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REVIEW

Why Do Immunosuppressed Patients with Inflammatory Bowel Disease Not Seem to Be at a Higher Risk of COVID-19?

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Abstract

The COVID-19 pandemic has created a public health emergency. In this context, there are major concerns for patients with inflammatory bowel disease (IBD), particularly for those treated with immunomodulators, biologics, and Janus Kinase inhibitors. Infection susceptibility is, in fact, one of the reported risks for immunotherapy drugs. This review provides the existing evidence from worldwide case series describing: (a) the risk for the SARS-CoV-2 infection and (b) the risk of a severe infection outcome in patients with IBD treated with immunotherapy. Further, the review discusses the potential mechanisms underlying why this group of patients with IBD might be protected from contracting the infection and from a worse disease. From the available data, it appears that these patients should have an enhanced adherence to the recommended preventive measures, suggesting a role in reducing their risk of infection. Furthermore, the immunotherapy may dampen the cytokine storm and inflammation associated with COVID-19. The results of this review seem to confirm that patients with IBD receiving immunomodulators, biologics, or Janus Kinase inhibitors do not have an increased risk of contracting SARS-CoV-2 infection or develop a more severe COVID-19. According to the current evidence, it is advisable to maintain immunotherapy, apart from corticosteroids, in patients with IBD in order to avoid relapse. This review reports only on the cases of patients who tested positive for SARS-CoV-2 by RT-PCR of a nasopharyngeal swab sample. This is a limitation and a more accurate epidemiological picture of the infection will be obtained only via the expanded use of antibody tests.

Keywords Inflammatory bowel disease · SARS-CoV-2 · COVID-19 · Immunotherapies · Adherence · Containment measures

Introduction

Rapidly developing infections due to the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have created a global public health emergency [1, 2]. Following the onset of the outbreak in China in December 2019, the pandemic has had a tremendous impact worldwide [3]. The infection can be asymptomatic or can cause coronavirus disease 2019 (COVID-19) [2, 4]. The most common symptoms of COVID-19 are fever and respiratory symptoms, but a significant proportion of patients (3–79%) can have gastrointestinal manifestations, and in severe cases, COVID-19 can be fatal [5, 6]. In this context, there are major concerns for patients with inflammatory bowel disease (IBD), particularly for those treated with immune modifying medications. Therapy with thiopurines, methotrexate, biological agents, especially tumor necrosis factor-alpha (TNF-α) antagonists, and Janus Kinase (JAK) inhibitors have been associated with an increased risk of serious viral and bacterial infections, including pneumonia [7–11]. Therefore, patients with IBD treated with immunomodulators, biologics, and JAK inhibitors, due to a state of impaired immunity, might be more susceptible to SARS-CoV-2 infection, and the risk of a severe clinical course of COVID-19 might be increased.

At the beginning of the pandemic, given the large number of COVID-19 cases in China, the Chinese Society of Gastroenterology recommended withholding immunotherapy [12, 13]. At one IBD center in Wuhan, a very high-risk area, several strategies were implemented to reduce the risk of viral infection and all patients treated with biologics and immunomodulators discontinued these therapies [14]. A

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survey from the European Crohn's and Colitis Organization (ECCO) on the management of patients with IBD during COVID-19 pandemic was conducted between March 20 and March 30, 2020 [15]. A total of 3815 physicians from 72 countries across the world participated in the survey. The survey form contained questions assessing the physicians' fear of infectious risk in patients with IBD and without IBD using a numerical scale from 0 to 10. The fear that patients with IBD could be infected with SARS-CoV-2 was greater than the fear for patients without IBD and 67.7% of respondents believed that immunomodulators and biological drugs could be a predisposing factor for infection. Accordingly, their strong apprehension that patients with IBD because of their immunosuppressed state could be more susceptible to SARS-CoV-2 infection resulted in a high average value on the survey scale (7.45, standard deviation [SD] = 1.95).

This review summarizes the existing evidence from worldwide case series describing the risk for SARS-CoV-2 infection and the risk of a severe clinical course of COVID-19 in patients with IBD treated with immunomodulators, biologics, and JAK inhibitors. The potential mechanisms underlying why patients with IBD on immunotherapy might actually be protected from contracting the infection and from a worse disease outcome will also be discussed.

