria

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Background: Adherent invasive Escherichia Coli (AIEC) invades gut epithelium and colonise the mucosa of patients with Crohn's disease (CD). Despite increasing use of faecal microbiota transplantation (FMT) to treat inflammatory bowel disease (IBD), mechanisms and factors affecting treatment outcome is unclear. This study aims to assess whether AIEC affects efficacy of FMT and explore underlying mechanisms of FMT success.
Methods: C57BL/6 wild-type mice were colonised with an AIEC strain (AIEC62d; 109 CFU) recently isolated from the mucosa of a patient with Crohn's disease in Hong Kong or non-pathogenic E. coli strain (K12) ($n = 24$/group). After 7 days of 2% DSS treatment, we switched to clean drinking water and gavaged these mice with faecal solution from healthy mice for three consecutive days. After a 7-day recovery period, we sacrificed all mice and assessed the length and histology score of the colon. Faecal AIEC load (CFU/mg) were quantified by plating on LB agar plate supplemented with 100 μg/ml ampicillin. Fluorescence in situ hybridisation (FISH) was performed to locate AIEC in the mouse gut. Colonic myeloperoxidase (MPO) and faecal lipocalin-2 (Lcn-2) (on going) were measured to assess the severity of colitis. Faeces were collected before and after FMT for 16s rRNA sequencing to analyse gut microbiota.
Results: FMT transiently reduced faecal AIEC load compared with the no FMT group, but faecal AIEC load increased again at the end of FMT treatment and reached the same level as the no FMT group by Day 14. FISH staining showed remaining AIEC inside the epithelial cells of mouse colon after FMT treatment. After FMT, K12-colonised mice, but not AIEC-infected mice, showed ameliorated colitis, as indicated by body weight gain, elongated colon, and improved colonic histology. Alpha diversity (Shannon diversity index) in AIEC-infected mice was significantly lower than K12-colonised mice before FMT. FMT increased microbial diversity in K12-colonised mice but not in AIEC-infected mice. The proportion of donor derived microbes in K12-colonised mice was significantly larger than in AIEC-infected mice. Several taxa including Faecalibacterium prausnitzii, Akkermansia muciniphila, and the genus Allobaculum (related to health) were successfully engrafted in K12-colonised mice but not in AIEC-infected mice.
Conclusions: This is the first study reporting that the presence of a microorganism (e.g. AIEC) by itself was sufficient to compromise the efficacy of FMT by hindering the engraftment of beneficial bacteria, leading to incomplete recovery of intestinal inflammation. Future FMT practice in IBD should consider patient stratification based on AIEC presence and their effects on FMT outcomes.

P831

Gut mucosal virome alterations and loss of viral-bacterial interactions in ulcerative colitis

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Background: Ulcerative colitis (UC) is associated with gut microbiota dysbiosis. Although alterations in faecal bacteriome and virome have been reported, little is known of the composition and function of the mucosa virome in UC. This is the first study that aims to delineate the configuration and function of mucosal virome in human health and UC.
Methods: We performed ultra-deep metagenomic sequencing of virus-like particle preparations and bacterial 16S rRNA sequencing on rectal tissues from 167 Chinese subjects (63 UC, 48 controls from Hong Kong; 20 UC, 20 controls from Beijing). We assessed mucosa virome and bacteriome alterations in UC and correlated alterations with patient meta-data. We also extrapolated mucosa virome enterotypes.
Results: In UC, there was an expansion of mucosal viruses, particularly Caudovirales bacteriophages, and a decrease in mucosa viral diversity, richness and evenness compared with healthy controls. Altered mucosa virome correlated with intestinal inflammation. Inter-individual dissimilarity between mucosal viromes was higher in UC than controls. Escherichia phage and Enterobacteria phage were more abundant in the mucosa of UC than controls (FDR adjusted p-value = 1.89e–18 and 4.50e–16, respectively). We clustered the mucosal viral communities of all study subjects into two enterotypes. Enterotype 2 viromes, predominated by UC subjects, displayed a significant loss of viral species. UC patients showed prominent

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abrogation of viral functions, whereas viral functions associated with bacterial fitness and pathogenicity were markedly enriched in UC mucosa. Intensive Trans-kingdom correlation between mucosa viruses and bacteria were observed in controls but these interactions were significantly lost in UC mucosa

Conclusions: UC is characterised by mucosal virobiota dysbiosis with functional distortion. Enrichment of Caudovirales bacteriophages, increased phage/bacteria virulence functions, and loss of viral-bacterial interactions in UC mucosa suggest that dysbiotic mucosal viruses and bacteria may play an important role in UC pathogenesis.

P832

EEN and CDED produce broadly similar taxonomic changes during the induction of remission, but many taxa rebound upon the transition from EEN back to free diet

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Background: Exclusive enteral nutrition (EEN; a liquid formula diet) is the treatment of choice in mild-to-moderate paediatric Crohn's disease (CD). The Crohn's disease exclusion diet [CDED; a whole food diet supplemented with partial enteral nutrition (PEN)] has been proposed as an alternative, more tolerable induction therapy. In both therapies it is hypothesised that through changes in dietary components the intestinal barrier integrity and microbiome community is affected and these lead to remission.

Methods: A 12-week study compared remission rates and tolerance of diet in children with mild-to-moderate CD using either EEN or CDED as a first-line induction therapy. CDED patients received 6 weeks of CDED +50% PEN followed by 6 weeks of CDED + 25% PEN. EEN patients received 6 weeks of EEN followed by 6 weeks of free diet + 25% PEN. Patients collected stool samples at the start (BL), Weeks 6 (W6) and Week 12 (W12) of therapy. 16S rRNA gene (V4V5) and shotgun metagenome sequences were conducted on stool samples. Changes in the microbiome at BL, W6 and W12 for EEN and CDED were analysed using Kruskal–Wallis, linear discriminant analysis and Bayesian methods to examine community changes.

Results: DNA sequences from stool samples were collected for 70 patients, 38 CDED patients (25 at all 3 times points) and 32 EEN patients (21 at all 3 times points). At W12, 21 of 25 CDED patients were in remission. Microbiome comparison of BL, W6 and W12 showed significant ($p < 0.05$) decreases in Haemophilus, Veillonella, Bifidobacterium, Prevotella, and Anaerostipes, and increases in Oscillibacter, and Roseburia. In EEN patients at W12, 14 of 21 were in remission. A comparison across timepoints in EEN identified significant ($p < 0.05$) differences in many of the same taxa identified in CDED. In addition, Lachnospira decreased and Subdoligranulum, Blautia, Ruminococcus and Erysipelotrichaceae increased. Although similar taxa were identified, the pattern between the two groups differed. CDED continued to change between W6 and W12 while EEN generally rebounded to pre-treatment levels at W12. In addition, linear discriminate analyses between W6 and W12 in EEN appear to show a return in W12 of some taxa seen pre-treatment. Finally, in CDED there were on average increases in diversity over treatment, while EEN saw on average decreases in diversity at W6, and increases at W12.

Conclusions: Both EEN and CDED resulted in remission and showed similar taxa changes during treatment. An examination of the taxonomic trends in the EEN study however, suggests that after the switch from EEN in W6 to a free diet + PEN, there is a rebound to a more pre-treatment distribution of taxa despite the use of PEN.

P833

Efficacy of vaccination against hepatitis A in inflammatory bowel disease patients: a single-centre cohort study

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Background: Inflammatory bowel disease (IBD) patients are vulnerable to viral infections. Cases of hepatitis A infection with a fatal outcome in immunocompromised patients have been reported. The aim of the present study was to investigate the efficacy of vaccination against hepatitis A virus (HAV) in a single-centre cohort of IBD patients.

Methods: Consecutive IBD patients were screened for HAV status and those not immunised with an age < 60 years received the respective vaccine (Havrix, GlaxoSmithKline®, Brentford, UK, 1 ml, two doses, one at baseline and the second 6–12 months after the first dose). Immune response was defined as a positive anti-HAV IgG measured at least 3 months after the second dose. Anti-HAV IgG was also measured randomly 3 months after the first dose in a subgroup of patients. The impact on immune response of certain epidemiological and disease specific characteristics as well as of treatment was also investigated.

Results: 356 IBD patients (females: 40.2%, Crohn's disease [CD]: 52.2%, median [IQR] age at diagnosis: 42.2 [27.8–56.2] and age: 50.0 [33.5–63.1] and disease duration: 2.7 [0.4–9.1] years at study entry) have been prospectively examined as of January 2010. In total, 115/356 (32.3%) were eligible for anti-HAV vaccination with the rest being either actively or passively immunised before IBD diagnosis. So far, 82/90 (90.1%) have adequately responded to vaccination. Interestingly, anti-HAV IgG turned out positive in 12/21 patients (57.1%) already after the first dose. Ulcerative colitis was associated with a greater success of anti-HAV vaccination (OR: 1.8 [1.5–2.2], $p = 0.01$, all patients with a negative post-vaccination anti-HAV IgG titre had CD). Patients receiving anti-TNFα agents responded less to vaccination (OR: 0.04 [0.00–0.24], $p < 0.0001$) and those not receiving any kind of immunosuppressive therapy responded better (OR: 9.7 [1.1–81.3], $p = 0.015$). No other association was found with gender, BMI, smoking status, disease classification and activity, anaemia and CRP regarding development of an adequate response to vaccination.

Conclusions: Two thirds of our IBD patients are already immunised against HAV before diagnosis. Response rate to vaccination

is strikingly high in the rest and especially in UC patients. One dose can provoke immunisation, a critical condition in selected cases where rapid introduction of immunosuppressant's is warranted. Anti-TNFα agents seem to influence vaccination success rate. These results need to be verified in other cohorts.

P834

Proteus is a key candidate in the pathogenesis of Crohn's disease: mucosa, stool genomics and functional analysis: the ENIGMA study

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Background: Proteus, Gram-negative facultative anaerobic bacilli, has recently been identified as a key genus in Crohn's disease (CD) recurrence after intestinal resection. In this study, we investigated the role of Proteus as a gut pathogen in mediating inflammation in Crohn's disease.
Methods: 54 pairs of faecal samples and 80 colonic samples (61 CD patients; 19 healthy controls) were collected. The abundance of Proteus were determined by quantitative PCR. Proteus was isolated from faeces and biopsies of CD patients by selection culture in conditional agar and confirmed by Proteus specific target sequencing. To study effects of isolated Proteus, we established an in vitro microbe-enterocyte co-culture system by using two normal epithelial cells INT407, NCM460 and two CRC cell lines CaCo2 and HT29. Pathogenic function of Proteus was determined by in vivo mouse models and in vitro cell assays. Bacterial invasion ability was measured by fluorescence staining and confocal microscopy. Intracellular gene expression profiles and regulated pathways in normal cells treated with or without Proteus were analysed by RNA seq and KEGG analysis.
Results: We confirmed the presence of Proteus in the gut and stool. The prevalence of Proteus in faecal samples was higher in CD patients compared with healthy controls ($p < 0.05$). Levels of Proteus were significantly increased in CD biopsies compared with control tissue. Amongst 24 Proteus-monoclones isolated from faeces and biopsy of CD patients, all of them belonged to members of *P. mirabilis* lineages. Proteus gavaged mice showed a shortened colon length compared with mice treated with *E. coli* 1655 (5.97 cm vs. 7.15 cm; $p < 0.05$). Mice depleted of bacteria and exposed to Proteus and DSS showed significantly higher severity of inflammation on HE staining. Compared with the cells co-cultured with *E. coli* 1655 or cultured in medium only (showed normal phenomenon), 70–80% of cells co-cultured with Proteus were unhealthy (rounded and detached) or dead. Increased necrotic cells were found in four cell lines co-cultured with Proteus due to bacterial invasion. Moreover, Proteus stimulated the production of pro-inflammatory cytokines including IL-18 ($p < 0.001$) and IL-1α ($p < 0.01$) in co-cultured cells (INT407 and NCM460). In keeping with this, Proteus induced key pro-inflammatory pathways including NOD-like receptor signalling ($p < 0.001$), Jak-STAT signalling ($p < 0.01$) and MAPK signalling pathways ($p < 0.01$) identified by RNA sequencing.
Conclusions: Our results show *P. mirabilis*, a urease producing organism in the gut, is associated with CD and can induce inflammation in cell lines and animal models of colitis. We contend that *P. mirabilis* and related species may act as a pathobiont and thereby play a critical role in the pathogenesis of CD.

P835

Characterisation of fungal microbiota in a Norwegian IBD cohort

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Background: While the role of bacterial microbiota in disease has been widely studied over the last years, the exact role of the mycobiome in IBD remains poorly understood. A few studies show changes in fungal microbiota associated with IBD status. However, there is little consensus regarding a definite fungal microbiome in IBD. The aim of this study was to characterise the fungal microbiota of patients, and to evaluate association between fungal abundance and patient characteristics.
Methods: The present study presents sequencing of the faecal fungi of 111 individuals (active CD (aCD = 22), active UC (aUC = 20), inactive CD (iCD = 15), inactive UC (iUC = 32), healthy controls (F = 22)). Patient characteristics (age, sex, medication, faecal calprotectin (fCalpro), faecal Neutrophil gelatinase-associated lipocalin (fNGAL), disease history) was available for all included individuals. ITS sequencing was done on amplicons targeting the ITS1 region of fungal DNA. Sequencing was done on a Illumina MiSeq sequencer. Filtered FASTQ sequencing data were aligned with the Targeted Host-associated Fungi (THF) database using Blast in QIIME. Chosen OTUs were compiled into six taxonomic ranks (Phylum-Species). Data analysis was performed in R, using tools of the phyloseq and deSeq2-packages.
Results: In contrast to other studies of fungal microbiota, we found no significant differences in either species or genus richness, diversity or evenness between IBD subgroups and healthy controls. There were several differences between sample groups on both genus and species level. Figure 1 shows top 10 differentially abundant genera (a) and species (b) for the contrast active IBD vs. healthy controls. *Candida Albicans* was significantly increased in aUC (logFC 5.4, adj. pVal < 0.001) but not in aCD (logFC 1.84, adj. pVal 0.2), while *Cryptococcus tephrensis* was significantly decreased in aCD (logFC -4.76, adj. pVal < 0.001) but not in aUC (logFC –0.96, adj. pVal 0.52). High levels of fNGAL was associated with increased abundance of the *Aspergillus* (adj. pVal < 0.001) genus, and decrease in *Clavispora* (adj. pVal < 0.001).

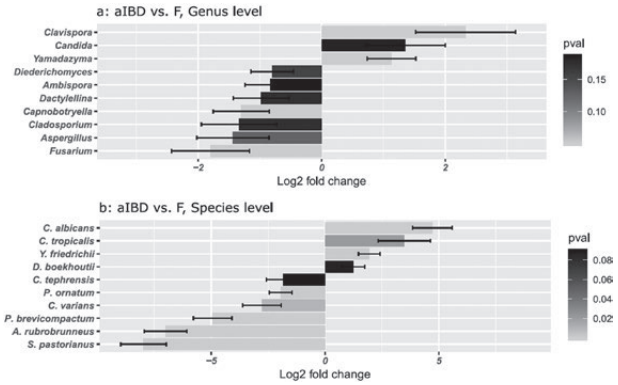

Figure 1. Top 10 genera (a) and species (b) for the contrast active IBD (aIBD) vs. healthy controls (F). Bars show mean log2 fold relative difference in abundance with standard error of the mean. p-values are adjusted for multiple comparison.

Conclusions: With its strictly controlled patient cohort and broad patient characteristics, our analysis serves as a rigorous addition to the understanding of IBD-associated changes in the fungal microbiome. We identify several novel changes in species and genera abundance associated with patient subgroups, disease activity and clinical parameters, further enhancing our understanding of the fungal microbiome in IBD.

P836

The predictive role of gut microbiota in treatment response to vedolizumab and ustekinumab in inflammatory bowel disease

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Background: The faecal microbiota is evolving as a useful predictive and diagnostic biomarker for IBD in the development of personalised medicine. We here investigated whether the faecal microbiota aids in predicting therapeutic response to vedolizumab (VDZ) or ustekinumab (UST) in Crohn's disease (CD) and ulcerative colitis (UC).

Methods: Faecal samples of 116 patients with IBD, treated with UST (n = 68 CD) or VDZ (n = 30 for CD, 18 for UC) with endoscopic active disease were collected prior to biological therapy. Quantitative microbiota phylogenetic profiling was conducted by combining 16S rRNA gene sequencing and microbial loads determination by flow cytometry.

Endoscopic response in the UST cohort was defined as a 50% decrease in SES-CD score at Week 24. Remission in the VDZ cohort was defined as an endoscopic Mayo-subscore of ≤1 at Week 14 in UC and absence of endoscopic ulcera at Week 24 in CD.

Multi-variate hyperbolic tangent neural network models (JMP) were trained to predict treatment response based on features describing the baseline faecal microbiota, clinical data (age, sex, BMI, diagnosis, disease duration and smoking) and biomarkers (CRP, albumin, haemoglobin and faecal calprotectin) or the combination. Microbiota features comprised enterotypes and quantitative abundances of taxa significantly (p < 0.1) correlated with outcome. The cohorts were split into training (2/3) and validation sets (1/3).

Results: Ten (14.7%) UST and 27 (56.2%) VDZ patients showed endoscopic response (UST) or remission (VDZ). 13 genera correlated with treatment outcome in the VDZ cohort and 14 in the UST cohort, with 3 overlapping. Neural networks were trained to predict treatment response in VDZ and UST (Figure 1) , based on clinical features and biomarkers, microbiota features, or both.

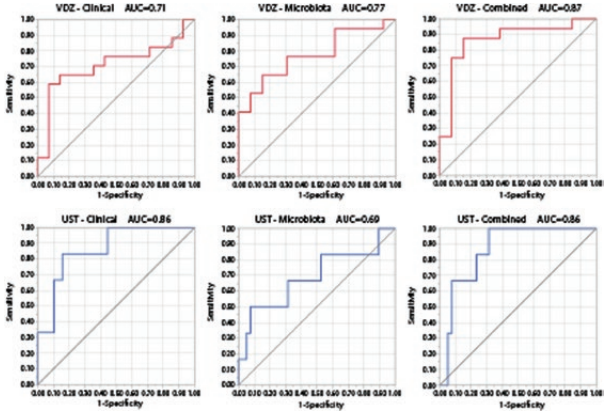

Figure 1: Receiver-operating characteristic curves of the different neural network trained for treatment response prediction for VDZ and UST

For VDZ treatment response prediction, all models had reliable training (AUC=[0.71–0.87]; sensitivity=[0.62–0.88], specificity=[0.55–0.85]), but the combined model had the best validation performance (misclassification rate=31%, N = 17). Similarly, UST response prediction was best with the combined model(training AUC=0.86, sensitivity=0.88, specificity=0.33, with a validation misclassification rate of 4% (N = 23).

Conclusions: Our analyses do show that quantitative faecal microbiota profiling is helpful in predicting therapeutic outcome and provides valuable additional information beyond clinical features and biomarkers. Nevertheless, these predictive models were trained on still relatively small cohorts, and therefore further validation in preferably large prospective randomised cohorts is needed.

