ECCO CONFER Cases

COllaborative Network For Exceptionally Rare case reports

Round 10

Case 1

Case Title	**Perianal Crohn's fistula in the absence of luminal disease - natural history, time to progression to luminal disease and management in contemporary clinical practice**
Principal Investigator	Tim Raine
Case Manager	Daniela Pugliese
Case Description	Perianal fistulae are typically encountered by the colorectal surgeon in the context of cryptoglandular disease. These are managed with appropriate antibiotic courses and surgical procedures to ensure adequate drainage, with the aim of enabling healing and closure of the fistula tract. Rarely, patients who are not known to have a history of luminal Crohn's disease may present with fistulae that respond poorly to conventional surgical approaches and/or show features of complexity (e.g. secondary fistula tracts). This should prompt further assessment and investigation which may uncover evidence of luminal Crohn's disease. However, patients may rarely have ***complex perianal fistulae in the absence of evidence of luminal Crohn's disease***. The natural history of these in terms of fistula resolution or progression to subsequent luminal Crohn's disease as well as the response to medication for Crohn's disease have not been well described in contemporary literature, particularly in the era of routine access to small bowel imaging and the use of anti-TNF therapies. This case series will acquire baseline and outcome data on: • Adult patients diagnosed with Crohn's perianal fistulae • *Without* a diagnosis of luminal Crohn's disease made prior, at the time of or within 6 months of the index fistula diagnosis • *With* evidence of appropriate diagnostic assessment within 6 months of the fistula diagnosis including *at least one of*: colonoscopy; MRI, CT or US small bowel; videocapsule endoscopy
Main Clinical Question	What is the natural history of patients diagnosed with isolated perianal Crohn's disease in terms of (1) fistula resolution and (2) progression to a diagnosis of luminal Crohn's disease? What radiological investigations are typically performed in such cases and what is the impact of medical treatment, including anti-TNF therapy, on fistula outcomes. *Impact on clinical practice:* Clinicians remain unclear on how to investigate and manage patients presenting with apparent isolated perianal Crohn's disease. What luminal endoscopy and imaging is appropriate? Is it appropriate to use anti-TNF therapies in the absence of luminal disease? What should we tell patients about outcomes and the likelihood of developing luminal disease? It is anticipated that this case series will provide information in all these regards.
Literature on the topic	According to a recent meta-analysis by Tsai et al. that identified 5 relevant historic epidemiologic studies, the prevalence of perianal

	Crohn's fistulae diagnosed prior to a diagnosis of luminal CD is around 3.8% of patients with a diagnosis of perianal Crohn's (Tsai et al, IBD 2021). These studies reported cohorts typically diagnosed in the pre-biologics era and with no information provided on the extent of the diagnostic workup conducted to exclude luminal Crohn's. A more recent case series of 45 patients with isolated perianal fistulae highlighted the potential for detailed small bowel assessment (with videocapusle endoscopy) to reveal small bowel lesions (McCurdy et al. JCC 2023). This same group reported poor response to anti-TNF therapy in 22 patients with isolated perianal fistulae treated with anti-TNF therapy (McCurdy et al. Dig. Disease and Sci., 2019). **We anticipate this ECCO CONFER series would provide a large cohort of patients informing understanding of diagnostic workup, natural history and outcomes for patients presenting with isolated perianal Crohn's fistulae in era of routine biologics usage.**

Case 2

Case Title	**Exposure to JAK-inhibitors during pregnancy and risk of adverse pregnancy outcome**
Principal Investigator	Mette Jusgaard
Case Manager	Uma Mahadevan
Case Description	The Janus kinase (JAK) inhibitors are a novel class of therapies that modulate the signaling pathways of various inflammatory cytokines, which play a crucial role in inflammatory bowel disease (IBD) and other immune-mediated disorders. They comprise four non-receptor protein tyrosine kinases, JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). Three JAK-inhibitors are licensed for the treatment of IBD including Tofacitinib, Upadacitinib and Filgotinib. Owing to their small size, they can cross the placenta during the first trimester.[1] In accordance with the American Food and Drug Administration and the European Medicines Agency, the pregnancy guidelines from the American Gastroenterology Association and the European Crohn's and Colitis Organization state that these medications are not recommended for use in pregnancy based on animal data and very limited human exposure data.[2,3] Tofacitinib causes teratogenicity in rabbits at concentrations more than six times higher than doses used in IBD-patients.[1] Upadacitinib was associated with musculoskeletal and cardiovascular malformations in pregnant rats and rabbits at doses matching doses used in humans (15, 30 and 45 mg/day, respectively). [4] Further, Filgotinib was associated with serious malformations in rats and rabbits, but also fetal death in a dose matching doses in humans (200 mg/day).[5] A retrospective review of pregnancy exposure to tofacitinib in both ulcerative colitis and post-marketing data for rheumatological disease did not show significant adverse outcomes among 11 maternal exposures around the time of conception.[6] No articles on upadacitinib or filgotinib exposure in pregnancy have been published. In accordance with the ECCO guideline and American recommendations, at least four weeks should pass between medication discontinuation and attempting conception.[1-3] However, for all three agents, a clear risk-to-benefit discussion must be held with the patient if a decision is made to continue through pregnancy in those with no other medical option.[1]
Main Clinical Question	Investigate pregnancy and newborn outcomes after maternal or paternal exposure to either tofacitinib, upadacitinib or filgotinib.
Two Studies	FEMALE STUDY: **Title:** Maternal exposure to JAK-inhibitors at conception and/or during pregnancy and risk of adverse pregnancy outcome" **Inclusion criteria's:** Treatment with a JAK-inhibitor (tofacitinib, upadacitinib or filgotinib) within 1 month of last menstrual period and/or in pregnancy. MALE STUDY: **Title:** Paternal exposure to JAK-inhibitors at conception and risk of adverse pregnancy outcome. **Inclusion criteria's:** Treatment with a JAK-inhibitor (tofacitinib, upadacitinib or filgotinib) within 1 month of the partner's last menstrual period.
Literature on the topic	1. Brondfield MN, Mahadevan U. Inflammatory bowel disease in pregnancy and breastfeeding. Nat Rev Gastroenterol Hepatol. 2023;20:504-23. 2. Torres J, Chaparro M, Julsgaard M, et al. European Crohn's and Colitis Guidelines on Sexuality, Fertility, Pregnancy, and Lactation. J Crohns Colitis. 2023;17:1-27. 3. Mahadevan U, Robinson C, Bernasko N, et al. Inflammatory Bowel Disease (IBD) in Pregnancy Clinical Care Pathway - A Report from the American Gastroenterological Association IBD