Methods

Search Strategy and Study Selection

References for this review were identified through searches of PubMed for articles published from December 1, 2019, to June 28, 2020, using combinations of the terms "COVID-19," "SARS-CoV-2," "inflammatory bowel disease," "IBD," "Crohn's disease," "ulcerative colitis," "azathioprine," "mercaptopurine," "methotrexate," "biologic," "TNF," "integrin," "IL-12/23," "JAK," "IL-6," "immunotherapy," "acute respiratory distress syndrome," and "cytokine release syndrome." Of all resulting articles, the guidelines and the recommendations of the major gastrointestinal societies for the management of IBD during the COVID-19 pandemic, the reviews, and the articles based on their clinical relevance to the aim of this review have been selected. Relevant references cited in retrieved articles were also reviewed. Clinicaltrials.gov for randomized clinical trials on the field of the paper was also searched. Articles published in English and Chinese were included. The final reference list was generated on the basis of originality and relevance to the topics covered in this review.

Data from Case Series of Patients with IBD Worldwide

In contrast to the clinicians' apprehensions, currently available evidence suggests that patients with IBD on immunotherapy, apart from corticosteroids, do not appear to have an increased risk of developing COVID-19, nor do they have a worse disease course of COVID-19 than those of the general population or patients with IBD treated with other drugs (Table 1) [16–29].

Surprisingly, on March 8, 2020, data collected from China showed that there were no patients with IBD infected with SARS-CoV-2 in the IBD Elite-Union, which incorporates the seven largest IBD referral centers with more than 200,000 patients with IBD [19]. In contrast to the initial recommendations at the beginning of the pandemic, further key recommendations for managing patients with IBD suggested not suspending immunomodulator and biological drug treatments [19].

An observational study was conducted on a cohort of 552 patients with IBD who were followed from February 19 to March 23, 2020, in a tertiary referral center at Bergamo, a city located in Lombardy, the Italian region with the highest incidence of new cases of SARS-CoV-2 infection [20]. The results showed that over a 1-month period, none of the patients developed COVID-19, and in particular, no patients were admitted to the hospital due to COVID-19. Approximately 17% of these patients were on thiopurines or methotrexate and 16% were on biologics and maintaining the same treatment.

In April 2020, a multicenter Italian study that enrolled 79 patients with IBD and confirmed COVID-19 had shown that active IBD, older age, and the presence of comorbidities were significantly associated with a higher risk of COVID-19 pneumonia and related death [21]. Instead, no association was found between concomitant use of biologics in 47 patients (63%) and/or thiopurines in six patients (8%) and a worse outcome of COVID-19.

Since the beginning of the pandemic, 15 patients with IBD and COVID-19 were identified among a large cohort of patients with IBD from France (Nancy) and Italy (Milan) [22]. Thirteen of the 15 patients were on azathioprine and/or biologics. Five of the 15 patients were hospitalized, but none required intensive care unit (ICU) admission, and no deaths were registered.

In a Spanish case series, published online in May 2020, only 12 out of 1918 patients with IBD followed at a large IBD Unit in Madrid were diagnosed with SARS-CoV-2 infection based on a positive result from a real-time reverse transcriptase-polymerase chain reaction (RT-PCR) of a nasopharyngeal swab sample [23]. The results included both hospitalized patients and outpatients isolated at

Table 1 Case series of patients with IBD worldwide: use of immunotherapy and COVID-19 outcome