P837

The common food additives sodium sulfite and polysorbate 80 have a profound inhibitory effect on the commensal, anti-inflammatory bacterium *Faecalibacterium prausnitzii*: the ENIGMA study

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Background: *Faecalibacterium prausnitzii* may be a key protective bacterium, and useful therapeutically to attenuate inflammation and promote gut homeostasis in Crohn's disease (CD). However, the reasons for its variable persistence during active disease and recovery remain unknown. We hypothesise *F. prausnitzii* is constrained by dietary factors that might promote inflammation; and food additives have been implicated recently in microbial changes that promote inflammation. We have investigated how 8 common food additives affect the growth kinetics of 3 strains of *F. prausnitzii*.
Methods: *F. prausnitzii* A2-165, KLE1255, and AHMP21 were cultured using a habitat-simulating medium supplemented with 0.2% (wt/vol) glucose (M2G), or M2G prepared to contain 0.1% (wt/vol) of either sodium sulphite, aluminium silicate, carrageenan, carboxymethylcellulose, polysorbate 80, saccharin, sucralose, or aspartame, intended to approximate concentrations found in food. The 3 *F. prausnitzii* strains were also grown with M2G medium and once these cultures had reached mid-exponential phase of growth, either sodium sulfite or polysorbate 80 was added to the cultures to 0.1% (wt/vol). Growth was monitored by optical density measurements.
Results: Figure 1 shows all 3 strains were strongly inhibited by sodium sulfite and polysorbate 80. The growth rates of all 3 *F. prausnitzii* strains were not affected by the other food additives, with the exception of a small but significant decrease for strain KLE1255 in the presence of sucralose ($p < 0.05$). Cell yield of strain A2-165 was unaffected by the remaining food additives, whereas the cell yield of strain AHMP21 was reduced by saccharin ($p < 0.05$); and by sucralose and saccharin for strain KLE1255 ($p < 0.05$). Growth of all 3 *F. prausnitzii* strains was immediately arrested when sodium sulphite was added to mid-exponential phase cultures; the effects of polysorbate 80 were more variable and probably cell-density dependent.

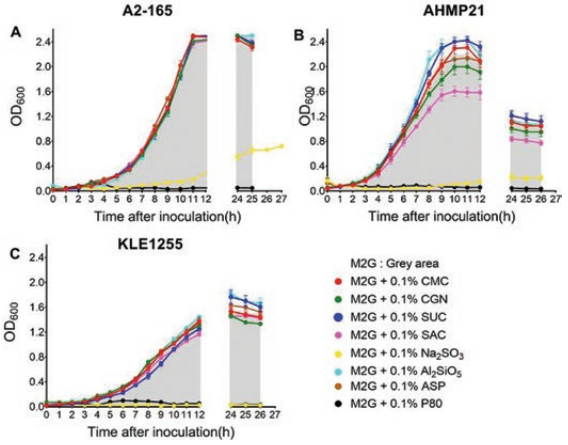

Figure 1. Effect of food additives (0.1% [wt/vol] final concentration) on the growth kinetics of F. prausnitzii strains A2-165 (A), AHMP21 (B), and KLE1255 (C). Data points are the mean ± SEM of optical density measurements at 600 nm ($n = 6$).

Conclusions: Sodium sulfite and polysorbate 80 have strong inhibitory effects on *F. prausnitzii* growth. Exclusion of such additives from the diet may be critical to improved Crohn's disease activity or prevention. This work is supported by The Leona M. and Harry B. Helmsley Charitable Trust.

P838

Effects of microbial metabolites on human intestinal epithelium

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Background: The intestinal epithelium is the interface between the microbiota and the underlying host mucosa. Intrinsic genetic as well as acquired defects in the epithelium have been described in inflammatory bowel diseases (IBDs) including Crohn's disease (CD). Bacterial metabolites, such as short chain fatty acids (SCFAs), are known to exert homeostatic, anti-inflammatory and anti-tumoural effects. However, the effects of SCFAs in the context of intestinal inflammation and specifically in CD, have not been extensively addressed. Results from our group reveal that the epithelial organoid system is a good tool to explore the impact of bacterial metabolites on the human epithelium. Our aim was to study the effect of faecal microbial SCFAs on the intestinal epithelium using organoid cultures from non-IBD controls and patients with CD.
Methods: SCFAs were extracted from faecal samples of non -IBD controls and active CD patients. The concentration of 13 SCFAs was measured in the derived faecal extracts (FEs) by HLPC. Organoid cultures, generated using biopsy samples from controls and CD patients, were incubated with faecal- SCFAs (1:50), or vehicle for 24 h. Total RNA was isolated from organoid cultures and the expression of genes associated with proliferation and other epithelial signalling pathways was analysed by qPCR.
Results: Despite the presence of active disease, faecal SCFA extracts from CD patients and controls showed comparable SCFA concentrations. Control FEs down-regulated KI67, CXCL1 and CLDN2 but their effect was significantly lower in healthy compared with CD organoids. MT1X was significantly increased by control FEs, however the effect was lower in CD-derived organoids. Remarkably, SCFA from control FEs reduced IL8 transcripts in control organoids, and did not affect IL8 expression in CD organoids. SCFAs derived from active CD patients showed a decreased ability to induce MT1X and to decrease CXCL1 in epithelial organoids from controls.
Conclusions: Both the ability of the CD epithelium to respond to SCFAs as well as the composition of the SCFAs from active CD patients show changes that suggest an altered microbial-epithelial interaction in CD. While SCFAs have potent effects on the epithelium, other metabolites and bacterial products may also be critical. Our current experiments include studying the effects of supernatants from specific gut commensal and pathogenic bacteria on human organoid cultures.

P839 has been withdrawn.

P840

Dietary interventions rapidly alter metabolomics profile of patients with inflammatory bowel disease after pouch surgery

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Background: Diet may play a role in the pathophysiology of inflammatory bowel diseases (IBD) via several mechanisms including metabolome alteration. We conducted an interventional cross-over study aiming to evaluate the short-term effect of two dietary regimens, the Mediterranean diet (MED) and the specific carbohydrate diet (SCD) on multiple biomarkers of patients with IBD after pouch surgery.
Methods: Two short (one-week) dietary interventions (MED and SCD) were provided to patients. After one washout week, patients were crossed over between diets. Both diets excluded industrialised and processed food. Faecal samples were collected and analysed for metabolomics profiling.
Results: Overall 28 patients (male gender: 50%, mean age: 49 ± 13 years, mean pouch age: 12 ± 9 years) were recruited. Of those, 15 had a normal pouch, 12 had pouchitis and 1 - familial adenomatous polyposis. All patients completed both investigated dietary regimens. MED and SCD were isocaloric (Kcal: 1910 ± 575 vs. 1857 ± 614, $p = 0.4$), however diets differed in their macronutrients composition: MED had higher carbohydrate content and lower protein, fat and saturated fat content compared with SCD (carbohydrate, gr/day: 204 ± 66 vs. 96 ± 48; protein, gr/day: 80 ± 26 vs. 119 ± 45; fat, gr/day: 78 ± 29 vs. 105 ± 40; saturated fat, gr/day: 16 ± 10 vs. 34 ± 14; all $p < 0.001$). Faecal metabolomics analysis detected a total of 1051 named biochemicals. Both MED and SCD induced significant changes in 182 and 313 metabolites, respectively, including changes in super-pathways associated with carbohydrate, lipid, amino acid, peptide, nucleotide, vitamin and xenobiotics metabolism. MED and SCD had a discordant effect on amino acid metabolism, specifically, branched chain amino acid metabolism was up-regulated in MED and down-regulated in SCD. Both diets affected vitamins and cofactors metabolism, most notably, up-regulation of vitamin A metabolism. Interestingly, both diets up-regulated mono and diacylglycerol and down-regulated endocannabinoids metabolism, however ceramides metabolism was down-regulated in MED and up-regulated in SCD. Hierarchical clustering analysis showed that samples from each study participant tended to be more similar to each other than to other participants.
Conclusions: In this cross-over trial, two unindustrialised dietary interventions (MED and SCD) rapidly altered the metabolomic profile of patients with IBD after pouch surgery, despite individual metabolomic signatures. Changes in these metabolites might alter signalling pathways associated with inflammatory responses via autophagy and activation of NLRP3 inflammasome. Thus, personalised dietary intervention may be used to modify inflammation in IBD via altering metabolomics profile.

P841

Small intestinal bacterial overgrowth in patients with Crohn's disease is not only associated with a more severe disease, but is also marked by dramatic changes in the gut microbiome

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Background: The main mechanisms that protect against small intestinal bacterial overgrowth (SIBO) are compromised in Crohn's disease (CD). Therefore, SIBO is a relatively common finding in patients with CD with a reported frequency of 17% to 62%. SIBO represents a clinically relevant event in CD that may affect the symptoms and outcomes. Gut microbiota dysbiosis is strongly associated with CD, but effect of SIBO on the colonic microbiome is not so clear. The aim of this study was to characterise the faecal microbiota composition in adult patients with CD, with or without SIBO.
Methods: A pilot comparative study among CD patients with (n = 36) and without (n = 35) SIBO was conducted, with a focus on differences in the gut microbiome. A lactulose hydrogen breath test (LHBT) was used to determine the presence of SIBO. V3-V4 16S rRNA deep amplicon sequencing on the Illumina MiSeq platform with Reagent Kit v3 (600 cycles) was used to analyse faecal microbiota.
Results: 51% of patients with CD had an abnormal LHBT, indicating the presence of SIBO. LHBT results were not associated with gender, age, body height, disease location, duration of the disease, treatment difference, presence of steroid dependency or steroid resistance.
CD patients with SIBO, when compared with those without SIBO, were characterised by a significant decrease in body weight within the last 3 months prior to the study, with an average loss in body mass of 2.5 kg ($p < 0.001$).
Patients with the higher Crohn's disease Activity Index (CDAI) scores (≥300) were more likely to have SIBO, when compared with those with CDAI < 300 (81% vs. 32%; $p < 0.001$). SIBO was significantly more common in patients with structuring or penetrating (B2/B3) behaviour than in patients with non-stricturing, non-penetrating disease (B1) (83% vs. 27%; $p < 0.001$). Patients with SIBO were more likely to have moderate or severe abdominal pain (64% vs. 25%; $p = 0.007$), bloating (86% vs. 31%; $p < 0.001$), flatulence (75% vs. 6%; $p < 0.001$) and fatigue (81% vs. 54%; $p = 0.023$), when compared with patients without SIBO. Some potentially harmful microbes were more abundant in CD patients with SIBO such as those belonging to the Fusobacteria, Proteobacteria, Erysipelotrichaceae, *Escherichia/Shigella*. Bifidobacteriales and Lactobacillales, generally considered to be beneficial, were lowered in patients with SIBO. Some bacteria, that may play a dual role (protective or detrimental) were increased (Bacteroidetes, Lachnospiraceae, Verrucomicrobiaceae, *Akkermansia*, *Blautia*, *Dorea*), while others (Enterococcaceae) were decreased in SIBO.
Conclusions: SIBO in patients with CD was associated not only with a more severe disease but also with significant changes in the gut microbiome that may worsen the symptoms and the course of the disease.

P842

Multi-omics analysis suggests an active role of fungi in Crohn's disease

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Background: Several studies have suggested a role of fungi in Crohn's disease (CD); from the reporting of ASCA in CD patients, the observation of fungal metabolites in patients in relapse, to recent mycobiome studies. However, the analysis of the gut mycobiome is made difficult by a very low diversity, combined with a relevant input of fungi from the diet. Therefore, discriminating between active and transient fungi using only metagenomics is not easy. To overcome this issue, we combined metabolomics data, which also indicate microbial activity, with bacterial and fungal communities' data.

Methods: Briefly, we produced volatile organic compound metabolomic data along with bacterial 16S rRNA and fungal 18S rRNA data from 43 donors (23 CD patients and 20 controls). These data were filtered and normalised and DIABLO (MixOmics), a statistical tool which integrates omics data, was used. This uses supervised analysis to highlight signature features and to identify correlated variables.

Results: We compared CD patients vs. controls and CD active patients vs. controls. The first comparison gave a balanced error rate (BER) of the cross-validation of the model < 35%. The model was made of two components, the first showed a higher Pearson correlation between Bacteria and VOCs (0.54). Meanwhile, the second showed a higher correlation between Fungi and Bacteria (0.66). We also found that branched-short chain fatty acids (high in CD) were correlated with bacteria OTUs assigned to gut fermenters, mainly Firmicutes. This result alone shows the potential of this approach to pinpoint microorganisms that are active in the gut of CD patients. The second comparison saw CD active (n = 11) vs. controls (n = 20). The difference in the number of samples gave a BER relatively high (around 45%). Again, two components were selected, but these gave a Pearson correlation between the omics higher than the previous comparison (up to 0.67 VOCs and Bacteria, 0.62 Bacteria and Fungi and 0.55 VOCs and Fungi). Correlation of variables showed that several OTUs assigned to Saccharomycetes yeasts and a mould (Aspergillus) were correlated to metabolites associated to fungi (e.g. heptanal and 3,7-dimethylocta-1,6-dien-3-ol), supporting a possible role of fungi in active CD. These fungi were also correlated to Clostridiales and Enterobacteriales.

Conclusions: The high BER do not allow us to draw definite conclusions and further studies, with a higher number of patients, are required. However, we can say that fungi are very likely to be active during relapse. We also show a powerful approach that allows to overcome the issues related to the interpretation of gut mycobiome studies, which are biased by the large input of yeasts from the diet.

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Post-vaccination kinetics of antibodies against hepatitis B surface antigen in inflammatory bowel disease patients: a single-centre cohort study

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Background: Inflammatory bowel disease (IBD) patients are susceptible to post-vaccination immunity loss long-term. No data exist regarding the kinetics of antibodies against hepatitis B surface antigen (anti-HBs) after baseline vaccination. Our aim was to investigate changes in serial anti-HBs IgG measurements in immunised IBD patients.

Methods: Consecutive IBD patients vaccinated and immunised against HBV either before or after diagnosis underwent measurement of anti-HBs IgG every 18–24 months during scheduled follow-up (FU) visits. Those with a negative (< 10 mIU/ml) anti-HBs IgG titer received a booster dose (Engerix, GlaxoSmithKline®, Brentford, UK, 20 UG/ml). Immune response was defined as a positive (>10 mIU/ml for those not receiving and >100 mIU/ml for those receiving immunosuppressants [IMS]) anti-HBV IgG titer measured at least 3 months after the booster dose.

Results: 349 IBD patients (females: 41%, Crohn's disease [CD]: 52.1%, median [IQR] age at diagnosis: 41.0 [27.1–56.0] and age: 48.8 [31.5–62.6] and disease duration: 2.0 [0.3–8.2] years at study entry) were prospectively screened and vaccinated if needed from January 2010 up to September 2018. In total, 151/349 patients (43.3%, females:43%, CD: 58.9%) have been followed up so far according to the protocol mentioned earlier. Thirty-two patients (21.2%, females: 34.3%, CD: 53.1%) lost immunity against HBV during FU, of those 17/32 (53.1%) while receiving IMS. So far, 18/32 patients have received a booster dose and 11/18 (61.1%) responded (7/11 [63.6%] under IMS therapy). A mean (±SD) anti-HBs titer of 41(±21.3) IU/ml was measured in four out of seven non-responders treated with IMS, inadequate however as per protocol (< 100 mIU/ml). Interestingly, 15/18 patients (83.3%, 11/15 under IMS therapy) developed higher anti-HBs IgG titer compared with the one measured after baseline vaccination. Loss of immunity and booster dose responsiveness were not associated with either disease characteristics or therapeutic regimens administered.

Conclusions: More than one fifth of our IBD patients vaccinated against HBV lose immunity overtime. A single booster dose can resume immune response in about two thirds of them. Immunosuppressants do not seem to influence either loss or resumption of immunity. These results should be interpreted with caution since our cohort is still small and verification in other cohorts is also mandatory.

P844

Mucosa associated candida in ulcerative colitis: prevalence and relationship to disease severity

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Background: Role of fungal dysbiosis in pathogenesis and severity of ulcerative colitis (UC) is not known. We planned to determine the relationship of presence, nature and quantify Mucosa Associated Candida (MAC) with the disease severity in patients with UC. We planned to determine the relationship of presence, nature and quantify Mucosa Associated Candida (MAC) with the disease severity in patients with UC.
Methods: In a prospective study of UC (n = 96) and non-UC controls (n = 20), clinical, endoscopic, histological and serological assessment was performed for disease severity. MAC was considered to be present if mucosal biopsy culture grew Candida. Mucosal brush cytology and brush culture was also performed. Candida species identification was done by MALDI. Serum β-D-Glucan was measured by Fungitell assay. Seven UC patients with evidence of Candida were treated with oral Fluconazole and re-evaluated after 14 days. Data are analysed using SPSS and $p < 0.05$ was considered to be significant.
Results: Cases and controls were similar in age and gender. Cases more often had MAC: biopsy culture [33% vs. 5%; p = 0.011], brush cytology [30% vs. 5%; p = 0.019]; brush culture [36.5% vs. 10%; p = 0.021]. Cases had higher colony counts (≥103 CFU/ml) compared with controls: [36% vs. 5%; p = 0.007]. Cases had higher non-C. *albicans* species compared with controls (25% vs. 0%; p = 0.029). Median β-d-glucan values were higher in cases compared with controls (103.2 pg/ml vs. 66.5 pg/ml; p = 0.011). Cases with MAC had higher median UCDAI, CRP, faecal calprotectin and histological activity compared with those without MAC. Patients with severe disease more often had confluent growth of Candida when compared with patients with moderate or mild disease (50% vs. 7.4% vs. 3%; p = 0.009). Post-therapy all patients(n = 7) showed significant reduction in UCDAI score (p = 0.017), histological score and faecal calprotectin values.
Conclusions: Patients with UC more often have evidence of MAC, higher Candida colony count, higher non-C. *albicans* species and increased β-d-glucan levels when compared with controls. Disease severity is associated with the presence of MAC and higher β-d-glucan levels.

P845

The changes of intestinal microbiota composition may predict the response of anti-TNF α in patients with Crohn's disease

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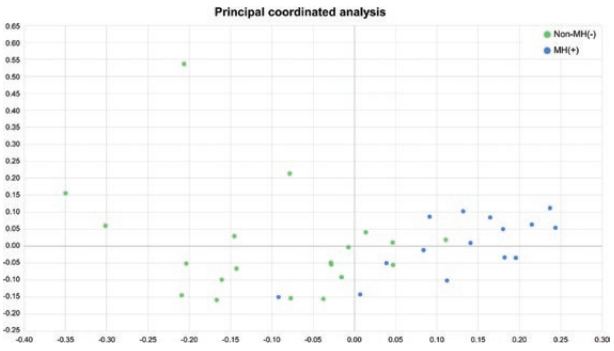
Background: Crohn's disease(CD) pathophysiology is thought to be associated with dysregulated mucosal immune response to gut microbiota. Infliximab can cause the improvement of disease activity and may be involved with the changes of intestinal microbiota. The aim of this study was to investigate the changes of intestinal microbiota composition during infliximab maintenance therapy and a relationship with mucosal healing in Korean CD patients.
Methods: A 16S rRNA sequencing was performed to analyse prospectively collected 35 faecal samples of 19 adult CD patients with clinical remission state. We obtained faecal samples twice at 1 week and 7 week after infliximab infusion and all the patients underwent endoscopy within last 3 months from enrolment to evaluate endoscopic mucosal healing(MH).
Results: Faecal microbial composition and biodiversity indexes did not significantly changed during infliximab infusion cycle. However, according to endoscopic MH, alpha diversity calculated by Shannon and Simpson index showed significant differences (p = 0.008, 0.001, resp.). In MH group, the relative abundance of phylum Firmicutes increased and Bacteroidetes decreased, also, there were significant differences in some genera, including Faecalibacterium, Prevotella, Blautia and Lactobacillus ($p < 0.05$).

