7th Interview COVID-19 ECCO Taskforce, published February 12, 2021

BACKGROUND AND INTRODUCTION

Following the first reports of cases of acute respiratory syndrome in the Chinese Wuhan municipality at the end of December 2019, Chinese authorities have identified a novel coronavirus as the main causative agent. The outbreak has rapidly evolved affecting other parts of China and outside the country. Cases have been detected in several countries in Asia, but also in Australia, Europe, Africa, North as well as South America. On February 12th 2020, the novel coronavirus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) while the disease associated with it is now referred to as COVID-19. Human-to-human transmission has been confirmed but more information is needed to evaluate the full extent of this mode of transmission. The evidence from analyses of cases to date is that COVID-19 infection causes mild disease (i.e. non-pneumonia or mild pneumonia) in about 80% of cases and most cases recover, 14% have more severe disease and 6% experience critical illness. The great majority of the most severe illnesses and deaths have occurred among the elderly and those with other chronic underlying conditions (https://www.ecdc.europa.eu/en/current-risk-assessment-novel-coronavirus-situation).

The aim of the current document is to provide to health care professionals some understanding and knowledge on the best care we can offer to our patients in general and particularly those under immunosuppressive/ immunomodulatory treatment in the current situation of the COVID-19 epidemy.

Due to the urgency, ECCO has suggested to gather together a group of gastroenterologists with special interest in Opportunistic Infections and infectious disease experts, in order to provide on a regular basis a guidance to the physicians of the ECCO community.

This guidance shall not replace any national recommendations from health care authorities but must be understood as an additional piece of information that will be updated when necessary based on our better understanding of this novel disease. Similarly, the following guidance is not accompanied by any ECCO recommendations.

The format below is based on an interview by gastroenterologists and experts in infectious disease from various places in Europe and reviewed by the COVID-19 Taskforce.

This taskforce is composed of members of the Opportunistic Guidelines Consensus, members of the ECCO governing board and infectious disease experts.

QUESTIONS AND ANSWERS

1. Do IBD patients have a greater risk of severe COVID 19 compared to the general population?

COVID-19 is a new disease, with a rapidly evolving evidence base. However, from our experience to date, IBD patients do not, as a whole, seem to be at increased risk of either contracting SARS-CoV-2 or following a more severe disease course. Early population studies from China, France, Italy and Spain have neither identified IBD nor immunosuppressive therapy to be risk factors for disease onset [Taxonera C; Alloca M; An P]. It is likely, however, that many IBD patients modified their behavior to reduce risk, with several countries promoting shielding. Recently, similar results were observed in 2 population based cohorts from Netherlands and Denmark showing a comparable or lower prevalence in IBD patients compared to the general population [Derikx LAAP; Attauabi M].

2. Do treatments for IBD confer a higher risk for a subgroup of patients?

Registry data is tentatively reassuring for most IBD therapy, with the majority of IBD drugs demonstrating no association with severe COVID-19, as defined by either critical care admission or mortality. The second analysis of the SECURE-IBD database included the first 1439 patients submitted to the registry. In addition to age and comorbidity, disease activity, current/recent use of corticosteroids, thiopurines, combination therapy with TNF-antibodies plus thiopurines and maybe 5-aminosalicylates (5-ASAs) were associated with severe COVID-19 infection, as defined as critical care admission, use of ventilator or mortality. TNF antagonist monotherapy, anti-integrins and IL12/23 pathway inhibitors and tofacitinib were not associated with severe COVID-19, with TNF antagonists conferring a protective effect in univariate analysis [Ungaro, R.C]. In an Italian case series, disease activity, use of steroids and UC were also associated with adverse outcomes [Bezzio, C].

What is certain, is the very real risk of disease flare when IBD maintenance therapy is stopped. Hence, in balance, ECCO promotes the continued management of IBD in line with standard guidelines. We also endorse stringent mask waring, hand hygiene and social distancing measures as per national recommendations and WHO/ECDC guidance.