	Country	Study period (2020)	IBD *n*	CD *n* (%)	UC *n* (%)	IBDU *n* (%)	AZA/6MP/MTX *n* (%)	Biologics *n* (%)	Biologics + IMM *n* (%)	Anti-TNF-α *n* (%)	Anti-TNF-α + IMM *n* (%)
Norsa et al. [20]	Italy	February 19–March 23	552	186 (36%)	336 (64%)	0	89 (17%)	82 (16%)	0	NA	NA
Bezzio et al. [21]	Italy	March 11–March 29	79[†]	32 (41%)	47 (59%)	0	4 (5%)	45 (57%)	2 (3%)	25 (%)	2 (3%)
Allocca et al. [22]	Italy/France	NA	15[†]	9 (60%)	6 (40%)	0	1 (7%)	11 (73%)	1 (7%)	7 (%)	1 (7%)
Taxonera et al. [23]	Spain	Through April 8	1918	920 (48%)	997 (52%)	0	391 (20%)	144 (8%)	157 (8%)	NA	NA
Rodriguez-Lago et al. [24]	Spain	February 27–April 8	40[†]	13 (32%)	23 (58%)	4 (10%)	11 (28%)	7 (18%)	2 (5%)	3 (%)	1
Gubatan et al. [25]	USA	March 4–April 14	168	66 (39%)	86 (51%)	16 (10%)	15 (9%)	48 (29%)	NA	34 (20%)	NA
Khan et al. [27]	USA	January 1–May 15	37,857	NA	NA	NA	2391 (6%)	NA	NA	4920 (13%)	NA
Haberman et al. [28]	USA	March 3–April 3	37[#]	20 (54%)	17 (46%)	0	NA	NA	NA	NA	NA
Lukin et al. [29]	USA	February 1–April 30	80[†]	38 (59%)[§]	26 (41%)[§]	0	7 (11%)[§]	38 (59%)[§]	4 (6%)[§]	16 (%)[§]	NA
Lukin et al. [29]	USA	NA	119[¥]	69 (58%)	46 (39%)	4 (3%)	5 (4%)	76 (64%)	4 (3%)	24	NA

	Other biologics^ *n* (%)	Other biologics^ + IMM *n* (%)	JAK inhibitor *n* (%)	COVID-19 cases *n* (%)	Hospitalized *n* (%)	Death *n* (%)
Norsa et al. [20]	NA	NA	0	0 (0%)	0	0
Bezzio et al. [21]	20	0	1	79[†]	22 (28%)	6 (8%)
Allocca et al. [22]	4	0	0	15[†]	5 (37%)	0
Taxonera et al. [23]	NA	NA	6 (0.3%)	12 (0.6%)	8 (67%)	2 (17%)
Rodriguez-Lago et al. [24]	4	1	0	40[†]	21 (53%)	2 (5%)
Gubatan et al. [25]	14	NA	0	5 (3%)	1 (20%)	1 (20%)
Khan et al. [27]	NA	NA	NA	36 (0.09%)	NA	NA
Haberman et al. [28]	NA	NA	NA	37[#]	4 (11%)	0
Lukin et al. [29]	22	NA	1 (2%)[§]	80[†]	17 (21%)[°]	0
Lukin et al. [29]	52	NA	7 (6%)	29 (24%)	NA	NA

Azathioprine, 6-mercaptopurine, methotrexate, biologics, and JAK inhibitor as monotherapy unless otherwise stated

IBD inflammatory bowel disease, *CD* Crohn's disease, *UC* ulcerative colitis, *IBDU* inflammatory bowel disease unclassified, *AZA* azathioprine, *6MP* 6-mercaptopurine, *MTX* methotrexate, *Anti-TNF-α* anti-tumor necrosis factor-alpha, *IMM* immunomodulator, *JAK* Janus Kinase, *NA* not available

[^]Anti-integrins, others. [†]Only patients with IBD and confirmed or likely diagnosis of COVID-19 have been included in the study. [#]Patients with immune-mediated inflammatory diseases, including IBD, with confirmed or likely diagnosis of COVID-19 have been included in the study. [§]Data available on 64 out of 80 patients with IBD and confirmed or likely diagnosis of COVID-19 included in a matched cohort of the study. [°]Data available on 80 patients with IBD and confirmed or likely diagnosis of COVID-19 included in a matched cohort of the study. [¥]Patients with IBD included in a longitudinal cohort of the study

home. This study concluded the incidence of COVID-19, and associated mortality did not increase in the population of patients with IBD receiving immunomodulators and/or biologics.

Another multicenter Spanish study assessed the course of the infection in 40 patients with IBD that tested positive for SARS-CoV-2 between February 27 and April 8, 2020 [24]. All patients had a good overall prognosis, including one-third of the patients who received immunomodulator therapy, and 18% of patients who received biologics.