	1W(n=18)	7W(n=17)	P	MH (n=15)	Non-MH (n=20)	P
Alpha diversity index						
Jackknife	228.5(192.97-320.0)	247.0(181.5-322.0)	0.352	298.00(241.00-356.00)	206.50(178.75-301.00)	0.074
Shannon	3.34(2.64-3.68)	3.08(2.71-3.70)	0.959	3.582(3.227-3.954)	2.912(2.541-3.503)	0.008
Simpson	0.073(0.048-0.117)	0.082(0.057-0.136)	0.691	0.058(0.043-0.067)	0.099(0.075-0.169)	0.001
Phylum level						
Firmicutes(%)	56.41(44.80-66.69)	52.65(41.32-59.06)	0.438	61.520(57.594-72.378)	46.612(33.266-56.036)	<0.001
Bacteroidetes(%)	23.65(17.60-45.28)	33.35(15.65-44.68)	0.717	21.639(10.426-33.358)	39.180(23.039-48.214)	0.017
F/B ratio	2.65(0.96-3.66)	1.85(0.88-5.11)	0.877	3.122(1.895-6.239)	1.266(0.762-2.661)	0.005
Family level						
Lachnospiraceae(%)	31.20(21.95-37.74)	32.36(18.08-40.31)	0.234	39.198(31333-48.458)	20.618(14.084-34.951)	<0.001
Enterobacteriaceae(%)	2.00(1.02-8.12)	5.05(1.75-10.09)	0.234	1.971(1.177-3.712)	5.839(1.532-9.724)	0.149
Ruminococcaceae(%)	8.14(0.30-18.99)	3.90(0.52-21.34)	0.918	15.899(2.974-22.052)	1.125(0.106-11.020)	0.001
Genus level						
Faecalibacterium(%)	0.925(0.010-8.740)	0.84(0.02-8.91)	0.910	8.664(0.847-11.829)	0.065(0.014-4.167)	0.019
Prevotella(%)	0.019(0.012-9.894)	0.02(0.01-29.67)	0.717	0.017(0.009-0.024)	3.969(0.018-39.124)	0.006
Escherichia(%)	1.352(0.103-6.527)	1.78(0.06-4.66)	0.408	1.285(0.083-2.114)	2.205(0.120-5.784)	0.438
Blautia(%)	6.69(4.40-13.61)	8.01(2.75-10.14)	0.326	9.631(6.754-13.658)	4.432(1.050-8.893)	0.003
Bifidobacterium(%)	2.05(0.29-5.67)	3.28(0.52-5.78)	0.034	4.67(1.90-5.79)	0.77(0.13-5.40)	0.099
Lactobacillus(%)	0.13(0.02-1.06)	0.02(0.005-1.828)	0.796	0.02(0.01-0.16)	0.31(0.02-6.19)	0.039
Species level						
Faecalibacterium prausnitzii group(%)	0.922(0.010-8.740)	0.847(0.026-8.771)	0.910	8.664(0.847-11.829)	0.059(0.014-4.166)	0.016
Prevotella PAC001304_s(%)	0.007(0.002-3.111)	0.008(0.001-11.72)	0.776	0.004(0.002-0.008)	0.915(0.002-25.103)	0.023
Escherichia coli group(%)	1.352(0.103-6.523)	1.776(0.065-4.658)	0.408	1.285(0.083-2.114)	2.199(0.120-5.781)	0.438
Blautia wexlerae(%)	2.54(1.08-10.25)	3.28(0.48-7.63)	0.642	6.051(2.665-11.057)	1.742(0.117-3.667)	0.009

Continous values are presented as median(range) or number(%). Relative abundance. Abbreviation: 1W, 1week; 7W, 7 week; MH, Mucosal healing; F/B ratio, Firmicutes Bacteroidetes ratio

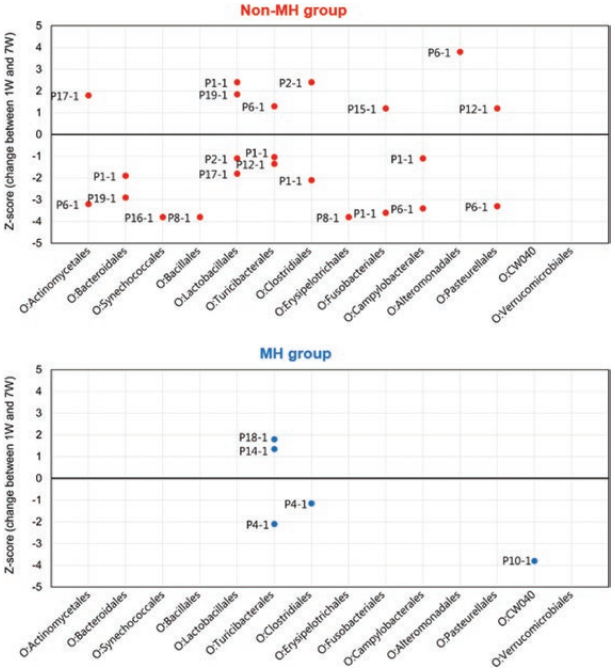
Comparison of relative abundance

The principal coordinate analysis showed a clear separation between MH group and non-MH group.



PCoA plots between MH and non-MH group.

Using z-score analysis, non-MH group showed more unstable and chaotic changes of many bacterial taxa at order level over time after infliximab treatment.



Z-score analysis at order level.

Conclusions: We could not find meaningful changes between 1 week and 7 week samples, however, more diverse and stable bacterial community was observed in CD patients with mucosal healing. Some species (eg. Faecalibacterium prausnitzii) showed significant increase in patients with mucosal healing. The changes of intestinal microbiota might be used to predict the response to anti-TNF agents in CD patients.

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Elafin-expressed *Escherichia coli* Nissle 1917 ameliorates experimental colitis in mice

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Background: The decrease of Elafin is associated with several inflammatory diseases. Elafin up-regulated EGFR-PI3K-Akt pathway, inhibiting pulmonary inflammation. *Escherichia coli* Nissle 1917 (EcN) is a probiotic not inferior to the established standard 5-ASA for maintenance of remission in UC. In this study, we confirm the anti-inflammation mechanism of Elafin in colon cells and evaluate the anti-colitis effects of Elafin-expressed EcN in dextran sulphate sodium (DSS)-induced colitis mouse model.

Methods: In vitro, we used lentivirus-mediated gene transfer system to transfer Elafin gene into Caco2 cells. And the mRNA levels of EGFR, PI3K and Akt was determined by qRT-PCR. Meanwhile we used genetical technology to obtain the genetical EcN expressed Elafin. C57BL/6 mice were administered intra-gastrically with either EcN-Elafin (1×10^9 CFU/ml), EcN (1×10^9 CFU/ml) or mesalazine (822 mg/kg) for 10 days. Acute colitis was induced by 3% dextran sulphate sodium (DSS) drinking water for 7 days. After mice were sacrificed, HE staining was performed in colon tissues to estimate mucosal injury.

Results: The Elafin-expressed cells and probiotic were constructed successfully (Figure 1A and B)

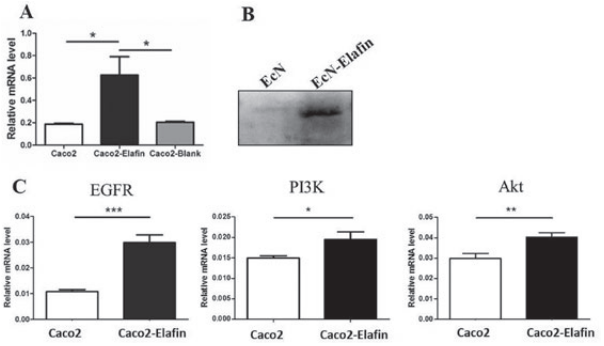

Figure 1. Elafin activates EGFR-PI3K-Akt pathway. The Elafin-expressed cells (A) and probiotic (B) were constructed. EGFR, PI3K and Akt mRNA levels of Elafin-expressed cells was determined by qRT-PCR(C). *$p < 0.05$. ns, not significant.

In Caco2 cells, up-regulated Elafin can lead to high mRNA levels of EGFR, PI3K and Akt (Figure 1C). In mouse model, colon length of EcN-Elafin group and EcN group was longer than DSS group, which was similar to mesalazine group (Figure 2A). EcN-Elafin group and EcN group reduced DSS-induced colon injury, which was similar to mesalazine group (Figure 2B)

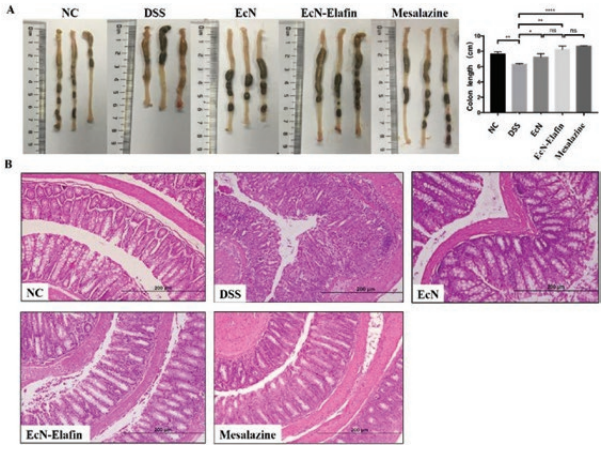

Figure 2. EcN-Elafin reduced DSS-induced colon damage. (A)The pictures and column chart of colon length in each group was displayed. (B) Typical microscopic images by HE staining of colon tissues. Scale bar: 200 μm. *$p < 0.05$. ns, not significant.

Conclusions: The genetical EcN expressed Elafin reduced DSS-induced colon damage. Elafin also up-regulate EGFR-PI3K-Akt pathway in colon cells.

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Perceptions of faecal microbiota transplantation in a paediatric ulcerative colitis population (PediFETCh Trial)

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Background: Faecal microbiota transplantation (FMT) has gained increasing attention in the treatment of IBD. Patient acceptance of FMT treatments is an important consideration, particularly in children. Existing data on patient perceptions of FMT is limited in its assessment of true experiences as respondents had not actually received FMT. The purpose of this study was to explore perceptions of FMT in a paediatric population undergoing FMT for UC or IBD-unclassified (IBD-U).
Methods: Paediatric patients enrolled in a randomised placebo-controlled trial of FMT for UC or IBD-U (PediFETCh Trial; NCT02487238), involving twice weekly enemas for 6 weeks, were invited to participate in face-to-face, semi-structured interviews. Interviews were recorded, transcribed verbatim, and analysed using open coding. A phenomenological approach was used to assess the experiences of each patient.
Results: A total of 8 patients were interviewed (Table 1). Major themes were: (i) understanding of FMT, (ii) psychosocial impacts of FMT, and (iii) comparing FMT perceptions pre- and post-treatment. Pre-treatment discomfort was associated with inoculation with 'someone else's poo', novelty of the treatment, and physical discomfort of enema therapy. Post-treatment, patients felt that FMT was 'manageable', and 'not a big deal at all'. There were no reported side effects from the treatment and no fear of experiencing side effects in the future. No faecal soiling accidents were reported post-treatment, and patients felt confident in their faecal continence. The majority (75%) of patients had a poor understanding of FMT therapy post-treatment, indicating a need for improved patient education. Sixty-seven per cent of patients chose to explore FMT because their current UC treatments were not working, 17% felt their decisions were heavily influenced by their parents, and 17% felt both factors contributed equally in their decision to pursue FMT. Participants were split between preference for FMT or medication therapy, with convenience of oral medications being an important factor, while others favoured FMT for its 'more natural' image and greater efficacy.
Conclusions: Three main themes were explored: psychosocial impacts, understanding of FMT, and experiences associated with FMT. These data offers valuable insight into methods for improving future patient experiences with FMT. Further analyses will assess parental experiences and explore differences between parent and child perceptions of these treatments.

VARIABLE	FMT (n = 8)
Age at FMT intervention; n (%)	
<5 years	1 (12.5)
5-9 years	1 (12.5)
10-14 years	3 (37.5)
15-18 years	3 (37.5)
Age at interview; n (%)	
<5 years	1 (12.5)
5-9 years	0
10-14 years	4 (50)
15-18 years	3 (37.5)
Male sex; n (%)	5 (62.5)
Diagnosis; n (%)	
UC	3 (37.5)
IBD-U	5 (62.5)
Disease characteristics; n (%)	
Proctitis	1 (12.5)
Left-sided	1 (12.5)
Pancolitis	6 (75)
Disease duration; mean ± SD (years)	3.7 ± 2.6
Medications; n (%)	
Immunomodulator	1 (12.5)
Anti-TNF + immunomodulator	1 (12.5)
5-aminosalicylate	5 (62.5)
None	1 (12.5)
Paediatric Ulcerative Colitis Activity Index score pre-intervention; n (%)	
<10	3 (37.5)
10-30	5 (62.5)
35-60	0
65-85	0
Paediatric Ulcerative Colitis Activity Index score post-intervention; n (%)	
<10	7 (87.5)
10-30	0
35-60	1 (12.5)
65-85	0
C-reactive protein pre-intervention; median, interquartile range (mg/L)	2.4 (1.8-4.6)
C-reactive protein post-intervention; median, interquartile range (mg/L)	1.2 (0.5-6.8)
Hemoglobin pre-intervention; median, interquartile range (g/L)	122 (119.5-126.5)
Hemoglobin post-intervention; median, interquartile range (g/L)	126.5 (118-128.5)
Fecal calprotectin pre-intervention; median, interquartile range (mg/kg)	1454.3 (986.6-1646)
Fecal calprotectin post-intervention; median, interquartile range (mg/kg)	317.7 (186.1-1287.8)

Characteristics of interviewed patients.

P848

Latent tuberculosis and active tuberculosis infection in patients with inflammatory bowel disease treating by biological agents: an experience of a medical centre in Taiwan

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Background: Inflammatory bowel disease (IBD) is a chronic and relapsing disease. Comparing with Western countries, low prevalence of IBD and high prevalence of tuberculosis infection were reported in Taiwan. Biological agents are a great advance in treating patients with IBD, but they can increase the risk of tuberculosis (TB) infection. This study was to investigate the incidence rate of latent TB and active TB infection in patients with IBD treating by biological agents.
Methods: From 2000 to 2018, we retrospectively collected patients with IBD treating with biological agents at a tertiary referral centre. All patients underwent a QuantiFERON-TB Gold test to screen for tuberculosis infection before and after biological treatment course. The diagnostic age, gender, cigarette use, types of IBD, chronic hepatitis B/C infection and results of QuantiFERON-TB Gold test were analysed.
Results: One hundred and fifteen patients with IBD receiving biological therapy were enrolled. There were 68 patients with Crohn's disease, and 47 patients with ulcerative colitis. Male patients were predominance (73%) and the diagnostic mean age of all patients was 37.9 years. Our patients were reported 14% of chronic hepatitis B carrier and no hepatitis C carrier. The results of QuantiFERON-TB Gold test were determinate in 105 cases (91%): nine were positive (8%) and 96 were negative (83%); and indeterminate in 10 cases (9%). Patients with positive results of QuantiFERON-TB Gold test were diagnosed as latent tuberculosis and treated with anti-TB therapy before initiation of the biological agents. Only one patient (0.87%) with ulcerative colitis developed active pulmonary tuberculosis after biological therapy.
Conclusions: Our study demonstrated the incidence of latent tuberculosis is higher than Western countries and similar to Asian countries. However, active tuberculosis infection is low in our participants after receiving biological treatment. Thus, screening and monitoring of TB infection is needed and important for patients with IBD before starting and during biological treatments in Taiwan.

P849

Urease-positive proteobacteria in Crohn's disease identified by novel ex vivo mucosal microbe culture combined with metagenomic sequencing (MC-MGS): the ENIGMA study

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Background: Longitudinal 16S analysis of Australian Crohn's disease patients suggest that the presence of *Proteus* spp. is predictive of, and associated with, Crohn's disease recurrence after intestinal resection.[1] This bacterium is remarkable for its urease production, recently identified as a key functional change.[2] Further characterisation of the mucosa associated microbiome (MAM) using metagenome sequencing has been limited by the overwhelming presence of human DNA. Here, we present a novel approach, microbe-culture metagenome sequencing (MC-MGS), to characterise and confirm bacteria associated with urease activity in the mucosa-associated microbiota in Crohn's disease.
Methods: Anastomotic biopsies from 5 Crohn's disease patients 6 months post-surgery, were stored in RNA later for DNA extraction. Matched biopsies stored in an anaerobically prepared glycerol buffer underwent microbe culture with a habitat-simulating medium (37°C, 24 h). Total and microbe enriched biopsy DNA, as well as MC-DNA, was sequenced to a depth of 3 gbp as 150 bp paired-end reads with the Illumina NextSeq500 platform. In addition to metagenome-assembled genomes produced using MetaBAT,[3] urease-producing (and other) bacteria were isolated using selective media under aerobic and anaerobic conditions.
Results: MC-MGS produced 16 metagenome assembled genomes representing a broad diversity of bacteria representing both facultative and fastidious anaerobes, including members of the *Proteeae* tribe (*Providencia/Morganella*). Axenic isolates of urease-positive bacteria were also recovered from the cultures produced from 3/5 biopsies, and included strains of *Klebsiella pneumoniae, Escherichia fergusonii, Morganella morganii* and *Enterococcus faecium*.
Conclusions: Urease-positive bacteria, principally members of the *Enterobacteriaceae* are associated with Crohn's disease. New combined culture and metagenomic sequencing techniques provide a holistic and functional characterisation of the IBD mucosa-associated microbiota, while also providing metagenome-assembled genomes, microbial consortia, and axenic isolates relevant to understanding Crohn's disease pathophysiology. This work is supported by The Leona M. and Harry B. Helmsley Charitable Trust

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P850

Measles virus immune status in a cohort of Spanish patients with inflammatory bowel disease

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Background: Despite vaccination against measles virus, outbreaks of this infection have been reported in western European countries. Little is known about measles virus serological status in adult patients with inflammatory bowel disease (IBD). On the other hand, few studies have analysed factors related to measles virus immune status. Our aim was to know the immune status against measles virus in a cohort of adult patients with IBD
Methods: Single-centre study in IBD patients attended at an Spanish IBD unit between 2015 and 2018. At the diagnosis of IBD or at the first visit to the Unit, all patients were assessed for their serological status regarding measles virus by the determination of IgG antibodies. Factors related to measles virus immune status were analysed.
Results: 430 patients were included, mean age 45.9 years, 51.9% male, 51.6% Crohn's disease, 44.7% ulcerative colitis and 3.7% unclassified colitis. In total, 36 patients (8.4%) were measles virus-IgG negative. There were no significant differences in percentage of seronegative patients according to gender ($p = 0.131$), type of IBD ($p = 0.512$) or treatment at the time of the testing [corticosteroids ($p = 0.560$), immunomodulators ($p = 0.581$) or biologics ($p = 0.784$)]. Regarding age, seronegative patients were younger than seropositive (mean 31.8 years vs. 47.2 years; $p < 0.001$). Analysing by subgroups, we found differences between patients born before and after 1982 (measles vaccination start time in Spain); thus, 24.5% patients born after 1982 were seronegative vs. 2.8% among patients born before 1982 ($p < 0.001$). We also found differences between patients born before and after 1991 (measles eradication time in our country) (18.4% seronegative among born after 1991 vs. 7.1% among born before, $p < 0.001$). In total, 16 of 36 patients (44.4%) were vaccinated. Of the remaining 20, 16 were not vaccinated because they were under immunosuppressive treatment, and one of them due to spontaneous seroconversion. There were no cases of measles.
Conclusions: Immunosuppressive and biological therapy does not affect the immune status against measles virus in patients with IBD. Seronegative patients are younger, probably due to the immunity was only conferred by vaccination given the non-exposure of these patients to the wild virus. Half seronegative were not vaccinated because they were under immunosuppression. Therefore, we would like to emphasise the importance of knowing the immunological status of patients at the baseline visit in order to adjust the vaccination schedule before starting treatment.

