Review paper

Inflammatory bowel diseases during the COVID-19 pandemic

Edyta Derda, Edyta Szymańska, Magda Sokolek, Jarosław Kierkuś

Department of Gastroenterology, Hepatology, Feeding Disorders and Paediatrics, The Children's Memorial Health Institute, Warsaw, Poland

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Address for correspondence: Edyta Szymanska MD, PhD, Department of Gastroenterology, Hepatology, Feeding Disorders, and Paediatrics, The Children's Memorial Health Institute, Warsaw, Poland, e-mail: edyta.szymanska@onet.com.pl, edyta.szymanska@ipczd.pl

Abstract

Since the beginning of the COVID-19 pandemic in 2020, the safety of those with compromised immune systems and chronic disease has been of particular concern for health care providers. Inflammatory bowel diseases (IBD) are chronic, incurable conditions of digestive system with unknown aetiology, but one of the causes is disordered immune response. Medical therapies most frequently used in IBD are immune suppressing or modifying with the rising use of biologic treatment. All these aspects make patients with Crohn's disease and ulcerative colitis a group of particular risk. Therefore, the aim of this review is to discuss potential mechanisms, risks, and management of patients with IBD during COVID-19 pandemic.

Introduction

The first cases of SARS-CoV-2 infection were reported in Wuhan China in December 2019, followed by the rapid global spread of the virus, which was declared a pandemic by the World Health Organization (WHO) in March 2020 [1].

Coronavirus disease 2019 (COVID-19) has influenced patients and medical system across the world. While all individuals are at risk for COVID-19, this risk is of particular concern to those with compromised immune systems [2, 3]. Patients with inflammatory bowel diseases (IBD) were considered to be more vulnerable, particularly those on immune suppressing/modifying medications [4]. Two years of experience has demonstrated that IBD itself does not increase non-gastrointestinal (GI) infectious disease risk [5]. However, there is evidence of increased risk of non-GI, opportunistic infections associated with therapies used in IBD [6, 7].

Mechanism of action and potential risk for IBD

Coronaviruses bind to target cells through angiotensin-converting enzyme 2 (ACE2), a monocarboxypeptidase cleaving several peptides within the renin–angiotensin system and other substrates [8]. The enzyme is constitutively expressed by epithelial cells of the lung, intestine, kidney, and blood vessels, and its highest concentrations in the body are present in the terminal ileum and colon [9]. It has been reported that 50% of SARS-CoV-2 distribution among different biological samples of patients with COVID-19 is in stool [10]. Moreover, more than one-fifth of the patients negative in respiratory samples are positive in stools [11]. These findings may explain why some individuals with COVID-19 present only with gastrointestinal symptoms, and it may suggest that SARS-CoV-2 can spread through the faecal route. The expression of ACE2 is increased in the gut of patients with IBD, and it has been reported that TMPRSS2, a specific fusion, or 'spike' protein, involved in the mechanism of ACE2 function is also up-regulated in IBD [12, 13]. These observations suggest that the inflamed intestine of IBD patients represents an optimal target for the virus. However, based on the data published so far, there is no evidence that COVID-19 occurs more frequently in IBD patients than in the general population, and that those individuals experience more severe course of the infection.

Currently, during pandemic there are 2 main issues concerning IBD and COVID-19:

– How should IBD be managed in an environment of COVID-19?
– How should IBD patients with known or suspected COVID-19 be treated?

The aim of this review is to discuss these topics based on European Crohn's and Colitis (ECCO) guidelines on the management of IBD during the COVID-19 pandemic [14].

Management of IBD patients during the COVID-19 pandemic

ECCO experts recommend following the guidelines of the WHO and the European Centre for Disease Prevention and Control (ECDC) – patients with IBD, like the general population, should adopt social distancing, hand hygiene, and the wearing of face masks [15, 16].

It is also recommended that travelling be limited as much as possible to reduce the acquisition of infection by travellers, importation of cases from affected countries, and transmission among travellers [14].

Patients with IBD treated with immunomodulatory agents have increased risk of influenza and pneumococcal disease [17, 18]. To avoid pulmonary comorbidities with these seasonal infections, all IBD patients should be vaccinated [19]. Generally, influenza and pneumococcal vaccination are recommended for most patients with immune mediated disorders, including IBD [20].

IBD treatment during the pandemic

The therapeutic approach for patients with IBD should weigh the risk of viral infection against the risk of disease recurrence/aggravation. Patients treated with immunomodulatory agents are considered to be more vulnerable to COVID-19 infection and its severe course than the general population. However, so far, there is no evidence proving that patients on immunomodulatory therapies deal worse with SARS-CoV-2 or experience disease flares during infection [21, 22].

The SECURE-IBD database including 959 cases of COVID-19 in IBD patients, does not indicate that immunomodulators, anti-TNF therapy, anti-integrins, and anti-IL12/23 were associated with increased mortality [23]. Therefore, ECCO guidelines recommend maintaining immunomodulatory drugs in IBD patients without COVID-19 infection [14].

In conclusion, the available data demonstrate that patients on immunosuppression are not at increased risk for severe disease and complications, compared with the general population.

Therefore, according to ECCO guidelines, there is no need to discontinue immunomodulators, biologics, and JAK inhibitors in IBD patients without symptoms suggesting COVID-19 infected (not tested or tested negative) [14]. Also, experts advise for those patients is to reduce corticosteroids whenever possible and to maintain infusion services whenever possible [14].

It is not recommended that the dose of immunomodulators or biologics be reduced to prevent COVID-19 infection, or to switch infliximab to adalimumab in a stable patient, unless it is not possible to provide intravenous infusions [14]. The experts underline that there is no need to assume that IBD patients are at increased risk of being infected. Table I presents the dos and don'ts in IBD patients during the COVID-19 pandemic.