A retrospective observational study of consecutive patients tested for SARS-CoV-2 between March 4 and April 14, 2020, at the Stanford University School of Medicine, California, was performed to evaluate the prevalence, symptoms, and clinical predictors of COVID-19 in patients with IBD [25]. A total of 14,235 consecutive subjects were tested for the virus and 8.2% tested positive (1160/14,235). Among the tested patients, the prevalence of IBD was 1.2% (168/14,235), which was comparable to the prevalence of IBD in the US adult population [26]. Sixty-three of 168 patients (37.5%) were treated with biologics or immunomodulators. The prevalence of COVID-19 in patients with IBD was 3.0% (5/168). The only strong independent predictor associated with an increased risk of COVID-19 among patients with IBD was an age greater than 66 years. Regarding the clinical course of the analyzed cohort of patients, the authors concluded that immunotherapy may have attenuated the viral respiratory inflammation, leading to an asymptomatic status or mild COVID-19 symptoms.

The impact of thiopurines and TNF-α inhibitors (infliximab) on the development of COVID-19 in a US cohort of 37,857 patients with IBD in the Veterans' Affairs Healthcare System was evaluated [27]. In this retrospective analysis, 36 incident cases of COVID-19 were registered from January 1 to May 15, 2020. The patients were considered negative in the case of a negative test or if they were not tested. Two cases of COVID-19 were found among the 2391 patients on thiopurines, and three cases were found among the 4920 patients on anti-TNF-α therapy. No data on the viral infection course were reported by the study. These results reinforce the observation that neither TNF-α antagonists nor thiopurines seem to be associated with an increased risk of contracting COVID-19.

A prospective case series from New York, the epicenter of the COVID-19 pandemic in the USA, reported 86 patients with immune-mediated inflammatory diseases (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, psoriasis, IBD), with confirmed or highly suspected COVID-19 assessed from March 3 to April 3, 2020 [28]. A group of 37 patients with IBD (43%) was included [28]. Overall, 62 of the 86 patients (72%) received biologics or JAK inhibitors. Although the study was characterized by a limited sample size, the incidence of hospitalization among patients with immune-mediated inflammatory diseases was similar to that among cases of COVID-19 in the general population in New York City [28].

In another study, published online in May 2020, the clinical outcomes of 80 confirmed or highly suspected COVID-19 in patients with IBD were compared to a matched cohort of 160 COVID-19 controls without IBD [29]. A higher significant prevalence of immunotherapy was reported in cases with IBD ($p < 0{\cdot}001$). A composite outcome of death, ICU admission, and endotracheal intubation was lower in patients with IBD than in controls (24% vs. 35%, $p = 0.352$). In addition, the prevalence and risk factors of COVID-19 were investigated in a separate longitudinal cohort of 119 patients with active IBD [29]. No differences regarding the use of biologics and immunomodulators were observed between the 29 patients positive for COVID-19 and the negative patients in the longitudinal cohort. The results of this study are consistent with all the above-reported data.

Data from the Surveillance Epidemiology of Coronavirus Under Research Exclusion-IBD Registry

The Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE)-IBD Registry is a large international registry that collects information on pediatric and adult patients with IBD and confirmed COVID-19 infection [30]. At the time of the first published data, May 18, 2020, a total of 525 cases were reported from 33 different countries [31]. Approximately 10% of patients were treated with azathioprine/6-mercaptopurine and 1% were treated with methotrexate. The most common class of IBD treatment was anti-TNF-α drugs (43.4% overall, 33.5% monotherapy, and 9.9% combination therapy with azathioprine, 6-mercaptopurine, or methotrexate). Anti-integrin was used by 9.5% of patients, anti-interleukin (IL)-12/23 by 10.5%, and JAK inhibitor by 1.5%. Strong risk factors for worse COVID-19 outcomes were older age, number of comorbidities, and use of systemic corticosteroids. No association between anti-TNF-α medications used as monotherapy and severe COVID-19 was found. Although the number of reported cases exposed to other biologic therapies, immunomodulators, and anti-JAK agents was quite small in comparison with the reported cases on TNF-α antagonists, it should be noted that most patients required only outpatient care, and just two patients died.