P851

Effects of manipulation of the gut microbiota on colon tumorigenesis in AOM-DSS model

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Background: The altered intestinal microbial profiles have been known to be associated with colorectal cancer as well as inflammatory bowel diseases. To determine the role of the commensal bacteria

in the sequential stages of colitis-associated cancer (CAC), we tried to explore whether the timing of antibiotics-induced gut microbial change affects colon tumorigenesis in the azoxymethane (AOM)-dextran sodium sulphate (DSS)-induced murine CAC model.

Methods: CAC was induced in the C57BL/6 mice by injection of 12.5 mg/kg AOM followed by three rounds of 2% DSS exposure to elicit colitis. There were a total of six different groups according to the timing of antibiotics administration. After sacrifice of the mice, colonic inflammation, proliferation and tumorigenesis were evaluated. To characterise the change of intestinal microbiota, high throughput Illumina MiSeq sequencing for sequential faeces were performed.

Results: Antibiotics treatment with full-time period decreased AOM/DSS-induced tumour numbers per mouse and mean tumour size, histological colitis and dysplasia scores, and pro-inflammatory and proliferatory cytokine expressions compared with AOM/DSS group without antibiotics treatment. Early antibiotics treatment group (from 3 weeks prior to AOM to first round of DSS) showed relatively lower histological scores and the number of tumours developed compared with AOM/DSS group, however, it was not statistically significant. On the contrary, late antibiotics treatment groups (from first or second round of DSS until the end of the study) demonstrated significant lower histological scores and the number of tumours developed compared with AOM/DSS group. Metagenomic sequencing analysis demonstrated that gut microbial community structures were similar between full-time antibiotics treated group and late treatment groups, while other groups showed distinct gut microbial profiles from each other in principal coordinate analysis. There was a positive correlation between the number of tumours and number of operational taxonimic units. The relative abundances of Bacteroidales order and Lachnospiraceae family had a tendency to be positively related to tumour burden.

Conclusions: Antibiotics-induced gut microbial change in AOM/DSS murine model, especially at the inflammation period of CAC, could attenuate colon tumorigenesis, suggesting microbial manipulation as a potential therapeutic option in CAC.

P852

Characterisation of Crohn's disease mucosa-associated microbiota by a novel combination of microbe culture and metagenomic sequencing (MC-MGS): the ENIGMA study

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Background: Mucosal microbiota characterisation by shotgun metagenome sequencing is challenging due to limited microbial density and predominant host DNA. We have developed and evaluated microbe-culture metagenome sequencing (MC-MGS) to better characterise the mucosa-associated microbiota, in this case from 5 Crohn's disease (CD) patients in the post-operative POCER study.[1]

Methods: Total DNA was extracted from biopsies stored in RNA later, and microbial DNA enrichment done with the NEBNext® protocol (New England Biolabs). In parallel, matched biopsies stored in anaerobically prepared glycerol buffer were used to produce microbial consortia with a habitat-simulating medium (37°C, 24 h). Total, enriched, and microbe culture DNA was sequenced using the Illumina NextSeq500 platform to produce 3 gbp of data per sample (as 150bp paired-end reads). The microbiota profiles for the respective samples was evaluated using GraftM[2], and metagenome-assembled genomes produced using MetaBAT[3].

Results: DNA sequence data directly isolated from biopsies, was >90% human and not microbial. Subtractive enrichment of microbial DNA resulted in a 2–8 fold increase in microbial read counts as assessed by GraftM and qPCR. In contrast, the MC-MGS datasets were exclusively microbial and represented 56–84% of the biodiversity captured from total biopsy DNA, and 75–92% of the biodiversity recovered after microbial DNA enrichment. MC-MGS samples also produced 16 metagenome assembled genomes representing diverse facultative and fastidious anaerobes (Table 1).

Sample	Bin Id	Marker lineage	Annotation	Species
CD10	final.contigs.fa.metabat-bins-5	o__Lactobacillales (UID544)	0 RAST	*Enterococcus faecium*
CD10	final.contigs.fa.metabat-bins-3	f__Enterobacteriaceae (UID5162)	0 RAST	*Escherichia coli*
CD10	final.contigs.fa.metabat-bins-6	c__Gammaproteobacteria (UID4442)	0 RAST	*Providencia / Morganella*
CD12	final.contigs.fa.metabat-bins-4	k__Bacteria (UID2372)	0 RAST	*Clostridium ramosum*
CD12	final.contigs.fa.metabat-bins-3	f__Enterobacteriaceae (UID5124)	0 RAST	*Escherichia coli*
CD12	final.contigs.fa.metabat-bins-2	o__Bacteroidales (UID2654)	0 RAST	*Bacteroides vulgatus*
CD12	final.contigs.fa.metabat-bins-5	o__Clostridiales (UID1226)	0 RAST	*Ruminococcus obeum*
CD12	final.contigs.fa.metabat-bins-6	o__Clostridiales (UID1226)	0 RAST	*Clostridium nexile*
CD14	final.contigs.fa.metabat-bins-4	k__Bacteria (UID2329)	0 RAST	*Fusobacterium ulcerans*
CD14	final.contigs.fa.metabat-bins-5	k__Bacteria (UID2372)	0 RAST	*Erysipelotrichaceae bacterium / Eubacterium*
CD33	final.contigs.fa.metabat-bins-5	o__Lactobacillales (UID544)	0 RAST	*Enterococcus faecium*
CD33	final.contigs.fa.metabat-bins-2	f__Enterobacteriaceae (UID5124)	0 RAST	*Escherichia coli*
CD33	final.contigs.fa.metabat-bins-7	o__Selenomonadales (UID1024)	0 RAST	*Acidaminococcus fermentans*
CD33	final.contigs.fa.metabat-bins-3	o__Bacteroidales (UID2621)	0 RAST	*Parabacteroides distasonis*
CD34	final.contigs.fa.metabat-bins-6	o__Lactobacillales (UID544)	0 RAST	*Streptococcus infantarius*

Table 1. Metagenome-assembled genomes produced from biopsy samples of CD patients by MC-MGS

Conclusions: The novel MC-MGS approach recovers much of the mucosa-associated microbiota, enabling production of both metagenome-assembled genomes and isolation of 'new' bacterial strains. MC-MGS provides a valuable new approach to provide a holistic, functional characterisation of the mucosa-associated microbiota in health and disease. This work is supported by The Leona M. and Harry B. Helmsley Charitable Trust.

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P853

The gut microbiota of pregnant inflammatory bowel disease patients shows a low diversity, but stable profile throughout pregnancy

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Background: Pregnancy constitutes an altered maternal physiological state, which is not only associated with immunological changes, but also results in an alteration of the intestinal microbiota. Towards the third trimester the faecal bacterial diversity was shown to decrease, resembling an inflammation-associated dysbiosis with an overall increase in *Proteobacteria* and *Actinobacteria*. Such alterations closely resemble faecal microbiota abnormalities observed in patients with inflammatory bowel disease (IBD), where a reduced diversity, reduced butyrate-producing bacteria and increased *Proteobacteria* are some of the most consistently reported findings. How pregnancy affects microbial signatures in IBD patients is currently unknown. The aim of our study is therefore to characterise changes in gut microbiota that occur from first trimester to the third trimester in pregnant IBD patients.
Methods: We analysed stool samples of 46 IBD patients (32 Crohn's Disease [CD; 70%] and 14 ulcerative colitis [UC; 30%]) from our prospectively followed-up pregnancy cohort. For the control group 120 stool samples from healthy women were used (unpublished data). Bacterial 16S rRNA gene sequencing (V4 region) was performed on Illumina MiSeq and analysed using QIIME.
Results: During pregnancy CD and UC patients showed a lower Evenness Alpha diversity than the control group (respectively q=8.18E–13 and q=4.83E–07), and IBD patients clustered separately from controls in both weighted and unweighted UniFrac principal coordinate analysis. For IBD patients, no differences in alpha or β diversity was seen between CD and UC patients. Overall, no changes in diversity were observed when comparing the different pregnancy trimesters in IBD patients. Microbial diversity was not associated with medication use or flaring of disease.
Conclusions: In this study, we found no significant changes in microbial diversity during pregnancy in IBD patients. As lower diversity is associated with a pro-inflammatory response, this stable microbiome could be beneficial for patients. In line with results on non-pregnant IBD patients, we found a lower diversity comparing the pregnant IBD (UC and CD) group and control group, and it is conceivable that a further decrease in diversity is therefore not observed in these patients.

P854

Insights into alteration of gut microbiota in inflammatory bowel disease patients with and without *Clostridium difficile* infection

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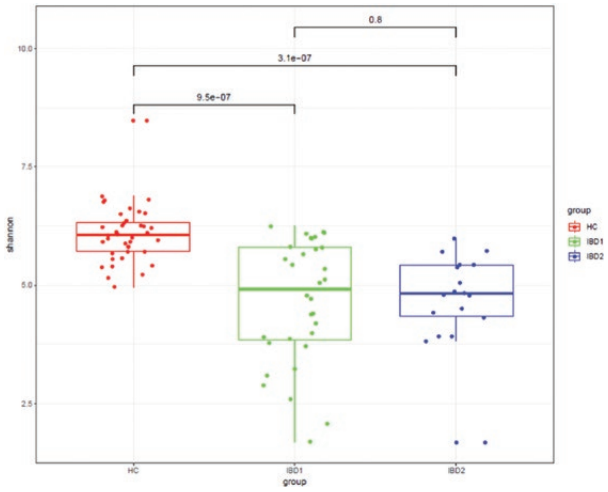
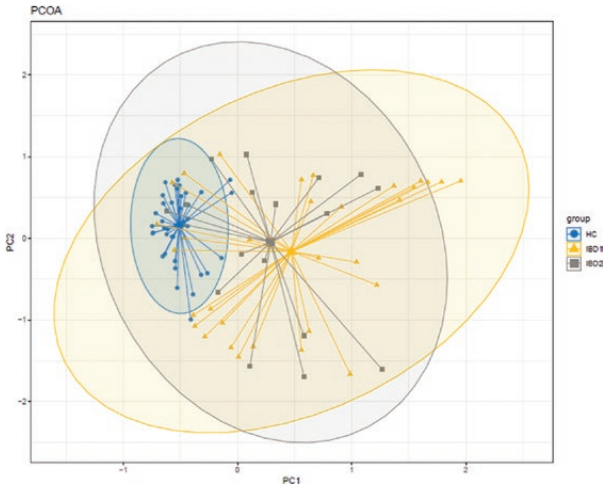
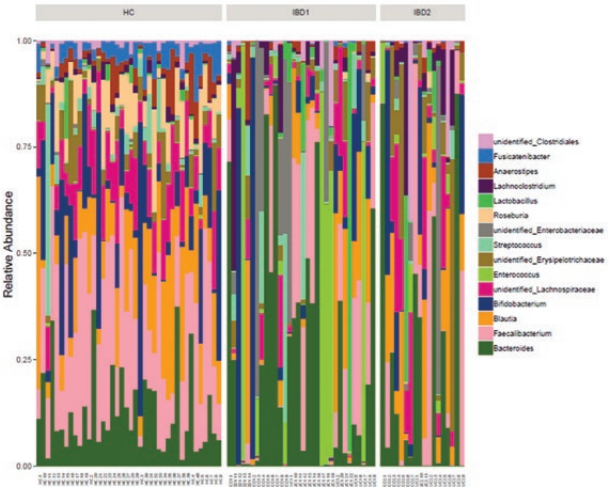
Background: *Clostridium difficile* infection (CDI) is common in inflammatory bowel disease (IBD) due to gut microbial dysbiosis. Our aim was to investigate the trend of gut microbial changes in IBD patients with CDI.
Methods: The faecal microbiota of 21 active Crohn's disease (CD) patients without CDI (Group CD1 , n = 13) with CDI (Group CD2, n = 8), 30 active ulcerative colitis (UC) patients without CDI (Group UC1, n = 19) and with CDI (Group UC2, n = 11) and 40 healthy controls (HC), was studied using 16S ribosomal RNA (rRNA) gene sequencing and metagenomics. Besides, Group IBD1 was defined as IBD without CDI (n = 32), while IBD2 was defined as IBD with CDI (n = 19).
Results: (1) The α diversity was decreased in IBD patients compared with HC. But there was no significant difference between IBD patients with and without CDI.



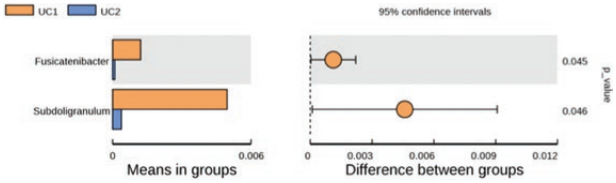
(2) The inter-group variability in community structure byβdiversity analysis using Principal Co-ordinates Analysis (PCOA) showed a clear separation between IBD patients with HC. But IBD patients with and without CDI could not be separated.



(3) Relative abundance of bacteria at the genus level show different global composition in IBD patients with or without CDI and HC to some extent.



(4) In UC patients, compared with UC without CDI, UC patients with CDI had lower abundance of bacilli and coriobacteriales OTUs at class level, lower abundance of coriobacteriales OTUs at order level and lower abundance of subdoligranulum and fusicatenibacter OTUs at genus level.



(5) Metagenomics revealed that *Bifidobacterium dentium*, *Pediococcus lolii* , *Clostridiales bacterium*, *Flavonifractor plautii*, *Pseudoramibacter alactolyticus*, *Anaerostipes caccae*, *Anaerostipes* unclassified, *Faecalibacterium prausnitzii* and *Edwardsiella tarda* were positively associated with CDI.

Conclusions: IBD especially UC patients with CDI is associated with a more pronounced microbial dysbiosis than patients without CDI, with specific alterations in intestinal microorganisms.

P855

Variable importance analysis based on gut microbiota and dietary factors between IBD patients and healthy controls in China

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Background: Gut microbiota and diet are believed to be associated with the pathogenesis and development of inflammatory bowel disease (IBD). Our study investigated the differences in gut microbiota and dietary factors between Chinses IBD patients and their cohabitating family member controls

Methods: We recruited Crohn's disease (CD) and ulcerative colitis (UC) patients with endoscopically confirmed disease from the IBD clinic in 6th Affiliated Hospital of Sun Yat-sen University in Guangzhou, China between March 2014 and September 2016. Each case was asked to provide a family member (primarily sibling) control. Individuals who had not taken antibiotics in the prior 2 weeks provided stool samples with 24 h dietary recalls. Physicians completed information to calculate the Mayo and CDAI scores using the most recent laboratory and endoscopic information. Faecal bacterial differential diversity were analysed with Miseq sequencing results of the V5–V6 region of the 16S rDNA. The Wilcoxon signed-rank test was used to make taxonomy-based comparisons of gut microbiota for 200 differential operational taxonomic units (OTUs) selection including levels of family, genus and species. Dietary records were entered and computed with the NCI Automated Self-Administered 24-h Dietary Assessment Tool and total energy (Kcal) adjusted protein, sugar, fibre, total monounsaturated fatty acids, and total saturated fatty acids were calculated. Statistically significant OTU and dietary factors were selected with Random Forests classifier using R selecting the top 200 factors using univariable inputs.

Results: Stool-dietary recall case–control paired results were available for 37 CD and 14 UC patients and their matched controls (n = 51). The median age at the time of stool collection was 29 in cases and 30 in controls. According to Mayo and CDAI scoring systems, 65% of UC and 70.7% of CD cases were in remission. No case had severe disease at the time of stool collection. The differences in out profiles were statistically significant for CD cases compared with controls ($p < 0.04$), but not UC ($p < 0.17$). Comparison between UC and CD pairs showed that only 2 OTUs had a similar distribution. When we examined univariable factors, contained both 16S rDNA and nutrition data, that differentiated cases and controls, Lachnospiraceae and Rumino-coccaceae were the most important families. Dietary factors ranked below the top 50 with monosaturated fat (rank 59) and protein (rank 67) the highest rated. Fibre ranked 158 out of 200.

Conclusions: Microbiota profiles are more important than dietary factors to differentiate IBD from controls, especially for CD.

P856

Compositional changes in the gut microbiota of Korean inflammatory bowel disease patients are linked to clinical phenotypes

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Background: Gut microbiota play a central role in pathogenesis of inflammatory bowel disease (IBD). We aimed to examine the differences of gut microbiota between Korean IBD patients and healthy controls (HC), and their relationship to disease phenotypes.

Methods: We collected faecal samples from 70 ulcerative colitis (UC) and 12 Crohn's disease (CD) patients, and 81 HC. Faecal bacterial taxonomic composition was investigated using 16S sequencing. The obtained sequences were analysed using the BIOiPLUG pipeline (https://www.bioiplug.com) to assess bacterial diversity and composition. The relationship between faecal bacteria and clinical pheotypes was analysed using Comparative Genomics (CG) pipeline of BIOiPLUG Apps. Clinical severity of UC was classified to remission, mild, moderate and severe by Mayo score. Disease extent of UC was classified to proctitis, left-sided colitis and extensive colitis.