However, it remains uncertain whether patients with IBD who are exposed to SARS-CoV-2 have a higher risk of developing symptomatic or severe COVID-19 [24].

Management of IBD flares during pandemic

Because COVID-19 symptoms can resemble IBD manifestations, all patients with a suspected IBD flare should be tested for SARS-CoV-2 infection [25]. In the case of a negative test, IBD patients should be treated according to the standard guidelines. Also, home drug delivery and remote patient programs should be advised [26].

Another important issue is an infusion service. When it is not possible to safely administer drugs intra-

Table I. Medical management of IBD patients without symptoms suggestive of COVID-19 infection (not tested or tested negative) and those tested positive for SARS-COV2 (both symptomatic and asymptomatic)

Medication	COVID-19 negative/not tested	COVID-19 positive
Immunomodulators	Do	Don't
Biologics	Do	Don't/Postpone
JAK inhibitors	Do	Don't
Corticosteroids	Do at a reduced dose (< 20 mg/kg)	Don't/Reduce the dose whenever possible
Budesonide	Do	Don't know
Infusions	Do (in stable patients whenever possible)	Do (in stable patients whenever possible)

venously, it may be reasonable to consider switching to sub-cutaneous alternatives. However, this decision must be made very carefully because elective switching from infliximab to adalimumab is associated with a loss of tolerance and efficacy within 1 year [27].

Endoscopy plays a very important role in the management of IBD. A first approach is to stratify patients according to the risk of SARS-CoV-2 infection as high or intermediate. Endoscopy should be performed in a negative-pressure room, if possible, in accordance with the guidelines for infection control in endoscopy [28]. Moreover, the endoscopy staff should follow standardised precautions [29]. During the pandemic outbreak, non-urgent endoscopic procedures should be postponed. To identify patients with suspected COVID-19 infection, all the patients with scheduled endoscopy should be contacted by phone the week before and again 1-2 days before the procedure [14].

Surgical treatment is needed in the most severe cases when all pharmacological therapies have failed and in some complications of IBD. However, emergency surgery is required only in life-threatening situations, such as bowel perforation, closed loop, or medically refractory acute severe colitis. Non-urgent surgery should be postponed to protect patients and healthcare workers [30, 31]. Testing all patients for SARS-CoV-2 before surgery is mandatory [32]. When rapid PCR tests are unavailable, chest CT can be the diagnostic procedure. If neither testing nor imaging is available, all patients must be considered positive [33].

Drug administration in SARS-COV2-positive IBD patients

ECCO experts recommend for IBD patients with COVID-19 infection, whether symptomatic or asymptomatic, postponement of biologic administration, cessation or reduction of corticosteroids whenever possible, and cessation of immunosuppression (azathioprine/mercaptopurine) [34]. It is also advised that azathioprine in combination with an anti-TNF agent be stopped and JAK inhibitors be discontinued [14, 32].

When it comes to steroid therapy, the guidelines recommend cessation of prednisone at a dose above 20 mg/kg, and the treatment be restarted only if nasopharyngeal swab PCR-SARS-COV2 tests are negative [32].

It is not certain whether oral budesonide or beclomethasone should be discontinued in patients who test positive, or whether IBD-related medications protect against severe forms of COVID-19 (related to cytokine storm) [14, 32]. These issues and more treatment ambiguities need further investigation. Table I presents the dos and don'ts in IBD patients who test positive for COVID-19.

Paediatric patients with IBD and COVID-19

There are few data available on paediatric patients with IBD and COVID-19.

Ludvigsson's meta-analysis of 45 publications on this topic shows that children have milder SARS-COV2 infection and have better prognosis than adults [35]. However, the included manuscripts concerned only healthy children.

A team from New York published a case of a paediatric patient with Crohn's disease (CD) who developed a multisystem inflammatory syndrome in children (MIS-C) after COVID-19 infection, who was successfully treated with infliximab, which is an anti-TNF-α antibody [36]. This case supports the role of TNF-α blockade in COVID-19 inflammatory cascade, but further research is needed.

The aforementioned SECURE-IBD database included 3 children aged 0–9 years and 28 paediatric patients aged 10–19 years with IBD and COVID-19. None of these cases required ICU admission, and no deaths were reported among them, although 11% of children in the 10–19 age group had to be admitted to hospital [37].

Fragaso and Rodrigez, based on the analysis of available publications, summarised the recommendations for the management of paediatric patients with IBD and COVID-19 infection. The guidelines for safety measures and the use of telemedicine methods to monitor patients remain the same as for adults [38].

According to the European Society of Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), preliminary data on paediatric IBD patients during the COVID-19 pandemic support the use of standard therapeutic methods, including the use of biologics, especially in patients with more severe disease course [39].

Because medications used in IBD have been studied in the context of the coronavirus in adult patients, it seems that treatment recommendations can be extrapolated to children.

When it comes to combined therapy, decisions should be made individually for each patient. However, currently there is no general recommendation to stop combined treatment in all cases or to discontinue immunosuppressive therapy except in SARS-COV-2-positive patients [40, 41]. Screening for COVID-19 prior to initiation of immunosuppressive therapy is recommended to avoid immunosuppression in infected patients [42].

Conclusions

The available evidence demonstrates that IBD is not a risk factor for COVID-19. Nonetheless, medical management should be re-evaluated in SARS-CoV-2-positive IBD patients.

A goal should be to treat active disease, achieve remission, and maintain this remission, while providing the same protective measures as the general population. Moreover, non-urgent surgeries and endoscopic procedures should be postponed.

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Conflict of interest

The authors declare no conflict of interest.

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