As of June 28, 2020, 1572 cases from 51 countries were reported to the registry, of which 156 were receiving thiopurine therapy, 11 methotrexate, 22 JAK inhibitor, and less than half were receiving biologics monotherapy (Table 2) [30]. About 71–83% of patients on biologics monotherapy required outpatient care only. The most

Table 2 SECURE-IBD registry: COVID-19 outcome in patients with IBD on immunomodulator, biological, and anti-JAK therapy

	Total *n*	Outpatient only *n* (%)	Hospitalized *n* (%)	ICU *n* (%)	Ventilator *n* (%)	Death *n* (%)	ICU/ventilator/death *n* (%)
6MP/AZA monotherapy	156	104 (67%)	52 (33%)	13 (8%)	10 (6%)	3 (2%)	15 (10%)
MTX monotherapy	11	6 (55%)	5 (45%)	0 (0%)	0 (0%)	1 (9%)	1 (9%)
Anti-TNF-α without 6MP/AZA/MTX	454	377 (83%)	72 (16%)	9 (2%)	5 (1%)	3 (1%)	10 (2%)
Anti-TNF-α + 6MP/AZA/MTX	150	101 (67%)	49 (33%)	10 (7%)	5 (3%)	3 (2%)	12 (8%)
Anti-integrin	153	108 (71%)	40 (26%)	7 (5%)	7 (5%)	5 (3%)	11 (7%)
IL-12/23 inhibitor	139	116 (83%)	19 (14%)	5 (4%)	4 (3%)	1 (1%)	5 (4%)
JAK inhibitor	22	17 (77%)	5 (23%)	2 (9%)	1 (5%)	1 (5%)	2 (9%)

Modified from Brenner et al. [30]

IBD inflammatory bowel disease, *6MP* 6-mercaptopurine, *AZA* azathioprine, *MTX* methotrexate, *Anti-TNF-α* anti-tumor necrosis factor-alpha, *IL* interleukin, *JAK* Janus Kinase, *ICU* intensive care unit

recently reported cases seem to confirm the previously published reassuring data [31].

Guidance on the management of patients with IBD during the COVID-19 outbreak has been issued by the International Organization for the Study of Inflammatory Bowel Disease (IOIBD), the American Gastroenterological Association (AGA), the European Crohn's and Colitis Organization (ECCO), the British Society of Gastroenterology (BSG), and the Crohn's and Colitis Canada (CCC) [15, 32–35]. All the listed societies recommend that patients with IBD should continue their current medications, including immunotherapy, in order to avoid relapse [36]. The only exceptions are steroids that should be discontinued, or the dose should be reduced if feasible.

The RECOVERY study is an ongoing large, randomized, controlled trial of different therapies for patients admitted to hospital with COVID-19 in the UK [37]. Very recent preliminary results of the study showed that the steroid therapy (dexamethasone at a dose of 6 mg once daily) administered to 2104 patients for ten days reduced deaths by one-third in patients who required ventilation and by one-fifth in those receiving oxygen only, compared with 4321 patients randomized to usual care ($p = 0.0003$ and $p = 0.0021$, respectively) [38]. These results are apparently in contrast with the suggestion of stopping or tapering steroids during the COVID-19 infection, but the RECOVERY study describes only the positive results of a short course of steroids in severe COVID-19.

Why do patients with IBD treated with immunotherapy seem to not be at higher risk of contracting COVID-19 or at higher risk of a worsened outcome? Several aspects must be taken into consideration.

Adherence of Patients with IBD with the Recommended Preventive Measures

A survey was conducted in China during the initial stage of the COVID-19 outbreak to analyze the degree of psychological impact, anxiety, depression, and stress in the general population [39]. The survey included 1210 participants, and nearly half of the respondents believed that they were not very likely to contract COVID-19 (36.1%) or were not likely to contract it at all (10.0%). Only 11.2% assumed that they could contract COVID-19 very easily. In contrast, 75% of participants were very worried or somewhat worried about other family members developing COVID-19.