Results: The mean age and sex ratio were not different between the groups. Community α-diversity of faecal bacteria measured in Chao 1 was significantly lower in UC and CD, compared with HC ($p < 0.01$). B-diversity measured by Bray-Curtis dissimilarity in UC and CD was significantly different from that of HC ($p < 0.01$). The β-diversity was also different between UC and CD ($p < 0.01$). The greater extent of the UC was related to the lower α-diversity of the faecal bacteria. Also, the worse severity of the UC was related to the lower α-diversity. There were significant differences in abundance of some bacterial species between the groups. *Eisenbergiella tayi, Parabacteroides goldsteinii, Akkermansia muciniphila*, and

Bacteroides intestinalis are 10 times or more abundant in HC than UC. *Clostridium innocuum* group, *Lactobacillus paracasei* group, *Lactobacillus crispatus* group, *Bifidobacterium dentium* group, *Butyricicoccus pullicaecorum*, *Eggerthella sinensis*, and *Proteus vulgaris* group are 10 times or more abundant in UC. *Leuconostoc lactis* group, *Coprococcus eutactus* group, *Akkermansia muciniphila*, *Lactococcus garvieae* group, *Adlercreutzia equolifaciens* group, *Weissella confusa* group, and *Lactococcus lactis* group are 100 times or more abundant in HC than CD. *Proteus vulgaris* group, *Morganella morganii* group, *Turicimonas muris*, and *Dysgonomonas capnocytophagoides* are 100 times or more abundant in CD.
Conclusions: Gut bacterial dysbiosis in Korean IBD patients is characterised by alterations in biodiversity and composition. The degree of dysbiosis is associated with disease severity and extent in UC. There are some differences in bacterial abundancy between IBD patients than HC. These data may help discriminate disease phenotypes, predict clinical course, and discover new therapeutic targets in IBD.

P857

The microbiota profile reflects disease severity in paediatric onset IBD

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Background: Over the last decade, reports have emerged that describe a distinct microbiotic profile (decreased diversity and density) in both Crohn's disease (CD) and ulcerative colitis (UC) which was again distinct from healthy controls. However, in recent years we have been able to sequence the microbiotic profile to the species level, which have changed the interpretation of some of the older studies. In this study, we aimed to describe the microbiotic profile in a cohort of paediatric IBD patients.
Methods: We collected faecal samples from a cross-sectional cohort. Faeces were stored at -80 degrees Celsius before analysis. The microbiome analysis was done using 16S and 18S rRNA sequencing with the miSeq instrument. The software 'BION' was used for OTU picking. The statistical program 'R' was used for further statistical analysis. Faecal calprotectin (FC) was analysed by ELISA on the same faecal samples. As faecal samples were not instantly frozen after collection, we only report on species presence/absence. Patient charts were retrieved and data recorded regarding medical treatment and surgery in the year after faeces samples were collected.
Results: 143 patients (77 CD / 58 UC / 8 IBDU) and 34 healthy controls were included. We found a significant difference in richness (number of observed species) between disease groups (controls vs. UC ($p < 0.001$), controls vs. CD ($p = 0.04$) and CD vs. UC ($p = 0.009$) with controls having the highest number of different species and UC the lowest. Moreover, a high degree of intestinal inflammation (assessed by f-calprotectin) and extensive disease localisation was associated with reduced diversity in UC ($p = 0.02$ and $p = 0.04$, respectively) but not in CD ($p = 0.94$ and 0.11, respectively). We identified 9 species that were significantly associated with a healthy microbiome and 2 species that were associated with IBD. The 3 species that were most significantly associated with a healthy microbiome were *Akkermansia muciniphila*, *Gemmiger formicilis* and *Bacteroides massiliensis*. No association was found between the microbiome composition and the need of medical treatment or surgery. Finally, using 18S rRNA analysis, we found no associations between the presence of parasites and IBD.
Conclusions: Patients with IBD had a decreased diversity in their faecal microbiome and the IBD type influenced the degree of the reduced diversity. Moreover, we identified 9 species that were more often present in healthy controls. Finally, we found that the composition of the microbiome was affected by the grade of the intestinal inflammation. These findings should be kept in mind when planning future studies with probiotics as a possible treatment of IBD.

P858

Impact of ileocaecal resection on gut microbiota in ileal Crohn's disease patients

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Background: Ileocaecal resection is the most commonly performed operation for Crohn's disease (CD), but it is presently unclear if this affects the gut microbiome. This study aims to compare the gut microbiota composition between CD patients with and without an ileocaecal resection.
Methods: Stool samples and clinical data were collected from 30 patients with ileal CD in remission with a history of ileocaecal resection and without previous bowel surgery (control group), matched for gender and age. The faecal microbiota composition was characterised by 16S ribosomal RNA sequencing. Microbial diversity was assessed using the Shannon index and principal component analysis. Taxonomic differences between the two groups were determined using the statistical framework analysis of composition of microbiomes (ANCOM).
Results: In total, 15 patients with and 15 patients without a previous ileocaecal resection were included. The median time between surgery and study enrolment was 12 years. Gut microbial diversity was significantly reduced in patients who underwent an ileocaecal resection compared with the control group. This was accompanied by an increased relative abundance of the family Veillonellaceae and a decreased relative abundance of the family Ruminococcaceae and the genus Faecalibacterium in patients with a history of an ileocaecal resection.
Conclusions: Gut microbial diversity is decreased in ileal CD patients who previously underwent an ileocaecal resection relative to ileal CD patients without a history of intestinal resection. This is associated with differences in the proportion of several bacterial taxa and suggests that ileocaecal resection has a profound impact on the gut microbiota in patients with CD.

P859

Hepatitis E seroprevalence in Portuguese inflammatory bowel disease patients under immunosuppression is higher than expected

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Background: Hepatitis E virus (HEV) infection has been recognised over the past decade as an emerging disease. Immunosuppressed patients can develop chronic HEV infection, with the level of immunosuppression determining the clinical course of infection. Inflammatory bowel disease (IBD) patients frequently receive immunosuppressant agents, but the risk of developing chronic HEV infection has not been extensively accessed in this group of patients. Seroprevalence in developed countries is variable with the reported prevalence in portuguese general population being 19.9%. The aim of this study was to determine HEV seroprevalence in patients with IBD undergoing immunosuppression.
Methods: We prospectively tested all consecutive IBD patients referred to the specific Infectious Diseases Prevention in Immunocompromised Patients outpatient clinic of our institution. Anti-HEV-IgG antibodies were detected in serum by commercial enzyme immunoassay (HEV Ab, DiaPro Diagnostic Bioprobes, Milan, Italy), following the manufacturer's instructions. Level of immunosuppression was defined according to IDSA criteria. Disease activity was defined as a Harvey–Bradshaw Index Score ≥5 or a Total Partial Mayo Index Score ≥2.
Results: A total of 62 patients were included (median age 48.8 years, IQR 39,2–58,6 years; 51.6% male), with a median disease time of 19 years (IQR 13–25 years). The majority were diagnosed with Crohn's disease (n = 57, 91.9%), the remaining with ulcerative colitis (n = 5, 8.1%). A minority of the patients had active disease (n = 7, 11.3%). Almost half of the patients were treated with combination therapy (n = 28, 45.2%), 22 (35.5%) were under anti-TNF therapy only and 12 (19.4%) on immunomodulator only. Additionally, 2 patients were receiving corticosteroids (prednisolone >20 mg/day). Overall, 51 (82.3%) patients were receiving high-level immunosuppression. Anti-HEV antibodies were positive in 22/62 patients (35.5%), equivocal in 1/62 (1.6%) and negative in 39/62 (62.9%). Although non-significant, anti-HEV positivity increased with the degree of immunosuppression as follows: 3/12 (25%) under immunomodulators, 7/22 (31.8%) under anti-TNF therapy and 12/28 (42.9%) with combination therapy. From the positive anti-HEV patients, only 1 patient had elevated transaminases. There was also no relation between anti-HEV positivity with transaminases elevation or disease activity.
Conclusions: A higher than expected prevalence of anti-HEV antibodies positivity was detected in our institution immunosuppressed IBD patients and, although non-significant, anti-HEV positivity increased with higher levels of immunosuppression.

P860

Evaluation of the probiotic features of two different multi-strain probiotic preparations from two different manufacturers

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Background: The aim of this work was to compare the probiotic adhesion features and immunomodulatory properties of 2 probiotic products characterised by the same bacterial content but manufactured in different places (Italy and USA).
Methods: The multi-strain probiotic products under investigation were composed by a mixture of 8 different strains. The two products were manufactured in Italy (VSL#3 - Lot 710061 expiry date 10/2019) and in US (Vivomixx - Lot 1708702 expiry date 31/03/2019). The cell viability in each lot was assessed by flow cytometry. The adhesive abilities of probiotics were evaluated on three different eukaryotic intestinal cell lines (Caco-2, HT-29 and mucus-producing HT29-MTX).
For the evaluation of immune-modulatory activity, human Dendritic Cells (hDCs) obtained from blood mononuclear cells were exposed for 6 days to cytokines cocktail (IL-4 20 ng/ml + GM-CSF 50 ng/ml) and then to both probiotic mixtures for 2 h with MOI 1:10. A positive inflammatory condition was obtained by incubating washed hDCs in fresh medium containing Salmonella sp. for additional two h. Finally, hDCs were then cultured for 23 h in complete medium with antibiotics for the final analysis of soluble and surface molecules with ELISA or cytofluorimetric analysis method, respectively.
Results: The two products showed a comparable amount of live cells, 2.2 1011 (FU/g) and 2.4 1011 (FU/g), respectively, for the VSL#3 and Vivomixx. The two tested products showed similar adhesive capacity to the 3 cell lines considered, with adhesion values in the range 67–71%. No significant differences were observed in the percentage of adhesiveness expressed by the two mixtures according to the type of cell line considered. Regarding the immune-modulatory ability of the two tested products, results showed that they have the same behaviours. The exposure of the probiotic mixtures to hDCs resulted in a meaningful reduction of the expression of IL-12 following Salmonella induction. We observed that both products slightly increase the proportion of HLA-DR+/CD11+ and CD80+/CD11+ hDCs. Moreover, both mixtures significantly reduce Salmonella-induced HLA-DR+/CD11+ and CD80+/CD11+ hDCs. Both probiotic products did not significantly induce TNF-α production by hDCs at basal condition, and they did not result in further TNF-α production if compared with that induced by Salmonella sp. alone even if the response of the two products was almost identical.
Conclusions: Investigative activities described in this work demonstrated a comparable adhesive performances and interesting immunomodulatory activity against inflammation induced by Salmonella sp. for both VSL#3 and Vivomixx showing same behaviours irrespective of the manufacturer.

P861

Differences in bacteroidal genotypes between newly diagnosed ulcerative colitis patients and healthy controls

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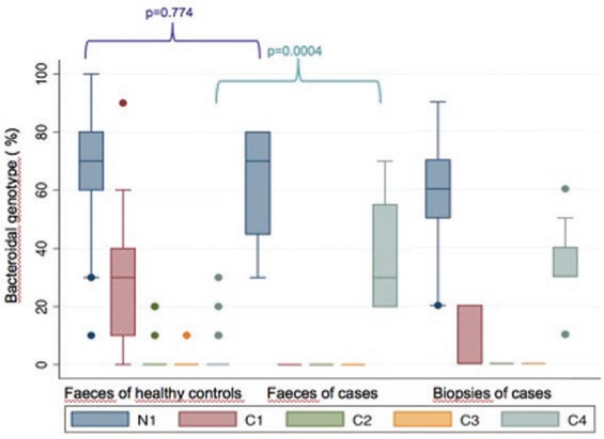
Background: Dysbiotic conditions and changes in the gut immune system can disturb the mutualistic relationship between the host and the gut microbiota, leading to inflammatory bowel disease. The aim of this study was to analyse the differences in a major type of

intestinal commensal bacteria belonging to Bacteroidetes phylum in both newly diagnosed patients with ulcerative colitis (UC) and in healthy controls (HC).

Methods: A prospective case–control study of the Bacteroidetes phylum composition in the intestinal bacteria obtained from faeces and biopsies of UC patients and from faeces of HC was performed. All newly diagnosed patients older than 18 years, who underwent colonoscopy in our IBD unit between July 2017 and July 2018 were consecutively included. Exclusion criteria were previous IBD treatment, antibiotics or probiotics in the last month, current malignancy tumours and any inmunomediate disease. A polymerase chain reaction designed to detect human-specific markers targeting Bacteroidetes-like 16S rRNA genes in DNA samples was used. The disease extension, Mayo endoscopic score (Mayo ES), faecal calprotectin and C reactive protein (CRP) were also recorded at the moment of diagnosis. Bacteroidal genotypes were compared between patients with UC and HC using the Mann–Whitney U test. A linear regression was performed to evaluate the relationship between calprotectin, CRP and bacteroidal genotype. A Spearman test was performed to analyse the relationship between clinical features and bacteroidal genotype.

Results: 11 UC patients (mean age 52, 58% male) and 22 HC (mean age 45.5, 60% male) were consecutively included. Seventy-five per cent had a Mayo ES of 2. 39% were E1, 36% E2 and 25% E3. A total of 5 bacterial genotypes of the genus Bacteroides: N1, C1, C2, C3 and C4 were found. The C4 genotype was identified in all UC patients (100%) whereas it only appeared in 4 of 22 HC (18.1%).



Bacteroidal genotypes in biopsies and faeces of UC patients and faeces of HC.

There were no differences between the genotypes found in faeces and biopsies of cases. The median of calprotectin was 498 µg/g when the percentage of C4 was < 25% and 708 µg/g when C4 were >25% (p = 0.458). No differences were found between CRP value and level of C4. No association was found between C4 percentage and either the disease extension or the Mayo ES.

Conclusions: C4 bacteroidal genotype is present in all newly diagnosed UC patients whereas it was only identified in a small number of healthy controls. No association was found between clinical, biomarkers or endoscopic features and percentage of C4 genotype.

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Nurses presentations

Nurses presentations

Nurses oral presentations

N01

Fatigue and physical activity in individuals with inflammatory bowel disease: a feasibility cross-sectional, correlational study

Please refer to N01 in the chapter for "Nurses poster presentations"

N02

Inflammatory bowel disease and pregnancy: the impact of education in knowledge and attitude of women in reproductive age; one-year follow-up study

Please refer to N02 in the chapter for "Nurses poster presentations"

N03

Can post biologic infusion monitoring be reduced? A mulit-centred retrospective study

Please refer to N03 in the chapter for "Nurses poster presentations"

Nurses poster presentations

N01

Fatigue and physical activity in individuals with inflammatory bowel disease: a feasibility cross-sectional, correlational study

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Background: Fatigue is a problematic and burdensome symptom experienced by individuals with inflammatory bowel disease (IBD). The optimal management of fatigue remains poorly understood, with physical activity likely to be a beneficial way to manage the symptom. However, physical activity levels are reduced in patients with IBD compared with healthy controls. This study aims to investigate the relationship between fatigue and physical activity and intensity of activity in individuals with IBD.
Methods: A multi-centred, cross-sectional, correlational feasibility study was employed. A consecutive sample of 21 patients with Crohn's disease or ulcerative colitis were recruited from two IBD centres in the Republic of Ireland. The IBD Fatigue scale was used to measure fatigue and triaxial accelerometers (ActiGraph wGT3X-BT) objectively measured physical activity levels and intensity of activity undertaken during seven consecutive days.
Results: A moderate level of fatigue (IBDF Section 1 Md (IQR) = 11 (6–12)), predominantly intermittent in nature (76.2%) was reported by participants (81% female; 66.7% Crohn's disease; 71% active disease). On average, participants self-reported sleeping 9 h per night. Over the week, the intensity of activity was predominantly sedentary (Md 5 days, 19 h, 33 min) or light (Md 21 h, 44 min). The median moderate-to-vigorous intensity of physical activity per day was 36 min and step count over the week was 50,732 steps. A strong, positive, statistically significant relationship was found between level of fatigue and average kCal per day ($r_s = 0.538$, $p = 0.047$, $n = 14$), indicating that those with greater physical activity energy expenditure had higher levels of fatigue. A moderate, positive, relationship was found between level and impact of fatigue, and light intensity of activity over the week (IBDF Section 1 $r_s = 0.391$, $p = 0.080$; IBDF Section 2 $r_s = 0.365$, $p = 0.104$, $n = 21$), indicating that those engaged in greater light intensity physical activity experienced higher levels and impact of fatigue. In contrast, a strong, negative, statistically significant relationship was found between time in vigorous activity over the week and impact of fatigue ($r_s = -0.812$, $p = 0.050$, $n = 6$) for those in remission, suggesting that participants undertaking more vigorous physical activity had a lower impact of fatigue.
Conclusions: A larger multi-centre study investigating the relationship between fatigue and physical activity and intensity of activity is feasible and warranted. It has the potential to contribute to the modelling and development of a physical activity intervention specifically designed for the management of IBD fatigue.

N02

Inflammatory bowel disease and pregnancy: the impact of education in knowledge and attitude of women in reproductive age; one-year follow-up study

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Background: Because inflammatory bowel disease (IBD) affects women in reproductive age, knowledge and beliefs about pregnancy must be assessed in those women. The aim of this study was to compare (a) knowledge level and beliefs about pregnancy before and after educational intervention and (b) the same parameters in the group of women who underwent this educational intervention to women who did not undergo training.

Methods: Eligible were outpatient IBD women of reproductive age. After obtaining a consent, demographics, clinical data and current treatment were recorded and all patients were invited to complete (a) the Crohn's and Colitis Pregnancy Knowledge Score (CCPKnow), which categorised in poor (0–7), adequate (8–10), good (11–13) and very good (≥14) level and (b) a structured tool formed for this study which assessed pregnancy beliefs. Subsequently, patients were randomly distributed in two groups, control group (CG) and intervention group (IG). Women in IG received a face-to-face educational training regarding pregnancy, and were given an educational leaflet. Then, patients were followed in the IBD Clinic at 3, 6, and 12 months after baseline with clinical assessment, laboratory tests and filling the same questionnaires.

Results: Overall, 43 and 39 women were allocated to the IG and CG, respectively (Table 1).

INTERVENTION GROUP			
PHASE	**POSITIVE IMPACT IN CCPKNOW**	**NEGATIVE IMPACT IN CCPKNOW**	**P**
BASELINE: Pre-education	• Use of 5-ASA, azathioprine, 6-MP and biological agent • Higher educational level • Beliefs that a woman must take medication to control a flare during a pregnancy and that a woman suffering from IBD is able to have a healthy baby	• Increase of age • Increase of years from diagnosis • Type of disease, • Corticosteroids • Belief of inability of breastfeeding	<0.05
Post-education	Nothing statistically significant		
3-MONTHS	Nothing statistically significant	Disagreement with the statement that: • I am considering not having a baby due to IBD • I am unable to breastfeed because I receive medication for IBD • I believe that I am able to take care of a baby	<0.05
6-MONTHS	Nothing statistically significant		
12-MONTHS	Nothing statistically significant		
CONTROL GROUP			
BASELINE	Agreement with the statement: • Medication which maintains remission should be continued during pregnancy • IBD women are able to have a vaginal delivery • Breastfeeding should be avoided under specific medication • Women with IBD are likely to have a difficult pregnancy	• Crohn's disease	<0.10
3-MONTHS	Nothing statistically significant	• Use of 5-ASA • Increase of age	<0.05
6-MONTHS	• Increase of hospital visits • Higher educational level • Crohn's disease • Disagreement with beliefs that a woman is less probably to be pregnant due to IBD or must stop every IBD medication when she tries for a baby	• Use of 5-ASA, biological agent	<0.05
12-MONTHS	• Higher educational level	Nothing statistically significant	<0.10

Basic demographics and clinical characteristics.

At baseline, both groups had poor knowledge. After educational program the level of Knowledge increased significantly in the IG over baseline and was persistently high during follow-up (Table 2).

