

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 epidemic.

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 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.

QUESTIONS AND ANSWERS

1. How to reorganize your IBD unit for regular visits in case social restriction has been decided by your national authorities and social distancing is applied in your hospital?

For those patients who are in regular monitoring, virtual clinics or online consultancy are advisable. Patients can be asked to send laboratory exams and a simple questionnaire on symptoms, concomitant medications and relevant questions in advance. The IBD team can schedule phone calls with the patients at the same date and time of the scheduled visit. In case patients cannot go to the laboratory due to social isolation, a home faecal test for calprotectin is a valid alternative if available. This can be done for all patients, including patients in remission with subcutaneous biologics or small molecules¹. Endoscopic procedures should be limited to situations where patients suffer from moderate-to-severe symptoms, and regular endoscopic follow up and screening should be postponed. Strict hygiene conditions for endoscopic procedures must be implemented according to national recommendations.

2. How to reorganize your IBD unit for visits in the framework of a randomized control trial in case social restriction has been decided by your national authorities and social distancing is applied in your hospital?

In this case, there can be different possibilities. First, only patients with no therapeutic alternatives should be included in a randomized controlled trial at the moment. As this situation may last longer, minimizing background corticosteroid exposure in those patients who are between the screening and the baseline time period is important. For our patients enrolled in clinical trials before the outbreak, we are asking sponsors: i) to postpone non necessary follow-up visit or to replace them with virtual clinics ii) to identify local labs that can make regular lab tests required by the protocol iii) to organize home delivery of study drugs, especially those who are administered orally or subcutaneously. Then, patients would come to the hospital only for key visits (end of induction, re-randomization, end of study) and to receive intravenous drugs. Adapting trial procedures in this scenario by the trial sponsors and coordinators is something very important to consider by the companies, in order to balance the need to give patients innovative therapies and the compliance to the Government restrictions.

3. In case of IBD urgency with or without fever, how to proceed?

Every hospital has restructured the patients' paths and flows to avoid any contact between those suspected to have COVID-19 from the rest of the patients. Depending on national and local protocols, patients with suspected COVID-19 symptoms should not go to the hospital, unless they have moderate-to-severe respiratory symptoms. Close contact with the referral IBD centre is important to give the right indications at the right time, including when to come to the hospital. If the patient lives far from the IBD referral centre, the IBD team can ask the IBD team from a nearer centre to take in charge these patients for hospitalization. The same concept may be applied in case of IBD flares or complications.

4. In asymptomatic patients with stable disease for more than 1 year, shall we delay/postpone infusion visits to limit contact with hospitals? If yes, for which type of IV treatment?

Infusion visits can be delayed depending on the drug and the local conditions. For those with normal calprotectin and/or other biomarkers, infliximab can be postponed to every 10 weeks². The GEMINI trial shows that patients randomized from vedolizumab to placebo can maintain remission up to week 24, therefore postponing vedolizumab to 4-8 weeks more than scheduled may be reasonable, according to local situations. However, maintaining the original schedule remains probably the best obvious strategy.

5. Is there any possibility to switch from IV biologics to subcutaneous injections? In which circumstances should I switch or not?

Elective switch in Crohn's disease from infliximab to adalimumab can lead to increased risk loss of response³, so switching to subcutaneous drugs should be limited to centres where infusions are no more available. In centres able to schedule infusions in order to avoid crowding and with appropriate sanitation done between each infusion, patients can continue their i.v. biologics. A different approach can be considered for those who start a new biologic. In this case, subcutaneous drugs may be

preferred, together with a program of remote patient's education, and home delivery service. Because of lack of any data on elective switch in UC patients, Infliximab should not be switched to adalimumab or golimumab.

6. If my patient under immunosuppressive/immunomodulatory treatment therapy has received instruction to stay isolated at home for suspected COVID-19 infection (fever, mild shortness of breath), shall I and the general practitioner advice to postpone treatments? Are they all the same?

There are no data showing that immunosuppressive therapies increase the risk of complicated COVID-19 or the risk of poor prognosis. The balance between the risk of IBD flare and the course of COVID-19 should drive the decision. Low CD4+ T cells in blood are associated with longer virus clearance time and more severe course of the disease⁴, therefore stopping thiopurines in case of suspected infection may be reasonable. The mechanism of action of methotrexate should not increase the risk of severe course and worse prognosis, but postponing the injection may be advisable. Biologics should be postponed until the resolution of infection. JAK inhibitors can decrease the number of lymphocytes, therefore stopping them until the resolution of infection may be advisable. COVID-19 evolves (to recovery or death) in about 3-4 weeks, then temporarily stopping immunosuppressive therapy should not have any impact on the risk of IBD flare.

7. Do we have further data to believe that patients on steroids are at risk of a worst prognostic in case of infection?

Severe COVID-19 is associated to cytokine release syndrome (CRS). IL-6 and IL-2R are highly expressed in these patients, and promising results have been achieved by tocilizumab (NCT04306705). The use of steroids is controversial. Experts suggest to avoid steroids during COVID-19⁵, but on the other hand, the use of low-dose, short-term steroids ($\leq 0.5-1$ mg/kg for 7 days) may be beneficial in controlling overwhelming inflammation and cytokine-related lung injury^{5,6}. As suggested by Chinese experts, the benefits and harms should be carefully weighed before using corticosteroids during COVID-19.⁵

8. In patients with active IBD disease, are there IBD medications that we should avoid to initiate at this point?

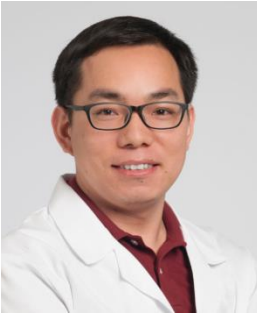
Generally speaking, IBD flares should be promptly treated to avoid hospitalization and complications needing surgery. All drugs indicated for treating IBD flares can be used at this stage. As mentioned above, adding thiopurines to steroids or to monoclonal antibodies should be used cautiously because the reduction in CD4+ T cells may delay virus clearance⁴. For the same reason, small molecules should be avoided, unless there are no valid alternatives.

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.

Two independent projects are being set up very recently to increase our knowledge on this novel disease in our IBD patients. We encourage you to participate.

The first project is an ECCO survey to better appreciate your view and understanding of the current situation. The coronavirus pandemic is a difficult time for everyone, including physicians and IBD patients. None of us have experienced a similar emergency, which requires dealing with complex situations, of which we know little or nothing, and which evolve day by day.

For this reason, we invite you to participate in a short survey on your current management, your fears and the difficulties you are facing every day in the context of this serious global pandemic.

The survey compilation takes only a few minutes and we ask you to respond before March 30 due to the emergency setting. This project is accessible until March 30 following the link: <https://survey.ecco-ibd.eu/index.php/433996?lang=en>

The second project is a global initiative from the International Organization for the study of IBD (IOIBD) to record timely proven cases of COVID-19 infection in our IBD patient. We encourage IBD clinicians worldwide to report ALL cases of COVID-19 in their IBD patients, regardless of severity (including asymptomatic patients detected through public health screening). Reporting a case to this Surveillance Epidemiology of Coronavirus) Under Research Exclusion (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. With the collaboration of our entire IBD community, we will rapidly be able to define the impact of COVID-19 on patients with IBD and how factors such as age, comorbidities, and IBD treatments impact COVID outcomes. This project, including a summary of all data collected to date, will be accessible following the link: <https://covidibd.web.unc.edu/>

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