3. On what basis should I advise vaccination for my patient? age? co-morbidities? health care professionals?

Three SARS-CoV-2 vaccines have been approved by the European Medicines Agency (EMA) on the basis of results from phase 3 studies evaluating clinical efficacy and safety [Baden LR; Polack FP, Voysey M]. All three employ the viral spike (S) protein, the main target for neutralising antibodies that block viral entry into the host cells. None are live virus vaccines.

The BioNTech-Pfizer and Moderna use a novel messenger RNA (mRNA) platform [Baden LR; Polack FP]. The mRNA for the spike is delivered as lipid nanoparticles that protect the mRNA from degradation and promote transportation into body cells. When the mRNA reaches the cytoplasm it is translated to generate spike protein. Post-translational modification facilitates immune recognition to stimulate antibody production and cellular immune responses. Both vaccines have received marketing authorization from European regulatory agencies (European Medicines Agency, EMA) and American (Food and Drug Administration, FDA). There is little to differentiate the Pfizer/BioNTech and Moderna mRNA vaccines bar the less challenging logistics with rolling out the Moderna vaccine.

The Oxford/Astra-Zeneca COVID-19 vaccine uses a replication-deficient chimpanzee adenovirus vector (ChAdOx1) to deliver the full-length SARS-CoV-2 spike protein DNA sequence into the host cell [Voysey M]. The adenovirus vector genes have been modified to prevent replication of the vector and to enhance vaccine immunogenicity. The UK MHRA granted a temporary authorisation of supply on 30 December 2020 and the European Medicines Agency granted a Conditional Marketing Authorisation (CMA) on 29 January 2021. It has also been approved in another 10 countries worldwide. Just published, the Russian Sputnik V vaccine is also a recombinant adenovirus vaccine, but utilises two different human adenovirus-based vectors, rAd26 and rAd5, for the first and second doses. This is to minimize the effects of immune responses generated against the vector components of the first dose from reducing the efficacy of the booster dose. In interim analysis of phase 3 clinical trials Gam-COVID-Vac (Sputnik v), was likewise well tolerated and showed 91.6% efficacy [Logunov DY].

National authorities are striving for extensive vaccination coverage to control the spread of disease. Many countries have put in place a vaccine strategy based on risk factors identifying those most vulnerable to

severe COVID-19. While IBD patients have not been identified as a high-risk group per se, IBD patients are likely to be prioritized for vaccination if they are receiving immunosuppressive therapy. Some IBD patients will be prioritized for other reasons, for example age, or working in the health care sector. The remainder will be invited for vaccination in the same way as the general population.

Vaccination trials for all three vaccines have demonstrated safety and efficacy in all adult age groups, including both healthy individuals and patients at risk of severe or fatal COVID-19. However, immunosuppressed patients (particularly recipients of immunosuppressant medication within the past 6 months), were excluded from these clinical studies. While patients with stable treated HIV infection have been included in some trials, the results are not yet available.

Patients will inevitably have questions regarding the advisability and timing of vaccination following prior COVID-19, and in patients with positive antibody tests. In general vaccination would not be advised until after recovery from acute symptomatic infection and any national advice should be followed as policies may differ. Seropositive status is not a contra-indication to vaccination and indeed the published studies included some such patients. Long Covid or chronic COVID syndrome (CCS) remains poorly understood, but vaccination is not known to be contraindicated, and has been advised if the patient is stable and not showing clinical deterioration [Green Book Chapter].

There is widespread concern for potential loss of vaccine efficacy with the evolution and spread of SARS-CoV-2 viral variants of concern (VOC) from UK, South Africa and Brazil. While *in vitro* studies show some diminution in neutralising titres against the South African variant, there is little evidence of vaccine failure. The available vaccines encode Spike protein that contains a variety of B- and T-cell epitopes and may therefore generate effective protection even against viruses harbouring mutations at one or more key antigenic sites. Fortunately, the novel technologies used for the current vaccines will enable rapid updating of the encoded spike sequences should this be required.