INTERVETION GROUP					
PHASE	**CCPKNOW**				
	POOR	**ADEQUATE**	**GOOD**	**VERY GOOD**	**p**
BASELINE: • PRE-EDUCATION	24 (55.8%)	11 (25.6%)	5 (11.6%)	3 (7%)	<0.01
• POST EDUCATION	0 (0%)	1 (2.3%)	1 (2.3%)	41 (95.3%)	
3- MONTHS	0 (0%)	0 (0%)	7 (7%)	36 (83.7%)	0.237
6- MONTHS	0 (0%)	0 (0%)	3 (7%)	40 (93%)	<0.01
12-MONTHS	0 (0%)	0 (0%)	0 (0%)	43 (100%)	<0.01
CONTROL GROUP					
BASELINE	28 (71.8%)	7 (17.9%)	4 (10.3%	0 (0%)	>0.05
3- MONTHS	23 (59%)	7 (17.9%)	4 (10.3%)	5 (12.8%)	
6- MONTHS	23 (59%)	6 (15.4%)	5 (12.8%)	5 (12.8%)	
12-MONTHS	23 (59%)	6 (15.4%)	5 (12.8%)	5 (12.8%)	

CCPKnow results.

In both groups, clinical characteristics and beliefs affected the CCPKnow score statistically (Table 3).

BASIC DEMOGRAFICS/ CLINICAL CHARECTERISTICS	**INTERVETION GROUP**	**CONTROL GROUP**
PARTICIPANTS	43	39
AGE (MEDIAN/RANGE)	28.5 (20-47)	36.9 (27-47)
EDUCATIONAL LEVEL: • Primary • Secondary • Tertiary	 • 2 (4.6%) • 21 (48.8%) • 20 (46.5)	 • 0(0%) • 24 (61.5%) • 15 (38.5%)
MARITAL STATUS: • Married • Unmarried • Divorced	 • 7 (16,3%) • 35 (81.4%) • 1 (2.3%)	 • 19 (48.7%) • 14 (35.9%) • 6 (15.4%)
LIVING CONDITION: • Alone • With family/ third person	 • 15 (34.9%) • 28 (65.1%)	 • 3 (7.7%) • 36 (92.3%)
JOB CONDITION: • EMPLOYED • UNEMPLOYED • STUDENT	 • 20 (46.5%) • 10 (23.3%) • 13 (30.2%)	 • 20 (51.3) • 0 (0%) • 19 (48.7%)
TYPE OF DISEASE: • CROHN'S DISEASE • ULCERATIVE COLITIS	 • 27 (62.8%) • 16 (37.2%)	 • 18 (46.2%) • 21 (53.8%)
YEARS SINCE DIAGNOSIS (MEDIAN/ RANGE)	8.5 (1-22)	9.7 (2-28)
HOPITAL VISITS DURING THE LAST YEAR (MEDIAN/RANGE)	6.1 (2-12)	5.4 (1-30)
BELIEF THAT DISEASE IS A SERIOUS HEALTH PROBLEM: • YES • NO	 • 27 (62.8%) • 16 (37.2%)	 • 26 (66.7%) • 13 (33.3%)
BELIEF THAT DISEASE IS A CHRONIC CONDITION: • YES • NO	 • 38 (88.4%) • 5 (11.6%)	 • 31 (79.5%) • 8 (20.5%)
TYPE OF MEDICATION: • 5-ASA • CORTICOSTEROIDS • 6-MP & AZA • METHOTREXATE • BIOLOGICAL AGENTS	 • 16 (37.2%) • 2 (4.7%) • 7 (16.3%) • 0 (0%) • 37 (86%)	 • 22 (56.4%) • 1 (2.6%) • 7 (17.9%) • 3 (7.7%) • 16 (41%)
SIDES EFFECTS: • YES • NO	 • 6 (14%) • 37 (86%)	 • 10 (25.6%) • 29 (74.4%)

Statistically significant results for both groups.

Differences in knowledge between groups were statistically significant in every phase of the study ($p < 0.05$), which indicates that a woman in IG is more likely to have a better knowledge level. Beliefs, in both groups, did not change significantly during the study.

Conclusions: CCPKnow level was enhanced and maintained in IG after one educational session statistically. Probably education in women with IBD bridges the gap between patients and healthcare providers and finally reduces the percentage of voluntary childness in IBD women.

N03

Can post biologic infusion monitoring be reduced? A mulit-centred retrospective study

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Background: Increased availability of biologic medication to treat inflammatory bowel disease (IBD) is beneficial to patients but puts increased pressure on infusion clinic capacity. Facilitating infusions in a safe and timely manner has become difficult. Manufacturers of both infliximab (IFX) and vedolizumab (VDZ) recommend patients are monitored post infusion for defined periods, to observe for potential post infusion reactions. Ustekinumab has no recommended post infusion observation period. We wanted to explore if we could consider reducing all post biologic infusion times.
Methods: We retrospectively reviewed infusion data (IFX and VDZ) a 12 month period across three sites (Royal London Hospital-RLH, University College London Hospital- UCLH, St Marks Hospital-STM) from IBD CNS (clinical nurse specialist) led infusion clinics and identified incidence and timing of infusion reactions.
Results: 4182 infusions of IFX for patients >18 years old (RLH n1152, UCLH n822, SMH n2208) were administered over the 12 month period. Sixteen infusion reactions were documented (0.4%) RLHn 9, UCLHn 3, SMHn 4. All reactions occurred within the first 20 min of the infusion starting. No infusion reactions were observed in the post infusion observation period. 2132 infusions of VDZ for patients > 18 years old (RLH n330, UCLH n626, SMH n1176) were administered over the 12 month period. Three infusion reactions were documented (0.14%) RLH n0, UCLH n2, SMH n1. All reactions occurred within the first 20 min of the infusion starting. No infusion reactions were observed in the post infusion observation period. In total patients were observed for 6665 h post infusion across the 3 sites for both IFX and VDZ.
Conclusions: We reviewed 6314 infusions (IFX n4182 VDZn 2132). Reactions occurred in n19 (0.3%) all within the first 20 min of the infusion starting. This suggests close monitoring of patients during the first 20 min is required. No reactions occurred within the manufacturers recommended post infusion observation period. This large multi -centre retrospective study demonstrates the risk of adverse reactions to either IFX or VDZ during the post infusion observation period is very rare. These findings suggest patients who have not had a reaction during their infusion do not routinely need post infusion observation. We hope to change practice by reducing the amount of time patients must spend being observed post infusion to enable a more efficient service whilst still providing safe and appropriate care.

N04

Interventions for managing fatigue in inflammatory bowel disease: A Cochrane systematic review

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Background: Fatigue is a common, debilitating and burdensome symptom experienced by individuals with inflammatory bowel disease (IBD). The subjective, complex nature of fatigue can often hamper its' management, and the effectiveness of treatments for fatigue in IBD remains unknown. The aim of this Cochrane review is to assess the efficacy and safety of pharmacological and non-pharmacological interventions for managing fatigue in IBD.
Methods: A systematic search was undertaken. Data were extracted and study quality was independently assessed by two authors. Standard Cochrane methodological procedures were used.
Results: Fourteen randomised controlled trials were included (3741 participants; all adults; 6 in Crohn's disease (CD); 2 in ulcerative colitis (UC); 6 in both CD and UC). The interventions varied widely and included nine pharmacological trials, four non-pharmacological trials, and one multi-modular trial. Only four trials were designed specifically as interventions for managing fatigue. None of the included studies were free from risk of bias. Only one meta-analysis was possible, due to the diversity and limited number of studies for each intervention. We found some evidence suggesting possible improvements in fatigue for adalimumab 40 mg administered every other week and adalimumab maintenance therapy (only for those known to respond to adalimumab induction therapy), ferric maltol, electroacupuncture, self-directed stress management, solution focussed therapy and physical activity advice. We found no clear improvements in fatigue for adalimumab 40 mg administered weekly, *Agaricus blazei* Murill-based mushroom extract, guided stress management or omega-3. There was also no significant difference in fatigue scores between cognitive behavioural therapy with therapist support, compared with information leaflet only group, however this was a feasibility trial and a trend was observed. Reporting in some of the trials was insufficient to assess the efficacy and safety of some therapies, including vitamin D3 supplementation, ferumoxytol, vedolizumab, and tight control customised management.
Conclusions: It is difficult to draw firm conclusions about the effectiveness of interventions to improve fatigue for individuals with IBD, as there is insufficient quantity and quality of evidence available. Further randomised controlled trials are needed to assess the efficacy of therapies specifically designed for fatigue management.

N05

A Nurse Practitioner (NP) supervised INFLAMMATORY BOWEL DISEASE (IBD) virtual immunomodulator therapy (IM) monitoring service is associated with reduced healthcare costs, increased patient adherence and persistence and improved treatment outcomes

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Background: Monitoring patients on IMs is a key role of the IBD nurse with 70% of IBD patients receiving IMs at some stage in their treatment journey. IMs are associated with significant risk if not monitored closely, particularly in the first weeks after commencement. Data suggest that 25–40% develop adverse events (AEs) necessitating treatment withdrawal. The main AEs are idiosyncratic

reactions typically occurring in the first 4 weeks, dose dependant AEs such as bone marrow suppression, hepatotoxicity and increased infection risk. Rarer AEs such as NMSC and lymphoma may occur with prolonged use. Despite publications describing the importance of education and blood test monitoring there has not been consensus on monitoring frequency in Australia. Use of TPMT and metabolite testing to guide initial dosing and dose escalation is not standardised and inaccurate patient perceptions about IM safety profile and high incidence of AEs can all affect patient adherence and persistence.

Methods: A literature review and service audit of prescribing and monitoring practices within our service was conducted in 2017, this identified key areas for improvement and risk reduction. A service action plan was developed and the NP supervised IM clinic was implemented in January 2018.

Issues	Risks	Plan
Lack of standard pre treatment screening Inconsistent prescribing and monitoring practices	Inconsistent dosing of therapies Subtherapeutic dosing High cost of inappropriate blood tests	Literature review Develop standardised screening treatment and monitoring guidelines
NO referral pathway for IM monitoring	Increasing patients lost to follow up & high risk of unmonitored AEs	Develop clear patient referral and follow up pathway
Pathology Provided by many different providers	Increasing nurse time chasing results	Develop structured monitoring protocol
No patient education prior to initiation of IM and high patient drop out rates due to fear of AEs	Poor patient adherence and persistence with treatment and monitoring	Develop patient held education and monitoring booklet
High numbers of abnormal blood results and AEs	Increasing burden on outpatient clinics	Develop a NP virtual clinic for review of abnormal results and AEs
Poor GP communication and involvement	Increasing workload for IBD Nurse coordinating monitoring	Develop GP shared care IM monitoring guidelines
No data collection	Poor documentation of Adverse events and treatment outcomes	Develop an IM database

Table 1 Service audit and action plan 2017

Results: 115 referrals were received January-Jun 2018. Thiopurine monotherapy was the most commonly prescribed IM accounting for 53% of referrals, with an additional 29% in combination with allopurinol. AEs were experienced by 62% patients. Eighteen per cent experienced side effects with the commonest being idiosyncratic reactions; nausea, vomiting and arthralgia. Forty-four per cent developed abnormal thiopurine metabolites evaluated by early implementation of metabolite testing.

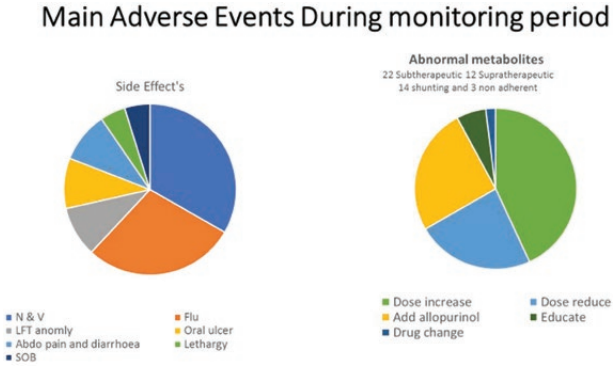

Table 2. Main adverse events (AEs) during monitoring period.

72 AEs were managed in the virtual clinic, of which 47 required dose or IM change, 16 required phone follow-up, 1 admitted and 7 required clinic appointments. Despite a high AE incidence, 109 patients remained on IMs at clinic discharge, all demonstrating therapeutic metabolites. Standardising monitoring and reviewing patients in a virtual clinic released 294 IBD appointments and was associated with a cost saving of $16 750.

Conclusions: Implementing a standardised screening, prescribing and monitoring protocol and referring patients commencing IMs to a nurse led virtual monitoring clinic is cost effective, safe and ensures patient adherence and persistence to therapeutic doses of IMs.

N06

Patient-reported outcomes in daily clinical care of patients with inflammatory bowel diseases

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Background: Personalised care of patients with inflammatory bowel disease (IBD) involves measuring outcomes that matter most to the patient. Patient-reported outcomes (PROs) measure various aspects of a patient's health condition and its impact on general well-being and psychosocial functioning. PRO's are directly reported by the patient without interpretation of a healthcare professional (HCP).

Methods: We developed an electronic PRO assessment tool for the evaluation of patients visiting the outpatient clinic at our referral IBD centre. This secured web-based tool incorporates questionnaires covering several aspects of IBD. Disease activity is measured using the PRO2 (Crohn's disease) or the Simple Clinical Colitis Activity Index (SCCAI) (ulcerative colitis). In case of non-remission (PRO2≥8/SCCAI≥3), the IBD control questionnaire is requested. IBD-related disability is evaluated with the IBD disk and health-related quality-of-life with the Short Health Scale. Visual analogue scales and open questions are also incorporated. The questionnaires are completed in approximately 5 min on a tablet in the waiting room, before the face-to-face contact between the patient and the HCP takes place. Results are displayed in real-time on a dashboard that can be reviewed by both the patient and the HCP.

Results: The use of a PRO assessment tool has several advantages. (i) It makes the contact between the patient and the HCP more efficient. (ii) Patients feel more engaged in their care since the interaction starts from their perspective. The visualisation on a dashboard further empowers patients by showing the evolution of PRO's over time, thereby incorporating also several biomarkers (e.g. haemoglobin, C-reactive protein) (Figure 1).

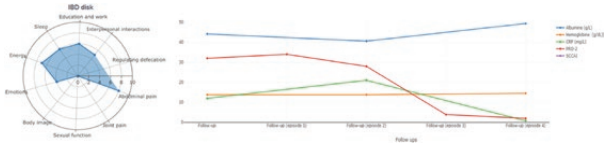

Figure 1. IBD dashboard

(iii) A pre-visit assessment gives patients more time to track down their biggest concerns. (iv) It provides a gigantic amount of systematically obtained objective patient data. Potential drawbacks of the tool are difficulties to deal with the tablet or to correctly understand the questions, and a poor patient motivation. The roles of the IBD nurse are (i) to assist patients when using the tool, especially at its introduction or in patients with advanced age and/or lower educational background; (ii) to help patients to interpret the data; (iii) to optimise patients' adherence to the tool.

Conclusions: Use of a PRO assessment tool improves personalised IBD patient care and facilitates prospective data collection. The IBD nurse needs to assist patients to get acquainted with the tool.

N07

'It's about willpower in the end. You've got to keep going': a qualitative study exploring the experience of pain in inflammatory bowel disease

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Background: Pain is a widely experienced symptom of inflammatory bowel disease (IBD), which has significant psychological and functional impacts on patients. Despite this, the aetiology of chronic pain and pain management is a poorly understood area of IBD research. This qualitative study aimed to gain an insight into the experiences of individuals with IBD and pain, the pain management strategies they use and any needs for future pain management interventions.
Methods: Participants who previously completed a questionnaire on pain in IBD and consented to follow-up interviews were selected using a purposive sampling framework. Fourteen individuals with IBD were interviewed (either face-to-face or telephone) using a topic guide. Interviews were transcribed and analysed using inductive thematic analysis.
Results: Themes identified were 'vicious cycles', 'findings solutions' and 'attitudes'. The experience and impact of pain were rarely viewed in isolation, but rather within the context of a cycle of IBD symptoms, particularly fatigue and urgency. Other 'vicious cycles' identified included anxiety, avoidance and inactivity and poor understanding and communication. Pain management strategies varied considerably between patients, with many using a variety of short and long-term strategies. The continued search for a solution to their pain had an emotional impact on individuals. There were contrasting attitudes from different participants, including defeat, tolerance and acceptance.
Conclusions: This study provides an understanding of the experience and impact of pain in IBD. The interaction of pain with accompanying IBD symptoms has an emotional and physical impact on patients, and creates a barrier to adequate assessment, understanding and treatment of pain. Due to inconclusive and inconsistent evidence in pain management for IBD, patients largely rely on their own experiences and a trial and error approach to apply helpful strategies. Over time this can be mentally draining and exhausting for patients. Adjuvant behavioural therapies may be beneficial for patients experiencing pain and psychological distress, and may enable self-management.

N08

Real-world experience: Treatment of iron deficiency anaemia (IDA) with intravenous (IV) iron in inflammatory bowel disease

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Background: IDA is common in patients with inflammatory bowel diseases, and the relevant ECCO 2015 Guidelines recommend IV iron as first-line treatment in patients with active disease, severe anaemia or unable to tolerate oral iron. Iron isomaltoside is an IV iron introduced to our hospital in October-16, and it allows delivery of high doses of up to 20 mg of iron per kg of body weight in a single administration. The purpose of this study was to evaluate our anaemia treatment service.
Methods: The medical records of patients who received iron isomaltoside between 16 October and 18 April were retrospectively examined, and data on demographics, IV iron dose, haemoglobin (Hb)/ iron parameters and adverse drug reactions (ADRs) was collected.
Results: A total of 90 patients were treated in the 18-month audit period; 65/90 (72%) were females. Twenty-six of 90 (29%) patients were on concomitant biological treatment, 4/90 (4%) on thiopurine and 7/90 (8%) on mesalazine. Mean patient weight was 68 (range: 35–121) kg, baseline Hb 100 (26–144) g/l and ferritin 28 (2–160) µg/l. Mean prescribed IV iron dose was 1292 mg, 44/90 (49%) patients were prescribed >1000 mg of iron, and 66% of patients received their total prescribed dose in one administration, while 16 fewer administrations took place compared with the administrations that would have been needed with our previous IV iron. At 1-month post-administration, mean Hb rose by 23 g/l to 123 (84–162) g/l, and ferritin by 60 µg/l to 88 (19–464) µg/l. At 6-months, mean Hb was maintained at 122 (73–161) g/l and ferritin further increased to 115 (12–452) µg/l. A total 2/120 (1.7%) of ADRs took place; none was serious, and the infusion was completed successfully in all patients.
Conclusions: Patients with gastroenterological diseases have high iron needs. Mean Hb increased satisfactorily post-IV infusion and was maintained at 6-months post-administration. Iron isomaltoside was an effective, well-tolerated and resource-saving treatment.

