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. STEROIDS, AZATHIOPRINE, JAK Inhibitors and BIOLOGICS: DR JEKYLL AND Mr HYDE
How shall I advise my housebound IBD patient who has been tested COVID-19 positive?

In housebound patients who report a clinical picture compatible with a mild to moderate form of COVID, I recommend to continue steroids in the rare steroid-requiring forms of IBD with no alternatives and at the lowest dose, but I suggest a pause in thiopurines and JAK-inhibitors up to 7-14 days after clinical recovery. We report in the April issue of the UEG Journal[1] the Saint-Antoine experience on the links between thiopurines, anti-TNF agents and viral infections that require hospitalization. For a total observation time of +15,000 person-years (4,800 for thiopurines, 3,800 for anti-TNF), we observed no death but 31 cases of serious viral infection (EBV, CMV, VZV, HSV), mostly in patients exposed to thiopurines. Tofacitinib has also been shown to strongly promote some (VZV) serious infections.

For patients exposed to anti-TNF agents and other biologics, I also recommend to postpone the next injection/infusion up to 7-14 days after clinical recovery. In our IBD unit, we keep in constant interaction

(routine phone visits, day-hospital venues for IV biologics, emergency calls) during the COVID crisis with our 2,600 patients with IBD (1300 are exposed to anti-TNF agents). Today, no cases of critical form COVID have been reported. Among multiple hypotheses for explaining this reassuring picture (relatively young age, trained immunity due to multiple vaccinations), one could speculate that anti-TNF agents could have a protective role against the transition from moderate to severe or critical forms of COVID. We all know that a single infusion of infliximab is able to reverse the digestive and systemic cytokine storm in acute severe colitis or in the most severe cases of colitis induced by check-point inhibitors.[2] In this context, Prof Beaugerie's team is currently working on designing a pilot trial evaluating the effectiveness of one infusion of infliximab versus best standard of care in patients without IBD but with pre-critical or critical forms of COVID.

2. SEROLOGICAL TEST, WILL IT HELP IN A NEAR FUTURE?

Serological tests measure the amount of antibodies present in blood to COVID-19 infection. Commercial and non-commercial serological tests are under development. Tests should be accurate and reliable; Food and Drug Administration has authorized one test developed by Cellex (qSARS-CoV-2 IgG/IgM Rapid Test). In European Economic Area Community, there are over 60 rapid SARS-CoV-2 antibody tests on the market. In addition, some in-house antibody detection tests for SARS-CoV-2 are being developed and validated by research groups. Serological tests can be easily implemented in the clinical laboratory of any hospital and are not so expensive as NAAT (Nucleic Acid Amplification Tests).

Serological tests are not a direct detection of the virus itself, rather a detection of the body's immune response to the infection that can provide insights into the kinetics of this response.

For the first days of SARS-CoV-2 infection, when the body's immune response is still on construction, antibodies may not be detected. That is why serologic tests alone have limitations for early COVID-19 diagnosis. Although Guo and collaborators[3] found an antibody response in infected patients using an enzyme-linked immunosorbent assay (ELISA) based on SARS-CoV-2 viral nucleocapsid protein as early as 1 day after the onset of symptoms, and IgM ELISA was detected in more cases than NAAT on day 5.5 of illness. The combination of IgM ELISA plus NAAT detected 98.6% of cases versus 51.9% with a single NAAT. Due to the high false-negative rates with NAAT tests[4,5], serological tests will be a useful supplement to RNA detection.

In addition, serological testing may be important in the management of COVID-19 patients; Zhao and collaborators found that higher titer of antibody response was independently associated with a worse clinical course[6].

In terms of public health, serological tests may be a key issue in the fight of pandemic by helping to identify those who have overcome the infection and have developed an immune response. Tests may help to answer the questions of how many people have been infected with the virus and to map levels of immunity in communities.

In addition to clinical data, serological tests may be used to identify those that can return to work considering that they are "immune" to the disease. Moreover, the test results may aid in choosing who may donate convalescent plasma, a potential treatment for patients with severe COVID-19 disease[7].

Serologic tests will be needed to evaluate response to vaccine candidates.

Some unanswered questions as such as whether asymptomatic infection generates a protective immune response and for how long those who have been infected will be protected against disease may be answered by kinetic of SARS-CoV-2 antibodies. Much more research is needed before these tests can be deployed to large populations screen but there is no doubt they will be useful.

3. SHOULD WE RECOMMEND VACCINATION AGAINST INFLUENZA AND PNEUMOCOCCUS IN NON-VACCINATED IMMUNOCOMPROMISED IBD PATIENTS DURING THE COVID-19 PANDEMIC?

Patients with IBD under immunomodulatory therapy show an increased risk of influenza and pneumococcal disease emphasizing that prevention of infections is essential in these patients[8,9]. Influenza and pneumococcal vaccination are suggested in the majority of patients with chronic autoimmune disorders including patients with IBD[10,11]. However, the vaccination rate against influenza and pneumococcal among IBD patients is still suboptimal. Particularly during COVID-19 pandemic additional pulmonary infections and complications in IBD patients at increased risk of SARS-CoV-2 infection should be prevented.

Influenza vaccine associates with reduced risk of respiratory morbidity and mortality in patients with autoimmune diseases and patients under immunomodulatory therapy[12]. It is therefore believed that patients with autoimmune disorders as well as IBD patients seem to benefit from the vaccine even though it may be less effective during immunomodulation[10,11]. If influenza infection rates can be reduced following annual vaccination, flu vaccine should consequently be considered in all non-vaccinated IBD patients in particular during COVID-19 pandemic. It is never too late to vaccinate as influenza activity can last as late as May and it is likely that co-infection with SARS-CoV-2 will intensify disease manifestations in IBD patients. As immunity to influenca vaccination occurs rapidly as soon as 10 days after immunization flu vaccine should therefore be considered in non-vaccinated IBD patients even at the end of the season. Current influenza vaccination in addition to a vaccine injection in fall may also intensify protection against the next seasonal outbreak and may be a good preparation for IBD patients if SARS-CoV-2 and influenza occur simultaneously in fall this year.

The risk of pneumococcal infection is also particularly high in patients with IBD. Immunocompromized patients with IBD are at increased risk of a more complicated disease course[9,13]. Vaccination against pneumococcol infection is currently suggested in IBD patients by different guidelines[10,14].Two pneumococcal polysaccharides are available: the 23-valent pneumococcal vaccine (PPSV23) and the 13-valent pneumococcal conjugate vaccine (PCV13) which cover most serotypes responsible for invasive pneumococcal disease. Primary vaccination is well tolerated and induces robust and long-lasting immune responses up to seven years. Those patients, who have not previously received pneumococcal vaccination, should receive a dose of PCV13 first followed by a dose of PPSV23 at least 8 weeks later[15].

In order to prevent additional pulmonary infections both pneumococcal and influenza vaccinations are highly recommended in IBD patients in the COVID-19 pandemic. IBD patients with co-morbidities, malnutrition and elderly IBD patients are probably of increased risk of superinfection and should preferably be selected for vaccination in particular if the availability of the vaccine is limited.

It has to be taken into account that at least in some countries vaccination programmes for IBD patients have currently been paused as the strategy is to avoid possible contacts between general practitioner and patients. As there is substantial geographic variability for pneumococcal and influenza vaccination, strategies should also be adapted according to the national guidelines.

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 very recently to increase our knowledge on this novel disease in our IBD patients. We strongly encourage you to participate.

The 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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