4. **Is a certain type of vaccine more appropriate for some patients? Do my IBD patient have any contra-indication to receive the vaccine? Would some immunomodulators (steroids, azathioprine, tofacitinib, anti TNF, etc) contra-indicate some types of vaccine?**

By late September 2020 over 200 COVID-19 vaccines based on ten different vaccine platforms had started pre-clinical development, of which 43 were in clinical trials [Tregoning JS]. Most current vaccines (approved or in development) are either non-live vaccines, (mRNA, virus-like particles, adjuvanted protein or inactivated whole virus) or replication deficient adenoviral vector vaccines. To date, such vaccines have proved to be safe in immunocompromised patients.

At least one live attenuated virus vaccine is in development. Such vaccines are contra-indicated as a rule in immunosuppressed individuals due to their capacity to multiply in the host, potentially causing disease due to uncontrolled vaccine virus replication.

The RNA vaccines however represent a novel immunization strategy, with the safety data currently largely limited to the two recently published trials [Baden, Polack]. Whether mRNA vaccines might pose any additional risk of immunopathology in immunosuppressed IBD patients warrants consideration.

With regards to acute immune reactions following vaccination, beyond the known risk of anaphylaxis in patients with a prior history in whom the mRNA vaccines are contra-indicated, any such risk, if it exists, might only become apparent after millions of doses have been administered. This might uncover a hitherto unknown prediposition in any subset of patients.

Vaccine-induced disease enhancement occurs when prior vaccination of healthy recipients is associated more severe disease following natural infection. It has been seen in the past with certain measles, respiratory syncytial virus (RSV) and dengue vaccines, triggered by a variety of mechanisms. Disease enhancement has also been observed in animal models with candidate vaccines for MERS and SARS-CoV-1. Much effort has therefore been devoted to design vaccines minimizing the risk of disease enhancement on subsequent SARS-CoV-2 infection. The mRNA and adenovirus vector vaccine platforms avoid the interference with protein targets and unwanted immune responses associated with inactivated alum-adjuvanted vaccines. Instead, the viral protein target is translated in the host cells, and undergoes in-host post-translational modification, duplicating the form and glycosylation of viral antigens generated during natural infection. Vaccines are engineered with the spike protein gene encoded so as to maintain it in pre-fusion conformational state for induction of neutralizing antibodies. This is also to avoid the generation of antibodies to the post-fusion state, which might stimulate virus entry on subsequent infection and the risk of enhanced disease.

Fears the possibility of disease enhancement have been allayed with the published Phase I, 2 and 3 safety evaluations in clinical trials of the SARS-CoV-2 mRNA and adenovirus vector vaccines in healthy subjects. The absence of any cases was supported by evidence of good humoral and cellular immune responses, manifesting good Th1 and Th2 balance. The possibility of disease enhancement occurring in IBD patients receiving immunomodulators will nevertheless warrant vigilance going forward especially for those agents with deleterious effects on T-cell responses.

Currently no specific studies have been published in patients with immunodeficiencies whether by disease or by medication. In general, the safety of all currently approved COVID19 vaccines will most probably not be a concern in immunocompromised patients. Similar to studies of other vaccines in immunocompromised patients [Boey L] most vaccines even show a better safety profile in transplant patients.

The concern, however, is the magnitude of the immune response which might be diminished due to medication suppressing the immune system. We therefore expect that the immune response following all vaccines will be lower regardless of the technology/platform used. Post-vaccination testing is not recommended as we do not currently know what level of antibody response, if any, correlates with quality or duration of protection.

Whilst there are some unknowns in vaccination efficacy in those on immunosuppressive therapy, the risk of contracting COVID-19 in general is known to be significant. Even though all data are not available yet and no studies have been done in immunocompromised patients, we would cautiously recommend to use the mRNA vaccine to vaccinate IBD patients on immunomodulatory medication since the vaccine's efficacy to protect against mild and severe disease was shown to be higher for mRNA vaccines (94-95%) compared to the viral vector-vaccines, where mild disease still occurs in about 30-40% of the vaccinated persons. [Voysey, Pollack et al, Baden].