N09

IBD nurse intervention for patients assigned to biologic therapy decreases uncertainty and improves patient-reported outcomes

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Background: Commencing biologics in patients with inflammatory bowel diseases (IBD) is a major milestone that carries concerns due to multiple uncertainties. Data regarding psychological factors associated with doubts and reservations, and coping tools to overcome these challenges are scarce.
Methods: We launched a prospective randomised controlled study allocating adult patients with IBD for whom biologic therapy was recommended in our tertiary referral centre, to either standard or intensified IBD-nurse care. The standard IBD-nurse care includes a comprehensive walk-through explanation of the recommended treatment plan. In the intensified intervention we added one IBD-nurse visit and two follow-up phone calls for check-ups and updates. Patients' uncertainty score, measured by Mishel uncertainty in illness Scale,[1,2] and patients' reported outcome measures (PROMs), assessed by the IBD disk,[3] were evaluated in both groups at recruitment and at Week 14 after commencing therapy. Differences between scores

at recruitment and at Week 14 were used to assess the impact of the IBD-nurse care.

Results: A total of 76 patients were recruited over 8 months' period, of whom 34 patients completed 14 weeks follow-up after biologic therapy initiation. Age, baseline C-reactive protein, haemoglobin and faecal calprotectin levels and types of biologics did not differ between the standard and intensified groups at baseline. Uncertainty scores significantly improved within each group at Week 14: Δ in the standard group- 0.428 (IQR 0.515 –0.767), $p = 0.001$, and Δ in the intensified group - 0.428 (IQR 0.089–0.767), $p = 0.002$. The domains regulating defaecation and emotions were stable throughout the follow-up period in the intensified group but have deteriorated in the standard group (Δ:0 [-1.5 -3.5], $p = 0.021$ vs. 1 [-2.0–4.5], $p = 0.018$, and 0 [–3.0 –2.5], $p = 0.004$ vs. 1 [0.0–2.5], $p = 0.152$, respectively). The domains energy and sexual dysfunction improved in the intensified group compared with the standard group (Δ: –1 [–4.0 –3.0], $p = 0.001$ vs. 1 [–4.0–3.5], $p = 0.015$, and –1 [-3.0–0] $p = 0.005$, vs. 0 [–2.0–2.0], $p = 0.411$, respectively).

Conclusions: IBD-nurse care is associated with improvement in uncertainty scores among patients commencing biologic therapy. Intensified IBD-nurse care is associated with even greater improvement in PROMs like managing defection, well-being and sexual dysfunction. IBD-nurse care should be routinely implemented in the multi-disciplinary care scheme for patients with IBD.

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N10

Living with and managing symptoms of fatigue, pain and urgency in IBD: an exploratory qualitative study

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Background: Background: as part of the IBD-BOOST study, we aimed to produce primary data to inform development of an online self-management intervention for symptoms of fatigue, pain, and urgency in inflammatory bowel disease (IBD).

Methods: Methods: using exploratory qualitative methods, we recruited people with IBD from clinic and community sources and conducted focus groups in different UK locations. Focus groups were facilitated by experienced qualitative researchers, assisted by observers, and recorded on a digital audio device. Following consent, participants were asked to share their experiences of living with symptoms of fatigue, pain, and/or urgency, and explain how they self-manage these symptoms. Recordings were transcribed by a professional transcriber. Using the Common Sense Model which proposes that illness perceptions directly influence coping strategies, which in turn influence outcomes, we created a coding framework and applied it over three rounds of thematic analysis. Eight patients were consulted to agree the final structure of data and themes.

Results: Results: 25 participants (16 female; ages 23–58 years) each attended one of the five focus groups ($N = 3, 7, 6, 6$ and 3). Twelve had CD, 11 had UC and two had IBD-U. Duration of disease was three – 30 years. Three core themes emerged: (a) The Negative Impact of Symptoms: perceived causes and knock-on effects across symptoms, persistence and unpredictability of symptoms, effect on identity, and unwanted psychosocial emotional and intimate consequences; (b) Positively Taking Control: the different ways in which participants achieve control, their coping strategies and self-appraisal of their situation, the adaptations and changes they choose to make to manage these symptoms; (c) seeking and receiving support: the value of receiving understanding from friends and family, work managers and colleagues, and healthcare practitioners, the practices these people offer which are helpful, and impact on the person with IBD when symptom-related needs are not recognised. The persistent impact on physical and emotional well-being can be stark, forcing unwanted adjustments and limitations in working, social and intimate arenas of life. Uncertain and unpredictable symptoms are challenging. Managing diet, pacing oneself, accepting background levels of fatigue, pain and urgency, seeking support, exercising and attending to mental well-being, are all perceived to be helpful in self-managing symptoms.

Conclusions: Conclusion: Fatigue, pain, and urgency symptoms can persist for patients, either singly or in combination. Participants revealed several strategies for self-management, providing patient-focussed evidence to inform the development of an online intervention self-management programme.

N11

Patients' challenges of living with, and managing inflammatory bowel disease: a meta-synthesis

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Background: IBD can impact negatively on patients' lives, creating challenges for those affected. From previous research, these challenges tend to increase with disease activity (Jelsness-Jorgensen et al. 2011). Common challenges identified by patients affected by IBD include disease-related symptoms such as loose bowel motions, fatigue (Loven Wickman et al. 2016) and a lack of knowledge regarding their disease (Lesnovska et al. 2013). The psychological well-being of those with IBD may also be adversely affected, causing challenges for patients (Devlen et al. 2014; Argyriou et al. 2017; Sun Kim et al. 2017). It is postulated that an enhanced comprehension of patients' challenges may lead to the development of mechanisms to enhance patient-related outcomes (Pittet et al. 2016), the development of self-management interventions (Irvine 2004) and improvements in patients' quality of life (Casati et al. 2000). A meta-synthesis of all available published qualitative literature on the challenges of patients living with IBD and there management of these is

warranted in order to establish a comprehensive account of the body of evidence published to date. The aim of this meta-synthesis was to examine qualitative studies and data which reported on patients' challenges of living with and managing IBD focussing on the following research questions: What are the main challenges experienced by patients with IBD in their everyday lives? What impact do these challenges have on patients' lives? What strategies do patients use to manage the main challenges experienced?

Methods: Searches were conducted in five databases to locate articles deemed eligible for inclusion. The search resulted in the screening of 1,413 studies, of which, 13 studies were deemed eligible for inclusion.

Results: Four themes were identified from the literature extracted through thematic analysis; the unpredictability of living with IBD, the emotional turmoil of living with IBD, the social side of living with IBD and striving to maintain a normal life in managing IBD.

Conclusions: Patients with IBD experience many challenges including physical symptoms, long-term effects of IBD, lack of support, change of role within their domestic and social environments including school and work settings. The collective impact of these challenges were identified are social exclusion and poor psychological well-being. Data regarding the management of the challenges experienced was notably lacking although some evidence of 'striving towards normality' was apparent. This meta-synthesis has highlighted the compelling need to review and modify individual care plans to enhance the patients' lived experiences of IBD and develop interventions to assist patients with self-management.

N12

Microscopic colitis: struggling with an invisible, disabling disease

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Background: Microscopic colitis causes chronic or recurrent non-bloody, watery diarrhoea, which is associated with urgency, faecal incontinence and abdominal pain. The patient's health-related quality of life is often impaired. In microscopic colitis health-related quality of life has been studied using questionnaires originally constructed and validated for patients with inflammatory bowel disease. The aim of this study was to explore the impact of microscopic colitis on everyday life.

Methods: Inductive, qualitative, semi-structured interviews were performed with 15 persons suffering from Microscopic colitis. Participants were selected from an outpatient clinic in the south east of Sweden. The inclusion criteria were designed to ensure that the sample reflected the patient population and provided maximum variation in terms of age, sex, type of MC (CC or LC), disease activity and duration. All interviews were conducted by the first author in a room at the hospital. The interviews lasted for an average of 28 min (range 15–50 min) and were based on a semi-structured interview guide. In order to gain a deeper understanding of the phenomenon, probing questions were posed to encourage the participants to elaborate on and describe the impact of the disease on their everyday life. Content analysis was used to explore the impact of the condition on everyday life.

Results: The qualitative inductive content analysis generated one theme and five subthemes. The theme was 'Struggling with an invisible, disabling disease'. The five subthemes were: Physical experience of bowel function; Associated symptoms affecting quality of life; Impact of the disease on everyday life; disease-related worry; and strategies for managing everyday life. The overall theme that emerged revealed that MC remains a histological disease that appears invisible both when patients seek healthcare to obtain a diagnosis and when experiencing a lack of understanding from their social network. Several participants expressed that the time from seeking help from primary care to diagnosis was long, as no blood or faecal tests and no examinations reflected their own perception of the symptom burden. They also described struggling to make their next-of-kin and social network believe that they were ill when healthcare providers had difficulties explaining their complaints.

Conclusions: The semi-structured interviews with persons suffering from microscopic colitis provided a wide spectrum of answers to the question of how everyday life is affected. Microscopic colitis can be a disabling life experience and patients develop different strategies to adapt, cope and regain their previous performance level.

N13

Quality of life among patients with IBD on biological treatment: does it matter if they are in remission?

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Background: When asked, patients with IBD on biological treatment often have worries and a reduced quality of life (QoL), even with disease remission. Despite low clinical scores (SCCAI and HBI) some patients scores low QoL on the Short Health Scale (SHS), especially worries.[1] This study aimed to investigate the possible reasons of this and aspects related to low QoL in patients on biological treatment in general.

Methods: IBD outpatients on biological treatment from or University hospital were consecutively invited to answer questions about QoL and disease activity. QoL were measured on the SHS and disease activity was scored on the SCCAI or HBI scale. Both patients in disease remission and patients with disease activity were included. Patients with a SHS subscore > 5 were asked to measure disability on the IBD Disk (10 items; VAS, 0–10 cm).[2] Subsequently, the patients were asked to add comments on the 3 most burdensome topics from the IBD Disk score. QoL-data were analysed using descriptive statistics. The comments were analysed inspired by Malterud´s principles of systematic text condensation.[3]

Results: 75 patients were included in a period of 3 month: 61% Crohn's disease (CD); 39% ulcerative colitis (UC); 67% women; 37% disease in remission. Despite lower QoL for patients with disease activity, we found no statistically differencies in disabiliy except from 'interpersonal interaction'. Overall, patients with CD scores significant more disability on body image and sexual function ($p < 0.04$) on the IBD Disk. Women had significant lower QoL than men in all scores and more emotionally and body image disability on the IBD Disk ($p < 0.01$). On the IBD disk, the mean score for patients in remission was highest on the topics energy (7.1), emotions (5.4), and joint pain (5.2). Patients with disease activity vs. remission scored higher on all topics on the IBD disk, except joint pain (4.2). The most commented items on the IBD disk, was energy (39), emotions

(36), abdominal pain (29) and sleep (28). Marked themes derived from the text condensations included 'interrupted sleep due to pain and urge', 'constant exhaustion', 'abdominal pain related to food', 'defaecation and bloating', and 'concern about the future and medical treatment'.

Conclusions: Patients with disease activity vs. remission revealed lower QoL, but showed no differencies in disability, except from 'interpersonal interaction'. Patients with disease in remission vs. activity scored higher on joint pain. Patients commented mostly on the topics energy and emotions. By text condensation of the comments by the patients, we managed to get a deeper understanding of aspects related to the reduced QoL.

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N14

Professional profile of nurses working with inflammatory bowel disease in Brazil

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Background: This study aimed to identify the profile of nurses working with inflammatory bowel disease (IBD) in Brazil and to characterise the Brazilian IBD units.

Methods: A cross-sectional and descriptive study was developed. Participants were: staff nurse, nurse-supervisors or nurse-teachers from public and private healthcare institutions with professional or academic experience in IBD. The identification of nurses was conducted through: the analysis of national curricula registered in the Brazilian National Council for Scientific and Technological Development, the access to the Brazilian Group of Studies of IBD´ records or referral by colleagues. An online questionnaire composed by 37 questions covering the professional profile and the academic and professional training in IBD was developed.

Results: 345 nurses were screened, 121 were eligible for the study and 70 answered the questionnaire. In the group: 88.6% were female; the age was 40.9 ± 10.1 years; 65.7% were from the Southeast region; 30% had work experience of 6 to 10 years and 48.6% work in public hospitals. Concerning academic training: the average time for graduation was 14.3 ± 9.9 years; 60% graduated from a private institution; 30% have a master's degree; 5.71% have a doctorate degree and 45.7% have not studied IBD during graduation. In addition, 74.3% reported insufficient knowledge to care for IBD patients and 84.3% would like to learn more about IBD. About the clinical experience, 61 participants (87.14%) have contact with IBD patients, of which: 40% in the outpatient clinic, 35.7% in stomatherapy and 35.7% in the hospitalisation unit. Eighty per cent of nurses work with adult population, 3.08% with paediatrics and 16.92% with both. Nursing care is based on the nursing process (50%) using as theoretical framework the Basic Human Needs Theory (35.7%). The most discussed topics during the nursing consultation are adherence to treatment (72.9%), ostomy (70%), quality of life (67.1%), disease activity (60%), diet and nutrition (54.3%) and treatment (50%). In most services, the team is multi-disciplinary and consists of: nurses (72.9%), coloproctologist (67.1%), gastroenterologist (58.6%), nutritionist (58.6%) and psychologist (44.3%). Regarding the centres´ structure: 44 (62.9%) have an infusion centre; 28 (40%) promote clinical cases discussion; 74.3% are integrated in a hospital; 71.4% have an endoscopy department; 70% hold a surgical hospitalisation unit; 62.9%, computed tomography; 55.7%, magnetic resonance imaging; 60%, emergency department and 55.7%, service of pathology.

Conclusions: We have identified a low number of IBD nurses in Brazil. There is a lack of IBD knowledge in nursing courses and most nurses would like to learn more about IBD.

N15

Microscopic colitis in two DGH, is there a clear pathway to diagnosis or treatment

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Background: Microscopic Colitis(MC) is an inflammatory bowel disease(IBD) usually characterised by non-bloody diarrhoea and a normal or near normal macroscopic colonoscopy; biopsies are required for diagnosis [2]. Calprotectin is unhelpful as often falls below the range that flags a referral, confusion with IBS is common. MC has distinct sub conditions Lymphocytic(LC) and Collagenous colitis(CC) MC is not a new disease; An epidemiological study in Sweden between 1993 and 1998, suggested the incidence was similar to Crohn's disease in the subsets and combined comparative to ulcerative colitis [1].In Nottingham in 2017 the numbers reflected an increase in diagnosis rates over time [3].

Methods: At two District General Hospital's one in the south of England(SDGH) serving a population of 330,000 and one in the north west(NWDGH) with a population of 380,000. Figures were looked at for diagnosis of MC year to date these are approximate as there was coding variance in both trusts.

Trust	Total Number MC	LC%	CC%	Male%	Female%
SDGH	47	61.7	38.3	4.25	95.75
NWDGH	76	68	32	2.63	97.37

Numbers by trust.

Results: Mean time from symptom onset was variable in both trusts, time from diagnosis to first treatment varied depending on

the referral pathway. NWDGH reports the 2 week wait path led to a speedy diagnosis, the Nurse led referral pathway in gastro was 10 weeks and Gastroenterology longer. At the SDGH the 2 week pathway was responsible for the biggest number of diagnosis, meaning 18 patients received a diagnosis in approx. 4 weeks there is no direct to nurse referral pathway and the routine gastroenterology wait is 18 weeks. Only 4 patients at the SDGH made it on the IBD service. Most patients lack support there was wide variation in the advice given depending on follow-up. Sixteen were discharged to GP care with a letter of advice and 18 were seen in gastro clinics, the advice on treatment varied from Budesonide to Loperamide or worse nothing at all.

Conclusions: This DGH experience in the North and South of England informs that diagnosis remains troublesome, pathways and treatment is variable. The exact numbers for prevalence and incidence remain insidious due to this and the need for histological diagnosis. It could be suggested that extended waits for diagnosis leads to a burden to the individual in terms of Quality of life (QOL) and the health and social economy; this is difficult to Quantify. Addressing coding issues may help to understand the impact of MC. IBD Nurses could bridge the support gap but service review would be needed This retrospective audit was limited skimming the surface of deeper issues.

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N16

The influence of children's inflammatory bowel disease (IBD) on the relationship between parents and their married life

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Background: Paediatric chronic illnesses, especially severe ones, greatly alter not only the quality of life of child, but also its family and especially its parents. The purpose of the study was to investigate whether and how the relationships between parents of children with UC (ulterative colitis) and CD (Crohn's disease) had been changed since the diagnosis of the disease.

Methods: The analysis was based on the results of the questionnaire containing 23 questions addressed to the parents of children with IBD. The questions were generally related to the awareness of the child's illness ,subjective assessment of its exacerbation, access to the different kinds of support, marriage misunderstandings due to illness or its exacerbation and the impact of disease on their free time and marriage life. From September 2017, 350 questionnaires were distributed to parents of children with IBD. Till now the 216 completed questionnaires have been returned and 211 of them were included into the analysis (5 were excluded due to lack of complete data). The Student *t*-test was used for the statistical analysis.

Results: 46% of respondents (n = 98) had to permanently resign from work, 64% (n = 134) declared the necessity to give up their hobbies and dreams, and 70% (n = 147) stated that the disease diagnosis had the impact on spending their free time. Only 20 respondents rate the disease at less than 6 in 0–9 scale. Respondents who evaluated the severity of the disease in the 10 points scale (0–9) on 7 or more (n = 161) substantially more frequently than the rest indicated the thinking about parting with a partner because of child's illness (n = 26, $p < 0.05$), the decrease in frequency sexual activity (n = 93, $p < 0.05$) and the sexual activity only for marriage obligation (n = 23, $p < 0.05$). Significantly more (79%, n = 166) of the respondents declared that during the child's disease exacerbation they are much less likely to have physical closeness than only due to diagnosis itself while only (21%, n = 45, $p < 0.05$). Chronic illness had also an impact on the desire to have another child - 43% of the respondents (n = 91) - stated that due to the IBD diagnosis in the their child they have been resigned from having the further offspring. Statistical analysis show any dependence between sex and the answers to the rest of the questions. Women (67% of the respondents) evaluated the severity of the disease in the 10 points scale (0–9) on average 8.5 while men only 7.

Conclusions: Based on above results we concluded that the diagnosis of IBD in the child have a significant impact on the relationship between the parents and their married life. Families are forced to change their way of life or resign from work to make the care of their child.

N17

Frequency of infliximab-induced skin lesions and their impact on quality of life in inflammatory bowel disease patients treated with infliximab

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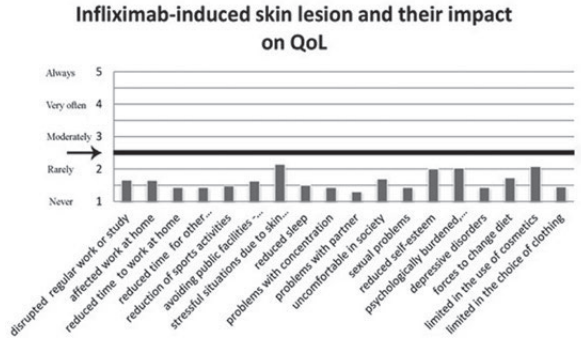
Background: IBD patients treated with infliximab (IFX) develop drug-induced skin lesions in 20–30%. The impact of IFX-induced skin lesions on quality of life (QoL) is unknown.

