Managing IBD in the COVID-19 era

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***Abstract*:** Over the last 2 years the lives of millions have changed because of the emergence of Coronavirus disease 2019 (COVID-19). Patients living with inflammatory bowel disease (IBD) represent a sizable population with their own sets of challenges to providers in the wake of so much uncertainty. The Centers for Disease Control considers immunocompromised individuals at higher risk of infection and complications from COVID-19. Early in the pandemic, the specific risks for IBD patients were unclear as guidance was based on expert opinion regarding the management of IBD during a COVID-19 era. Fortunately, after considerable work in the field, the overwhelming evidence suggests that IBD patients as a whole do not appear to be at increased risk for more severe disease from COVID-19. Certain risk factors such as age, steroids, comorbidities, combination immunomodulatory therapy, and IBD disease activity have been associated with worse outcomes. Most IBD medications are low risk, with the exception of immunomodulator monotherapy and combination therapy with thiopurine and anti-TNF. Vaccination remains safe and effective for all IBD patients, although additional booster doses may be necessary, particularly in patients taking anti-TNF agents.

Keywords: anti-tumor necrosis factor, COVID-19, hospitalization, inflammatory bowel disease, systemic corticosteroids, vaccination

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Introduction

Over the last 2 years the lives of millions have changed because of the emergence of Coronavirus disease 2019 (COVID-19). After the World Health Organization declared a global pandemic, lockdowns, restrictions, and changes to daily living began to take shape all over the globe. Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal system that consists principally of two conditions, ulcerative colitis (UC) and Crohn's disease (CD), characterized by a dysregulated immune response in the intestine.[1] As a result, the current mainstay of treatment for IBD is the use of immunosuppressive drugs aimed at targeting the immune system. It has been well established that these agents increase the risk for serious and opportunistic infections.[1,2] The Centers for Disease Control considers immunocompromised individuals at higher risk of infection and complications from COVID-19.[3,4] Early in the pandemic, the specific risks for IBD patients were unclear. Early guidance was based on expert opinion and was provided by national and international societies, such as the American Gastroenterological Association (AGA)[5,6] and the International Organization of the Study of Inflammatory Bowel Disease (IOIBD) on the management of IBD during a COVID pandemic.[7] However, much research on COVID-19 and IBD has been conducted since the early days of the pandemic. We aim to provide an overview of the current evidence on the risks of COVID-19 in IBD patients, safety of commonly used IBD medications in COVID-19, treating the IBD patient with COVID-19, and COVID-19 vaccination.

COVID-19 risk in IBD

Risk of infection

Early in the pandemic, studies of COVID-19 outcomes in the IBD community were limited. Many investigations, primarily out of Europe, reported concerning data regarding a heightened risk of COVID-19 in IBD patients. An Italian prospective observational cohort of 79 IBD patients published in March 2020 observed

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a 28% hospitalization rate and 8% mortality from COVID-19.[8,9] Another observational study from a single tertiary IBD center in Italy reported a high incidence of COVID-19 infection in IBD patients compared to non-IBD patients.[10] A larger follow-up Dutch study emerged from Creemers *et al.* who observed a similarly higher rate of COVID-19-related hospitalization in IBD patients *versus* the general population.[11] Importantly, these early accounts were limited by sample size and likely differential access to testing.

These early numbers caused concern for IBD providers and patients alike as they suggested possible increased risk of infection and worse outcomes. Fortunately, after considerable work in the field over the last 2 years of the pandemic, the overwhelming evidence suggests that IBD patients are not at increased risk for COVID-19 infection.[1,8,12–17] Hadi *et al.*[14] discovered a lower incidence rate ratio (IRR) for COVID-19 amongst IBD patients compared to non-IBD patients (IRR 0.79, 95% CI: 0.72–0.86). Furthermore, Singh *et al.*[15] reported no increase in the relative risk of COVID-19 in IBD compared to general population, with no difference between UC or CD. Researchers from that same study did note a heightened risk for adverse outcomes (hospitalization and death) from COVID-19 in UC compared to CD.[15] The rationale for this finding was hypothesized to be that UC patients were older in this study.[15] A Canadian cohort study found prevalence of COVID-19 infection by polymerase chain reaction (PCR) detection to be lower in IBD patients (3.5%) compared to the general population (4.3%).[16] These results were supported by a large meta-analysis performed by Tripathi *et al.*[13] that included over 50,000 IBD patients who were recognized to have a 1.01% prevalence of COVID-19 infection. Of those infected with COVID-19, CD comprised of 52.7% *versus* 42.2% with UC.[13] Regardless of the study, it remains hard to quantify the impact of social behavior on the data regarding infection rates in COVID-19, particularly those from studies early in the pandemic. It is likely that many patients with immune-mediated diseases, including IBD, adhered more strictly to government restrictions and social distancing, thus decreasing infection risk in this population.