A more recent Chinese survey involving patients with IBD collected feedback on their quality of care during the COVID-19 pandemic (Table 3) [40]. The survey was completed by 2277 patients, and over half of the respondents (58%) were concerned about the risk of contracting SARS-CoV-2 infection for themselves and their family. However, no data were collected on the fear of infectious risk associated with immunotherapy.

The European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA) conducted a large survey between March 30 and April 16, 2020, to analyze fears, concerns, and behavior of patients with IBD during the COVID-19 outbreak (Table 3) [41]. A total of 3815 participants from 51 countries worldwide completed the survey. Most patients were concerned about the risk of developing COVID-19 (85%), and, in particular, almost two-thirds of participants (64%) believed that the use of immunotherapy was associated with a higher risk of infection. Most participants were anxious about contact with other people (85%). However,

Table 3 Perception of patients with IBD during the COVID-19 pandemic

	Chen et al. [40]	D'Amico et al. (EFFCA survey) [41]	Grunert et al. [42]
Country	China	51 countries	Germany
Participants, *n*	2277	3815	415
Men, *n* (%)	1379 (61%)	1072 (28%)	188 (45.3%)
Crohn's disease, *n* (%)	1639 (72%)	2211 (58%)	215 (51.8%)
Ulcerative colitis, *n* (%)	555 (24%)	1528 (40%)	192 (46.3%)
Indeterminate colitis/IBDU, *n* (%)	NA	76 (2%)	5 (1.2%)[#]
Fear of contracting COVID-19	1331 (58%)	3242 (85%)	233 (56.1%)
Fear of higher risk of infection due to immunotherapy	NA	2427 (64%)	239 (57.7%)[‡]
No change of IBD therapy on their own initiative	1744 (77%)	3670 (96%)[§]	383 (96.2%)[¥]
Change of daily habits	NA	3724 (98%)°	275 (66.3%)^ 381 (91.8%)^^
Use of protective aids during daily life	NA	3183 (83%)°	143 (34.5%)

IBD inflammatory bowel disease, *IBDU* inflammatory bowel disease unclassified, *NA* not available

[#]3 patients (0.7%) not specified, [‡]fear of a worse COVID-19 due to immunotherapy. [§]Out of 3813 respondents. °Out of 3814 respondents. [¥]Out of 398 patients. ^Patients who leave the house less frequently than before the COVID-19 pandemic. ^^Patients who wash their hands more frequently than they did before the COVID-19 pandemic

despite these concerns, 88% of patients did not want to stop drug therapy, and 96% did not discontinue their IBD therapy on their own account because of worries.

In a German cross-sectional survey, the perception of COVID-19 pandemic among 415 patients with IBD was compared to a matched cohort of 116 participants without IBD (Table 3) [42]. Enrollment occurred between April 2 and April 17, 2020. Patients with IBD were more concerned about the risk of contracting SARS-CoV-2 infection than the control group ($p = 0.009$), particularly those treated with immunotherapy. Moreover, patients with IBD taking biologics, anti-TNF-α drugs associated with thiopurines, and JAK inhibitors were more afraid that these medications could worsen the COVID-19 course with respect to patients with IBD on 5-aminosalicylates and the control group. Nonetheless, only 3.8% of patients with IBD reported that they have reduced the therapy by their own initiative.

The results of both the EFCCA and the German surveys [41, 42], also considered in light of the Chinese surveys [39, 40], suggested that patients with IBD should have very high compliance with the recommended measures of containment (staying at home, respect of social distancing, use of protective precautions during daily life), in the fear of a possible higher risk of COVID-19. The enhanced attention to the appropriate preventive strategies could have a role in reducing their risk of infection.

Immunomodulators Use During the COVID-19 Pandemic

Preliminary data from the SECURE-IBD Registry and from recent global case series of patients with IBD have provided cautionary support for the safety of thiopurines and methotrexate during the COVID-19 outbreak either in contracting the virus or in developing the disease [20–31]. Mercaptopurine has shown to restrain the maturation of the Middle East respiratory syndrome coronavirus (MERS-CoV) in vitro by blocking a viral protease [43]; however, the study has not been replicated for SARS-CoV-2 and no specific data are available on methotrexate.