Parenthood Project Working Group. Gastroenterology. 2019;156:1508-24.
4. Rinvog® (upadaticinib). Medical information - Use in Pregnancy. 2023.
5. Jyseleca® (filgotinib). Medical information - Use in Pregnancy. 2023.
6. Mahadevan U, Dubinsky MC, Su C, et al. Outcomes of Pregnancies With Maternal/Paternal Exposure in the Tofacitinib Safety Databases for Ulcerative Colitis. Inflamm Bowel Dis. 2018;24:2494-500.

Case 3

Case Title	**Safety and efficacy of JAK inhibitors in patients with primary sclerosing cholangitis associated with inflammatory bowel disease.**
Principal Investigator	Daniela Maggi and Alessandra Soriano
Case Manager	Triana Lobaton
Case Description	JAK inhibitors have proven efficacy in inducing and maintaining remission in inflammatory bowel disease (IBD). Around 5% of IBD patients (most frequently with ulcerative colitis, UC) develop primary sclerosing cholangitis (PSC). IBD-PSC patients represent a phenotypically peculiar disease entity, with increased risk of colorectal cancer. Additionally, liver transplantation is the definitive treatment of PSC, given the lack of any effective medical therapy. Our clinical experience showed that treatment with tofacitinib in patients with UC and concomitant PSC can lead to improvement of PSC laboratory markers and imaging findings, and that such improvement may be related to tofacitinib dosage. Given the potential involvement of JAK/STAT signalling in PSC pathogenesis, we argue that in the IBD-PSC setting JAK inhibitors may have a promising role in treating PSC as well. The aim of this ECCO CONFER Project is to explore the course of PSC in IBD-PSC patients while treated with JAK inhibitors for IBD. This case-series will acquire baseline and outcome data on: 1. IBD activity before and after JAK-inhibitor treatment (clinical, biochemical, endoscopic findings) 2. PSC lab test, imaging findings (and histopathology if available), before and after JAK-inhibitors course, including possible changes after dosage variations. 3. Any adverse event. 4.
Main Clinical Question	Main clinical questions are: • Can we expect a collateral favorable effect of JAK-inhibitors on PSC in terms of lab test, imaging findings(and histopathology, when available) in PSC-IBD patients? • If any, how does this favorable effect correlate with IBD (mainly UC) activity? • Are JAK-inhibitors anyhow safe in patients with chronic and progressive cholestatic liver disorders such as PSC?
Literature on the topic	Our literature search (including PubMed/Midline search by using "primary sclerosing cholangitis AND tofacitinib")six results were found of which only four were relevant (i.e. 1 retrospective study, 2 reviews, 1 abstract): • Schregel I, Ramos GP, Ioannou S, et al. Evaluation of Tofacitinib in Primary Sclerosing Cholangitis and Associated Colitis: A Multicenter, Retrospective Study. Clin Gastroenterol Hepatol. 2023;S1542-3565(23)00073-3. • Magrì S, Chessa L, Demurtas M, Cabras F, Mocci G. Review article: safety of new biologic agents for inflammatory bowel disease in the liver. Eur J Gastroenterol Hepatol. 2021;33(5):623-630. • Wang Y, Wan Z, Jin R, et al. Tofacitinib for extraintestinal manifestations of inflammatory bowel disease: A literature review. Int Immunopharmacol. 2022;105:108517. doi:10.1016/j.intimp.2022.108517 • A.E. Lewis, S. Ioannou, M.A. Quintero, et al. Colitis patients with PSC may gain additional benefit from the use of tofacitinib. Gastroenterology, 158 (6) (2020), pp. S450-S451.