Chronic Inflammatory Bowel Diseases

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Susceptibility and disease course of COVID-19 among patients with inflammatory bowel diseases (IBD) are unclear and epidemiological data on the topic are still limited. There is some concern that patients with immuno-mediated diseases such as IBD, which are frequently treated with immunosuppressive therapies, may have an increased risk of SARS-CoV-2 infection with its related serious adverse outcomes, including intensive care unit (ICU) admission and death. Corticosteroids, immunomodulators, and biologic drugs, which are commonly prescribed to these patients, have been associated with higher rates of severe viral and bacterial infections including influenza and pneumonia. It is not known whether these drugs can be so harmful as to justify their interruption during COVID-19 infection or if, on the contrary, patients with IBD can benefit from them. As shown by recent reports, it cannot be excluded that drugs that suppress the immune system can block the characteristic cytokine storm of severe forms of COVID-19 and consequently reduce mortality. Another cause for concern is the up-regulation of angiotensin converting enzyme-2 (ACE2) receptors that has been noticed in these patients, which could facilitate the entry and replication of SARS-CoV-2. The aim of this narrative review is to clarify the susceptibility of SARS-CoV-2 infection in patients with IBD, the clinical characteristics of patients who contract the infection, and the relationship between the severity of COVID-19 and immunosuppressive treatment.

Keywords: COVID-19 ; Crohn's disease ; ulcerative colitis ; ACE2 ; corticosteroids

1. Introduction

In December 2019 the first case of infection by a new type of coronavirus was documented in Wuhan, China [1]. After a few months, on 11 March 2020, the World Health Organization (WHO) declared a state of pandemic. The disease responsible for the infection is a new coronavirus, which was initially named 2019-nCoV, then changed to SARS-CoV-2 [2]. It is now well known that the presence of comorbidities increases the risk of infection and worsens the outcome in SARS-CoV-2 infection [3][4]. This explains the growing interest regarding the relationship between IBD (inflammatory bowel diseases) and COVID-19. There are several reasons why we might expect a greater risk of SARS-CoV-2 infection and/or a worse course of the disease in patients with IBD: first of all, the weakening of the immune system and the greater risk of infection of these patients, due to the immunosuppressive drugs they take [5]. Secondly, the hyperproduction of cytokines seems to increase the expression of angiotensin-converting enzyme 2 (ACE2) [6]. In these patients, there is also an increased expression of ACE2 in the gut mucosa [7] and an increase of ACE2 serum levels (as well as Ang1–7 and the ACE2: ACE ratio) [8]. This could play a protective role in the blood [9] by acting as a competitive receptor for the virus and thus leading to the reduction of the viral load that would infect the host.

Since it appears that ACE2 expression is increased in IBD, both mucosal [7] and serum [8], and since IBD patients often take immunosuppressive therapy resulting in deregulation of the immune system, one might expect to see different forms of COVID-19 in these patients compared to the general population.

The aims of this narrative review are to verify the susceptibility to SARS-CoV-2 infection in IBD patients, the clinical characteristics of infected patients, and the relation between COVID-19 severity and immunosuppressive therapy, through an extensive review of the available literature

2. Inflammatory Bowel Diseases, COVID-19 and Children

The incidence rate of COVID-19 in children appears to be lower: in a study by Carparelli et al. [10], among 600 analyzed patients, including pediatric patients, COVID-19 was diagnosed in 25, none of whom <18 years. In most cases, symptoms were absent or mild. No death was recorded. In a study by Brenner et al. [32] the treatment with sulfasalazine/mesalazine (57% of hospitalized patients vs. 21% of non-hospitalized) and the use of corticosteroids (29% vs. 8%) were associated with the risk of hospitalization. Additionally, in pediatric patients, similarly to what was found in adults, the use of TNF antagonists (tumor necrosis factor) alone was associated with a lower probability of hospitalization (7% of hospitalized patients vs. 51% of non-hospitalized).

A publication by Turner et al. [33] underlines the importance of maintaining the underlying IBD treatment. In fact, the risk of inappropriate management of IBD therapy is substantial, as demonstrated by the increased IBD exacerbations in China and South Korea. In fact, data recorded from January 20 to March 20, 2020, show that 233 patients should have had Infliximab infusion during this period, but 28% was postponed and 0.9% cancelled. Of the 66 patients who did not assume the therapy correctly, 14 had an exacerbation, of which 10 required hospitalizations. Conversely, among 1431 pediatric patients with IBD over the same period, only 17 (1.2%) had a flare-up of the disease. The same article reports the South Korea experience: until March 20, 2020, a diagnosis of COVID-19 was made in 525 patients with an age of 19 or less. The indication was to continue therapy without any modifications. However, 13 patients postponed anti-TNF therapy due to fears related to the virus; of these, 3 (23%) had a worsening of the underlying disease.

A study by Sansotta et al. [34] highlights that, although all patients were instructed to continue therapy, none had a severe course and there were no cases of hospitalization. During this period, two patients experienced fever and gastrointestinal symptoms. After accessing the hospital and after the molecular swab, the results of which were negative, an IBD exacerbation in one case and a Salmonella infection in the other were diagnosed. It is remarkable to note that, although COVID-19 can present itself with gastrointestinal symptoms, all other possible causes must be taken into account. The results of our review are briefly summarized in **Figure 1**.