Gut Expression of Angiotensin-Converting Enzyme 2 in Patients with IBD on Biologics

SARS-CoV-2 enters the host cells using the viral receptor angiotensin-converting enzyme 2 (ACE2) [44]. ACE2 is highly expressed not only in lung cells but also in multiple tissues, including intestinal epithelial cells from the terminal ileum and colon, which are the principal localizations of IBD inflammation [45]. This finding suggests that the virus can potentially infect and replicate in the gut. A confirmation to this observation is that SARS-CoV-2 RNA has been detected in the stool of 53% of patients hospitalized with COVID-19 and that several patients with COVID-19 experienced gastrointestinal symptoms [5, 46]. The expression of ACE2 was shown to be higher in the gut of patients with IBD than in that of control patients without IBD [16]. ACE2 activity was found to be higher in the non-inflamed colon than in the inflamed colon of patients with IBD [44]. The possibility that patients with IBD could be more susceptible to COVID-19 has been considered; however, it has not been demonstrated and seems to be in contrast with the previous data. A recent study conducted in 65 patients with IBD with or without endoscopic and histologically active

inflammation showed that the level of gut expression of ACE2 was lower in patients on anti-TNF therapy, vedolizumab, and ustekinumab than in patients not receiving drugs [47]. The authors concluded that the use of biologics during COVID-19 pandemic is likely to be safe.

Role of TNF-Alpha and Anti-TNF-Alpha Therapy on COVID-19

Cytokine release syndrome (CRS) and its most severe form, secondary hemophagocytic lymphohistiocytosis (SHL), resulting in acute respiratory distress syndrome (ARDS), are considered the potential etiologies for developing severe forms of COVID-19 [48–51]. Respiratory failure from ARDS is the leading cause of mortality [6, 52]. Both CRS and SHL are characterized by a hyperactivation of T cells and an excessive production of several pro-inflammatory cytokines, including IL-6, TNF-α, and interferon-gamma (IFN-γ).

Immunosuppression could decrease the risk of the aberrant hyperinflammatory response seen in some patients with COVID-19; therefore, it is possible that certain immunotherapies may mitigate the cytokine storm and be of benefit for these patients [53]. This has been suggested by several studies on tocilizumab, an anti-IL-6 monoclonal antibody approved for the treatment of rheumatoid arthritis. These reports have highlighted the benefits of tocilizumab for severely ill patients with COVID-19, and there are many ongoing clinical trials assessing the efficacy of tocilizumab in patients with COVID-19 [54–56].

Sarilumab, another antibody that blocks the IL-6 receptor, employed in patients with rheumatoid arthritis is currently under phase 2/3 clinical trials for the treatment of COVID-19 [57].

As for IL-6, TNF-α is responsible for systemic inflammatory reactions and has been shown to be a central cytokine in the activation and maintenance of CRS [58]. After binding to its receptor, ACE2, to gain access to host cells, SARS-CoV-2 is able to enhance TNF-α production and induce a TNF-converting enzyme (TACE)-dependent shedding of the ACE2 ectodomain, which facilitates viral entry into the cells [59, 60]. Additional observations argue for a role of TNF-α in COVID-19; elevated serum concentrations of TNF-α in infected patients were correlated with the severity of the disease and adverse outcome, and patients admitted to the ICU due to severe COVID-19 had significantly higher serum levels of TNF-α than non-ICU patients [2, 61]. TNF-α inhibition induces a rapid decrease in IL-6 and IL-1 in patients with active rheumatoid arthritis [62], while TNF-α neutralization revealed protective effects against SARS-CoV in infected animals [63, 64].

The COVID-19 Global Rheumatology Alliance registry is a physician-reported case registry of patients with rheumatic diseases diagnosed with COVID-19 [65]. Preliminary data of 600 cases from 40 countries have recently been published and report that anti-TNF-α treatment, the most commonly used biologic, was associated with a significant reduced risk of hospitalization for individuals with COVID-19 ($p = 0.01$) [66].

In light of these findings, one could speculate that TNF-α antagonist monotherapy may be effective in COVID-19 [67].