Methods: In this prospective cross-sectional observational study all adult IBD patients on IFX maintenance treatment at our tertiary referral centre were enrolled. Patients with IFX-induced skin lesions were identified and referred to a dermatologist. All skin lesions were documented by photography. Patients filled in a questionnaire on QoL combining The Chronic Urticaria Quality of Life Questionnaire and Dermatology life quality index. The impact of skin lesion on QoL was rated with a score from 1 to 5. Scores >2.5 were considered to have an important impact.

Results: From January to March 2018, 171 patients, aged 20 to 78 years, on IFX maintenance treatment (55.6% men) were included

in the study. IFX-induced skin lesions were identified in 40 patients (23.4%): among them eczema (45%), psoriasis (20%), xerosis (10%) and others (25%). Twenty-one patients (52.2%) had skin lesions for more than half a year. Skin lesions did not have an important impact on any of the studied domains (Figure 1).



Infliximab-induced skin lesions and their impact on QoL

Conclusions: In our study, we confirmed the high incidence of infliximab-induced skin lesions. However, the new finding is that the impact of these lesions on quality of life is not great.

N18

Mood disorders in a IBD population: a single-centre cohort

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Background: Chronic medical conditions, such as inflammatory bowel diseases(IBD),have been associated with impaired quality of life (QoL) and the presence of mood disorders compared with the general population. The aim of this observational study was to evaluate in a single-centre cohort of IBD patients: QoL, state and trait anxiety, depression and alexithymia.

Methods: Consecutive adult IBD outpatients from January to March 2018 were enrolled in the study. Main inclusion criteria were: confirmed diagnosis of Crohn's disease (CD) or ulcerative colitis (UC) from at least 1 year and age between 18 and 70 years. Disease activity was evaluated by the Harvey–Bradshaw Index (HBI) for CD and the partial Mayo Score (pMS) for UC. Quality of life was evaluated with the SF36 and the results summarised in the physical and mental component scales (PCS and MCS). The PCS and MCS composite means and standard deviations (SD) are 50 ± 10 for the U.S. general population. Anxiety was evaluated with the State-Trait Anxiety Inventory which consists of two axes (Year 1 for state anxiety and Year 2 for trait anxiety; STAI scores >40: clinically significant symptoms of anxiety); depression was measured with the Beck Depression Inventory-II; alexithymia was investigated through the TAS-20.

Results: 48 patients were enrolled (M/F 26/22, mean age at test 39 (SD 13.6) years; mean time from diagnosis 11.5 (SD 8.2), CD/UC 32/16). Thirteen of our patients had active disease at the time of the study and 20 was on biologic therapy. The mean PCS value was 50.3 (SD 11.9) and the mean MCS value was 40.15 (SD 7.60). Twenty patients (41.7%) had a pathological STAI1 (existing anxiety) and 25 (52.1%) a pathological STAI 2 (a predisposition to anxious reactions as a personality characteristic). Thirty-three (68.7%) had minimal depression while only one (2.1%) was severely depressed. Six patients (12.5%) reported borderline alexithymia and four clear alexithymia (8.3%). PCS and MCS scores were negatively correlated with depression and anxiety scores (worse quality of life in term of physical and mental aspects, worse depression and anxiety) while they were not related to alexithymia. No correlation was found between scales used and age at test, time from diagnosis and pMS. Instead, we found a relationship between HBI and all scales: presence of depression ($r = 0.57$, $p = 0.0007$), state anxiety ($r = 0.4$, $p = 0.02$), trait anxiety ($r = 0.5$, $p = 0.003$), alexithymia ($r = 0.34$, $p = 0.05$), mental scale ($r = -0.54$, $p = 0.004$) and physical scale ($r = -0.5$, $p = 0.004$). QoL and mood disorders were not influenced by the use of biologics or disease type(CD or UC.

Conclusions: Mood disorders affect IBD patients at any age and independently from the therapy used or the time from diagnosis. More attention should be given to the psychological aspects of IBD patients to improve their QoL.

N19

Validity of a Korean Version of inflammatory bowel disease–fatigue scale

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Background: Fatigue is one of the main symptoms of inflammatory bowel disease (IBD)
and is frequently reported by people in both active and remission disease. The incidence of inflammatory bowel disease (IBD) is rapidly increasing in Korea. However, there is no disease-specific tool to measure fatigue in Korea. This study was a methodological research implemented to evaluate the validity of the Koreans version of Inflammatory bowel disease fatigue scale (IBD-F) for use with IBD patient .

Methods: A cross-sectional descriptive study was used with 220 patients with Crohn's and ulcerative colitis. Bilingual nursing professor, medical doctor and clinical nurse specialist performed translations and reverse translation. Content validity, construct validity, concurrent validity and reliability were conducted. To assess the concurrent validity, the correlation coefficients between the Korean version of IBD-F and IBDQ were calculated.

Results: : Preliminary analysis process of exploratory factor analysis to examined KMO measure (0.905) and Bartlett's test of sphericity was carried out($p < .000$). Principal component analysis with varimax rotation was used. Only factors with an eigen value great than 1 were extracted. Three factors (12 'daily life' question, 3 'close relationship' question, and 2 'social life' questions)were identified, explaining 74% of the variance. Concurrent validity tested with quality of life for IBD was analysed with Pearson's Correlation Coefficient($r = 0.602$, $p \leq 000$). Internal consistency reliability tested with Cronbach's $\alpha = 0.825$.

Conclusions: This findings show that the Korean version of the IBD-F is reliable and valid for evaluating empowerment in patient with IBD, Crohn's disease and ulcerative colitis in Korea

N20

Experience with therapeutic drug monitoring on adalimumab in paediatric inflammatory bowel disease (pIBD)

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Background: Adalimumab (Ada)/(Humira®), a TNF-α inhibitor, has been approved for the treatment of Crohn's disease (CD), ulcerative colitis (UC) and inflammatory bowel disease Unclassified (IBDU) in Paediatric Inflammatory bowel disease (pIBD). After loading with Ada, drug levels get maintained with 2 weekly injections.
Aims: The aim of the study was to evaluate whether proactive therapeutic drug monitoring (TDM) with antibodies (AB) is enabling clinicians to improve clinical outcomes, additionally to looking at biomarkers and PCDAI/PUCAI indices. Data suggest that drug levels between 5 and 10 with negative AB should be aimed for to improve clinical outcomes and biomarkers.
Methods: Retrospective review of pIBD patients on Ada over a 4 year period. All patients were on an immunomodulator.
Results: UC *n* = 9, all male, age at diagnosis 3–12 years (median 7 years) age at commencement of Ada 9-17 years (median 13 years) interval from diagnosis to Ada 1–9 years (median 6 years). Six of 9 (67%) had levels of 5.7–15.2 (median 10) with negative AB, 2/9 (22%) developed AB of 10 with levels of 0.3 and 5.9 each, no intervention in 7/8 (87%) as normal PUCAI, 1 (11%) patient did not improve and drug discontinued. 1/9 (11%) had low levels of 1–2.1 with AB of 78–192. After reloading, drug levels of 4.4 and AB of 83 with improved PUCAI. CD *n* = 26, 12 female, age at diagnosis 3–13 years (median 9 years) age at commencement of Ada 5.5–15 years (median 12.5 years), interval from diagnosis to Ada 0.5–11.5 years (median 3 years). 1/26 (4%) had levels of 0.8 and antibodies of 231. This patient continued with Ada treatment and improved from moderate to mild disease. 25/26 (96%) had levels of 3–17(median 9.6), 12/25 had AB of 0, 9/25 had AB of less than 20, and 2/25 had AB of 122(drug level 3.9) and 168(drug level 11.1). Seventeen/26 (65%) remained on 2 weekly Ada, 17/17 were in clinical remission with low PCDAI. 8/26 (31%) escalated treatment due to worsening of PCDAI, 6 of those (75%) by shortening intervals (to weekly) and 2 (25%) switched to vedolizumab. 1/26 discontinued Ada due to anxiety/poor compliance. IBDU: *n* = 4, all female, age at diagnosis 5–9 years (median 5.5 years), age at commencement of Ada 10–15 years (median 12.5 years), interval from diagnosis to Ada 5–7 years (median 5 years). All had levels of 6.1–13.8 (median 10.6), 3/4 had positive AB (median 13, range 0–168) and remained on 40 mg, 2 weekly. 1/3 had mild, 2/3 quiescent disease. 1/4 escalated treatment to vedolizumab due to worsening clinical symptoms.
Conclusions: Our study suggests that our approach of proactive TDM improves clinical outcomes (PUCAI/PCDAI) and increases and maintains adequate levels and reduces AB formation in some patients.

N21

The interpretation of thiopurine metabolites in clinical practice: IBD nurses experience in three North West England NHS trusts

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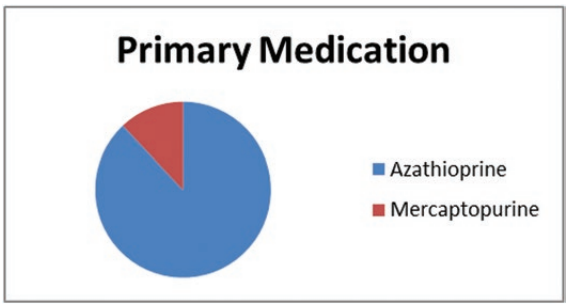
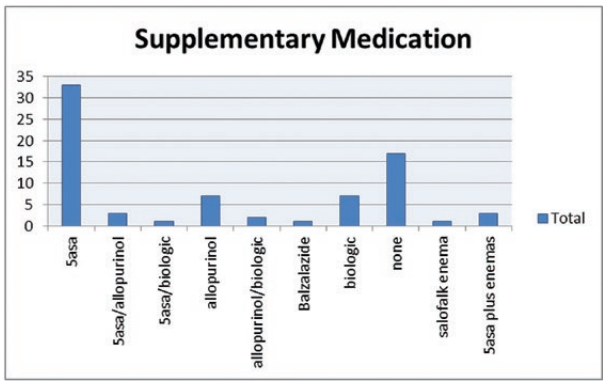
Background: Thiopurine metabolite testing in clinical practice has become more accessible in the UK with interpretation of results being determined by a wider health professional cohort.[1] It is important for Primary Care to understand the rationale behind its use. The aim of the study was to examine how effective the interpretation of the results were by investigating the outcomes taken in three NHS trusts in the North West of England.
Methods: A retrospective multi-centre study was conducted to examine the aspects of current existing interpretation and if the use of therapeutic drug monitoring could be improved in each of the participating NHS trusts.

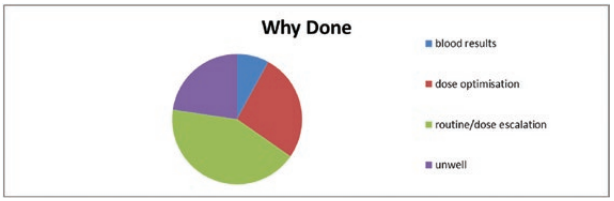


Primary medication 2.

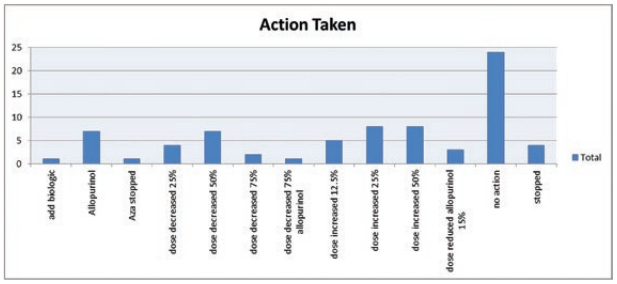


Supplementary medication 3.

Results: Twenty-five patients from each of the three participating trusts (*N* = 75) were entered into the study. There were more males than females (M = 55%, F = 45%) with 61% being under the age of 45 years. Of these patients 88% were on Azathioprine vs. 12% on mercaptopurine with supplementary medication of 5asa preparations (44%) and existing allopurinol (17%) recorded, however 22% were on no other medication for their disease.



Dose optimisation.



Action taken.

Conclusions: The majority of thiopurine metabolite blood tests were undertaken for dose optimisation purposes as part of routine monitoring for the drugs (AZA, 6MP). Fifty per cent of patients had their doses altered with 14% having Allopurinol added to their treatment plan and 32% had no action from having the blood test done. The use of faecal calprotectin as a supplementary biomarker was evident in 54% of the participants. The study highlighted the use of appropriate treatment paradigms, enabling the drugs full potential to be achieved prior to escalation to biologic therapies. Thiopurine metabolite testing alongside other biomarkers is an effective resource in managing patients on immunosuppressant therapies, with the use of Allopurinol enabling satisfactory outcomes.

Reference

1. A-Rahim YI, Farrell RJ. Overview of Azathioprine and Mercaptopurine use in inflammatory bowel disease. Wolters Kluwer. 2018 www.uptodate.com, 1 September 2018.

N22

Audit into initial response to vedolizumab infusions for IBD

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Background: Vedolizumab is a humanised IgG1 monoclonal antibody, aimed at reducing GI inflammation, (NICE 2015). This audit will look at the average time patients start to see improvements in their symptoms following commencement of Vedolizumab. According to NICE (2015), the majority of patients are expected to respond within 6–12 weeks.

Methods: The Ambulatory Unit currently infuses 39 patients with Vedolizumab. Forty-nine per cent (n = 19), are male with and 51% (n = 20) are women. Forty-six per cent (n = 18) with Crohns Disease (CD) and 54% (n = 21) with ulcerative colitis (UC). All patient who attended where asked to fill out a short questionnaire in relation to how quickly they had seen an improvement in their symptoms, in particular, fatigue, loose stools, pain and rectal bleeding. They were asked to give an idea on a weekly timescale as to how quickly those aspects of the disease had resolved. Questionnaire where given out on the Ambulatory Unit and patients made aware that their responses would not alter their treatment. As this an audit that does not require patient-specific information to be included, no ethical approval was required.

Results: Comparing Crohns to ulcerative colitis, the significant findings were as follows. Fatigue was not a significant factor for 33% (n = 6) of the CD patients and 9% (n = 2) of the UC patients, however for those for whom it was a concern, 66% (n = 12) of the CD and 80% (n = 17) of the UC patients reporting improvement after Week 8. Loose stools was resolved in 66% (n = 12) of the CD patients by Week 8, however 11% (n = 2) stated it was not a factor in their disease. When looking at UC, 33% (n = 7) found symptoms reduced at Week 8, 38% (n = 8) stated reducing in symptoms after Week 8 and 9% (n = 2) stated they did not suffer from loose stools. From a pain perspective 66% (n = 12) of the CD patients experience relief my Week 8, whereas 54% (n = 12) of the UC patients found relief after Week 12. The final aspect looked at was rectal bleeding, 61% (n = 11) of the CD patients stated this was not a symptom of their disease as oppose to it being a after for all bar 1 of those with UC. For those who did experience rectal bleeding of those with CD, 27% (n = 5) found a response by Week 8 whereas of those with UC 52% (n = 11) found relief after Week 8.

Conclusions: The results suggest the complexity of inflammatory bowel disease both in terms of management and patient experience. The majority of CD patients had resolved most of their symptoms by 8 weeks, however the UC patients in particular in relation to fatigue, pain and rectal bleeding did not gain a good response until after 8 weeks. However the CD group was smaller than the UC group presented here which could alter the results presented, with that in mind a bigger cohort study over a longer period may prove useful.

N23

IBD patients experience of the care given at the Stockholm Gastro Centre

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Background: Patient-reported Experience Measure (PREM) is questionnaires measuring the patients experience of and satisfaction with the care. The aim with PREM is to give the healthcare professionals important information about possible deficiencies in order make improvements. To be able to improve the care, the patients experiences and knowledge may be determinant, and PREM is one tool to use that captures these aspects. The national quality registry, SWIBREG, is used in all parts of Sweden and today approximately 45 000 patients are registered. Four questions have been designed to measure the patients experience of the care given and it is today possible to assess these data in the registry. The aim is to access PREM in patients with IBD and to compare the results with those 2 years ago when the last measurement was done at Stockholm Gastro Center.

Methods: The questionnaire was sent by mail to all patients with IBD at the Stockholm Gastro Center (n = 1157) during the period January-February 2018. At Stockholm Gastro Center the aim is to assess PREM once a year, during this time period. The questions are concerning experience regarding given information, participation, accessibility, and the behaviour of the healthcare professionals. A three- and four-graded Likert scale was used. The results were registered in SWIBREG and then analysed descriptive but also comparative with the results from 2 years ago.

Results: A total of 440 patients answered the questions. The results show that 94% of the patients experienced the given information to be very good or rather good. A total of 6% stated it to be rather bad or very bad. The question concerning participation showed that 91% experienced it to be adequate. A total of 97% of the patients

experience the accessability to the care at Stockholm Gastro Center to be very good or rather good. Regarding the healthcare professionals behaviour, 99% of the patients experienced it to be very good or rather good. Only 1% stated it to be very bad or rather bad. No big changes could be found when comparing with the results with those 2 years ago. Overall the results have decreased a bit but no significant changes were found.

Conclusions: PREM shows that the majority of the patients experience that the given information, the assessibility, and the behaviour of the healthcare professionals to be good. Most patients also experience an adequate participation in the care. No significant changes could be found when comparing the results from this year with the results from 2 years ago, however, the results are a bit impaired this year.

N24

Experience with Ustekinumab (STELARA®) in Paediatric inflammatory bowel disease (pIBD) – A case series

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Background: Ustekinumab (UST) is a monoclonal antibody against IL 12/23 and is thought to drive inflammation in psoriasis and gastrointestinal inflammation. Two phase 2b studies have shown that UST induces and maintains clinical response in Crohn's disease (CD). Data of the effectiveness of UST in pIBD are lacking.

Methods: The aim of the study was to evaluate effectiveness and safety of UST as a treatment for pIBD after failure of anti-TNFa and Vedolizumab. Methods Retrospective study of demographic characteristics, medical history, dosage and schedule of UST administration, as well as data on pre and post ESR, calprotectin and PCDAI.

Results: A total of 5 patients on UST were identified, age range 8–15 years, median 12 years, age at diagnosis 2–10 years, median 5 years, 3 males. Crohns $n = 4$ and UC $n = 1$, followed up for up to 15 months following initiation of treatment. All 5 patients had previously failed at least two biologic treatments. All 5 patients received UST 8 weekly at IV – Single, initial dose of 6 mg/kg, as intravenous infusion over at least 60 min. SC – Subsequent doses. The first subcutaneous dose of 90 mg if >40 kg and 45 mg < 40 kg. In 4/5 patients UST significantly reduced ESR, 4/5 significantly reduced calprotectin and all improved PCDAI and PGA scores.

https://planner.smart-abstract.com/ecco2019/submission/en/abstract/13317/content#

Start date	Pre ESR	Post ESR	Pre Calprotectin	Post Calprotectin	Pre PCDAI	Post PCDAI
March 2018	No data	17	>1800	915	10	
June 2018	46	23	4817	1960	55	5
September 2018	15	12	1525	Pending	25	20
August 2017	19	8	5309	2023	40	20
June 2018	90	10	156	38	45	5

Conclusions: Ustekinumab seems to be effective and safe treatment in pIBD patients with no reported adverse events. We suggest multicentre prospective Paediatric studies to advance knowledge and improve patient outcomes.

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