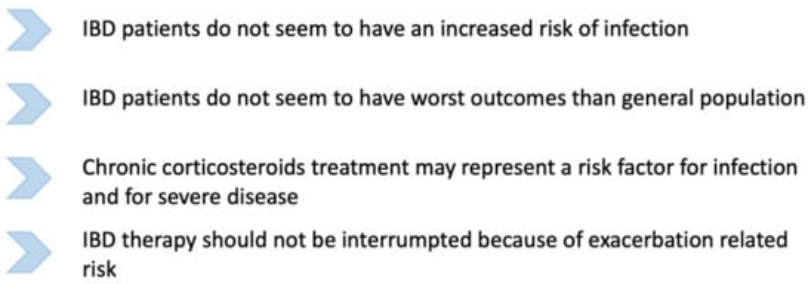

Figure 1. The main findings of our review are summarized in the figure.

3. Inflammatory Bowel Diseases and ACE2

There are many reasons why we might expect an increased risk of SARS-CoV-2 infection and/or a worse course of the disease in IBD patients, as already mentioned in the introduction. There is conflicting evidence regarding the effective increased expression of ACE2 and TMPRSS2 in patients with IBD. In fact, it has been found that ACE2 levels would be down-regulated during inflammation at the level of ileum of patients with CD (Crohn's disease), but not in the colon of patients with UC [63].

Another study showed that the expression of ACE2 would be increased in the inflamed colon and rectum of IBD patients compared to the non-inflamed one of patients with disease in remission and in controls, while at the ileal level the expression would be reduced [64].

Regarding the increase in ACE2 seric level and its potential protective role, it has been demonstrated, in vitro, that human recombinant ACE2 inhibits the attack of the virus on the cell, depending on the amount of virus and the dose of recombinant human ACE2, thus establishing a dose-dependent mechanism [65]. The first patient that has been treated with hrsACE2 is a 45-years-old woman. She manifested cough, asthenia, myalgia, fever, dyspnoea, nausea, diarrhea, areas of bilateral consolidation on lung RX, and the molecular swab for SARS-CoV-2 was found to be positive. Treatment with hydroxychloroquine and nadroparin was then started. Following the radiographic progression and the worsening of patient's symptoms, which required intubation, treatment with hrsACE2 was then started, with intravenous infusions at a dosage of 0.4 mg/kg for 5 min twice a day. After the first administration, body temperature returned to normal in a few hours and there was a sharp reduction in angiotensin 2. HrsACE2 administration was continued for 7 days. The course was complicated by methicillin-sensible *S. aureus* bacterial pneumonia and *Enterobacteraerogenes* bacteraemia with the subsequent need for antibiotic therapy (firstly cefuroxime, then linezolid and aztreonam). The patient was then extubated on day 21 and discharged on day 57 from the onset of symptoms (after a rehabilitation period for the myopathy).

Therapy with hrsACE2 resulted in a reduction in IL-6, IL-8, and ferritin. TNF-α and CRP (C-reactive protein) underwent an initial increase (probably due to bacterial infection), followed by a clear reduction. What is most surprising is the reduction in SARS-CoV-2 copies detectable in plasma: 2500 copies/mL the day the therapy was started, 270 copies/mL the next day; subsequently they became undetectable [66]. The administration of hrsACE2 is particularly effective in the transformation of angiotensin 2 into Ang1–7. This may have a key role in therapy since angiotensin 2 infusion has been associated with an increased thrombotic risk and with increase in IL-6 levels [67][68]. On the contrary, and as already

mentioned, the increase in Ang1–7 (which represents an alternative pathway to Ang2) determines anti-inflammatory and anti-fibrotic effects.

4. Drugs and Inflammatory Bowel Diseases: What Have We Learned?

The relationship between drugs used to treat IBD and COVID-19 is complex and not yet fully understood.

Most of the articles we analyzed agree that the greatest risk both in increasing the incidence of infection and in worsening symptoms is related to the use of corticosteroids. In fact, steroid therapy would increase the risk of needing oxygen therapy [47] (p = 0.007), the risk of developing a severe form of disease [27][32][46], and even the risk of hospitalization (p = 0.015) [20].

In a study by Agrawal et al. [43] the use of Vedolizumab has been associated with a higher risk of hospitalization (but not of severe COVID-19 forms) compared to anti-TNF monotherapy, although it is considered safe. The explanation for this phenomenon probably lies in the fact that patients treated with Vedolizumab have shown a greater tendency to develop gastrointestinal symptoms during infection, especially those with IBD in a remission phase [43].

The finding of more severe forms of SARS-CoV-2 disease in IBD patients undergoing thiopurine therapy compared to patients with anti-TNF therapy may be due to a negative effect of the former or a protective role of the latter. The possibility of interrupting thiopurine therapy in patients at high risk for COVID-19 with disease in remission phase on therapy with thiopurine + anti-TNF [35] has been proposed.

Data concerning the use of 5-ASAs are conflicting. Ungaro et al. [35] have associated the use of mesalamine/sulfasalazine with severe forms of infection compared to patients with different therapies. However, this supposed association remains just a hypothesis which needs to be confirmed and at the moment there is no indication to interrupt the treatment. A connection between the use of mesalazine and severe infection disease has also been noticed by Brenner et al. [32]. In contrast, Khan et al. [46] found no differences between mesalamine and anti-TNF treatment in a sample of 649 patients with IBD and COVID-19.

However, all studies seem to agree on the importance of not interrupting therapy (except, maybe, for corticosteroids) because of the exacerbations related risk.

Biological drugs, which are considered potentially protective, and especially anti-TNFs, are placed outside the box. Allocca et al. [20] found a reduction in the risk of pneumonia and hospitalization (OR 0.15 and 0.31) in patients receiving monoclonal antibodies therapy. Patients on anti-TNF therapy have developed severe forms of the infection to a lesser extent than the others in a study by Ungaro et al. [35]. Moreover, biologics have shown a protective role against the infection (1.6% vs. 7.6%) in a study by Bezzio et al. [36].