Hence, another possible therapeutic approach for COVID-19 may involve targeting TNF-α; some authors have postulated that there is sufficient evidence to conduct clinical trials with anti-TNF-α drugs [68]. A randomized, open-label, controlled clinical study evaluating the efficacy and safety of anti-TNF-α (adalimumab) in the treatment of patients with severe COVID-19 pneumonia has been recently registered in the Chinese Clinical Trial Registry [69].

Vedolizumab and Ustekinumab Use During the COVID-19 Pandemic

From the data of the SECURE-IBD Registry and from the cohorts of patients with IBD treated with biologics, no major concerns have emerged regarding the use of the α4β7 integrin specific antibody, vedolizumab, or the anti-IL-12/23 p40 subunit antibody, ustekinumab, during the COVID-19 outbreak [20–31]. The risk of severe infections and particularly severe respiratory tract infections does not appear to be increased in some previous studies of vedolizumab and ustekinumab use in patients with IBD [70–72].

Role of JAK Inhibition and Anti-JAK Therapy on COVID-19

JAK inhibition may have a potential therapeutic role in the management of COVID-19 [73]. Baricitinib is a selective inhibitor of JAK-1 and JAK-2 and is approved for use in rheumatoid arthritis. Due to its dual anti-inflammatory effects and Numb-Associated Kinase (NAK) inhibition, it can dampen the host inflammatory response and the cytokine storm (including IL-6 and IFN-γ) responsible for the more severe forms of COVID-19 [73, 74]. NAK is involved in SARS-CoV-2 cell entry which results in viral infection [73]. Based on these and other observations, baricitinib is currently being considered for the treatment of COVID-19 with hyperinflammation and ARDS, and several clinical trials are under way [75].

Tofacitinib is an orally partially selective JAK inhibitor approved for the treatment of ulcerative colitis and has been associated with an increased risk of infectious viral complications, particularly for herpes zoster infection [10, 11]. Tofacitinib showed no detectable inhibition of NAK [73]. Some concerns may arise regarding tofacitinib use during the COVID-19 outbreak due to its potent multi-cytokine

suppressive effect. However, no evidence of an increased risk of COVID-19 with tofacitinib use has been observed, and gastroenterological societies recommend continuing the drug in patients with IBD who are already on treatment [36]. Currently, the available data are very limited.

Conclusions

The results of this review seem to confirm that people with IBD receiving immunomodulators, biological agents, or JAK inhibitors, despite their immunosuppressed condition, do not have an increased risk of contracting SARS-CoV-2 infection or develop a more severe course of infection.

We have to consider that these patients have been informed about the risk of contracting any kind of infection and could have assumed a more conservative behavior than the general population. Furthermore, the immunosuppressed state may protect patients from developing a harmful uncontrolled and overactive immune response against the virus. Thus, TNF-α antagonist monotherapy might have a protective effect, damping the cytokine storm associated with severe COVID-19.

This review, however, reports only on the cases of patients who tested positive for SARS-CoV-2 by RT-PCR with a swab sample; the patients in question could have been symptomatic, and, therefore, tested purposely for identifying the presence of the virus, or were asymptomatic and tested for different reasons. This is a limitation, and a more accurate epidemiological picture of the infection will be obtained only via the expanded use of antibody tests [76]. In contrast to RT-PCR-based diagnosis, antibody tests measure the host immune response to SARS-CoV-2 infection which can define its extent in the tested population. Moreover, the comparison between antibody responses of populations with and without IBD and the influence of eventual immunosuppression could explain if IBD itself and/or its treatment has actually been protective against this viral infection.

According to the current evidence, it is advisable to maintain immunotherapy, apart from corticosteroids, in patients with IBD in order to avoid relapse. Undoubtedly, each case should be evaluated individually using a risk versus benefit-based approach. The COVID-19 outbreak is a fast and evolving situation, and the risk of developing COVID-19 in patients with IBD treated with immune modifying drugs requires more information. Therefore, further studies are highly warranted to better clarify the impact of immunotherapy in patients with IBD in the face of COVID-19.

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Compliance with Ethical Standards

Conflict of interest MLS has served as a speaker and/or an advisory board member for Abbvie, Celltrion, Janssen, Pfizer, and Takeda outside the submitted work.

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