Interview realized on behalf of the COVID-19 ECCO Taskforce with

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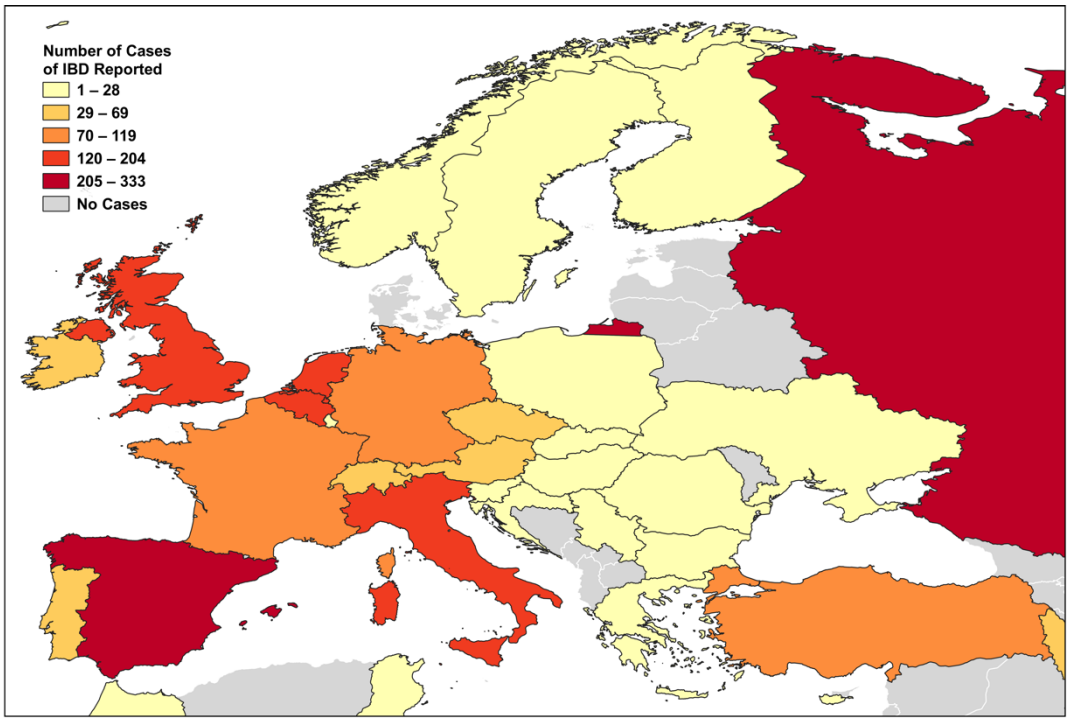
Note

Since the infection is dynamic and knowledge and evidence are growing rapidly, some of this guidance will be regularly updated based on tailored recommendations for each region according to the best evidence. A very important project has been set up to increase our knowledge on this novel disease in our IBD patients. We strongly encourage you to participate. Surveillance Epidemiology of Coronavirus) Under Research Exclusion (SECURE)-IBD registry was established in March 2020 to monitor and report on outcomes of COVID-19 occurring in IBD patients. With tremendous support from the global community of IBD healthcare providers, we have over 4,500 reported cases from 65 countries, of which 2,034 are from Europe (Figure). We made some important observations impacting the care of IBD patients. We continue

to record patients in the registry and study the impact of other medications, as well as other factors in COVID-19 outcomes, including the impact of vaccines. We encourage IBD clinicians worldwide to continue to report ALL cases of COVID-19 in their IBD patients, regardless of severity. Reporting a case to the SECURE-IBD registry should take approximately 5 minutes. Please report only confirmed COVID-19 cases, and report after sufficient time has passed to observe the disease course through resolution of acute illness and/or death. This project and data with weekly updates are accessible at https://covidibd.org/

Figure: COVID-19 cases among inflammatory bowel disease patients in Europe reported to the SECURE-IBD registry between March 2020 and January 19, 2021



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