Risk of hospitalization, mechanical ventilation, and death due to COVID-19

While the risk of acquiring COVID-19 does not appear to be increased in IBD, once infected, the data remains conflicted regarding the risk for hospitalization. A multicenter study in the United States found COVID-19 hospitalization and mortality in IBD patients to be similar to the general population.[18] Parekh *et al.* found comparable results of hospitalization (26.4%) and case fatality (3.1%) rates compared to non-IBD patients.[8,18,19] In contrast, a Swedish population-based cohort reported IBD patients had a higher chance of hospital admission (aHR = 1.32, 95% CI 1.12–1.56), but no difference in risk for development of to severe COVID-19.[16,20] A retrospective propensity-matched cohort study has also suggested increased rates of COVID-19 hospitalization in IBD.[14] However, large population-based studies have not seen a clear increased risk in adverse outcomes in IBD patients with COVID-19. In the UK OpenSAFELY study, researchers analyzed a cohort of over 17 million people, and discovered the risk of COVID-19 hospitalization, ICU admission, and death was higher in patients with immune-mediated inflammatory diseases after adjusting for age, sex, smoking status, and other comorbidities.[12,21] Compared to non-IBD patients, the IBD population showed an increased risk for hospital admission (HR 1.31, 95% CI 1.24–1.38) and death (HR 1.15, 95% CI 1.07–1.24), but not for the need of mechanical ventilation or renal replacement therapy (RR 1.0, 95% CI 0.60–1.66).[21] Similarly, a Dutch population cohort study found higher incidence rates for hospitalization from COVID-19 in IBD patients (4.7, 95% CI 3.0–7.1) versus the general population (2.8, 95% CI 2.6–2.9).[11] Reassuringly, researchers observed a similar rate of ICU admission (12.5% *versus* 15.7%, $p = 1.00$) and mechanical ventilation (6.3% *versus* 11.2%, $p = 1.00$) between IBD patients and the general population.[11]

Risk factors for severe COVID-19 in IBD patients

Although IBD patients as a whole do not appear to be at increased risk of adverse outcomes from COVID-19, certain IBD patients may be at increased risk. Risk factors for severe COVID-19 (e.g. hospitalization, ICU admission, and death) in IBD include advanced age, number of comorbidities, systemic corticosteroid use, combination immunomodulator and TNF antagonist therapy, and IBD disease activity (see Table 1).[9,12,13,15,16,19,22–24]

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Table 1. Association between risk factors and severe COVID-19 disease. Severe COVID-19 disease is defined as requiring hospitalization, ICU admission, mechanical ventilation, and/or death.

Risk factor	Articles cited	Reported OR/aOR
Advanced age	Brenner et al. (2020) Rizzello et al. (2020) Wetwittayakhlang et al. (2021) Parekh et al. (2022)	aOR 1.04, 95% CI 1.01–1.02 OR 1.08, 95% CI 1.02–1.09 OR 11.1, 95% CI: 1.8–68.0 aOR 1.03, 95% CI 1.02–1.04
⩾2 Comorbidities	Brenner et al. (2020) Rizzello et al. (2020) Wetwittayakhlang et al. (2021)	aOR 2.9 95% CI 1.1–7.8 OR 3.1, 95% CI 1.2–7.6 OR: 4.9, 95% CI: 0.8–28.6
Systemic corticosteroids	Brenner et al. (2020) Parekh et al. (2022) Wetwittayakhlang et al. (2021)	aOR 6.9, 95% CI 2.3–20.5 aOR 2.90, 95% CI 2.09–4.0 OR: 4.6, 95% CI: 0.7–30.1
Combination immunomodulator + anti-TNF	Ungaro et al. (2022)	aOR 1.82, 95% CI 1.26–2.62
IBD disease activity	Bezzio et al. (2020)* Wetwittayakhlang et al. (2021)	OR 8.45, 95% CI 1.26–56.56 OR 3.8, 95% CI 0.7–20.8

*Association between risk factor and COVID-19 related death.

Bowel Disease (SECURE-IBD) registry conducted a number of studies on risk factors for severe COVID-19. Bezzio *et al.* established early in the pandemic a strong association between both active IBD disease (OR 8.45, 95% CI 1.26–56.56) and the Charlson Comorbidity Index (CCI) (OR 16.66, 95% CI 1.80–153.9) and death from COVID-19 in IBD patients.[9] The first data published from SECURE-IBD by Brenner *et al.* identified age (adjusted odds ratio [aOR] 1.04, 95% CI 1.01–1.02), greater than two comorbidities (aOR 2.9 95% CI 1.1–7.8), systemic corticosteroids (aOR 6.9, 95% CI 2.3–20.5) and 5-aminosalicylic acid (5-ASA) use (aOR 3.1, 95% CI 1.3–7.7) to be independent risk factors for severe COVID-19 in IBD patients.[25] A more in-depth consideration of comorbidities' effect on COVID-19 outcomes from the SECURE-IBD registry was published by Parekh *et al.* Researchers from this group adjusted for independent comorbidities and expectantly found numerous non-IBD comorbidities to be associated with worse outcomes, with chronic kidney disease and chronic obstructive pulmonary disease appearing to be the highest risk conditions, conferring over a threefold higher risk of increased hospitalization or death from COVID-19.[8,19] People living with multiple comorbidities have long been shown to experience adverse events from COVID-19 infection.[19,26,27] A French nationwide study observed that advanced age, diabetes, underlying cardiovascular or respiratory disease, and end-stage renal diseases conferred an increased risk of COVID-19-related hospital admission in IBD patients.[28] While Singh *et al.* observed no difference in risk of severe COVID-19 according to the presence of IBD [risk ratio (RR), 1.15, 95% CI 0.92–1.45), IBD patients who did progress to severe COVID-19 were older and had more comorbidities.[18] These reports have since been validated in a larger cohort study at a tertiary care referral center in Montreal, Quebec, Canada performed by Wetwittayakhlang *et al.*[16] These studies highlight the key advances the field has made in understanding how to risk stratify IBD patients in terms of outcomes from COVID-19. Identifying risk factors for severe disease can aid gastroenterologists when advising patients on their COVID-19 risk.

COVID-19 symptoms in IBD

Symptoms from COVID-19 in IBD patients mirrors the general population with 67.5% presenting with fever (most common) and cough (59.6%).[12,29] A Canadian study found that 22% of IBD patients who tested positive for SARS-CoV-2 were asymptomatic, and the majority (70.7%) had mild symptoms of fever, myalgia, and dysosmia.[16] Of note, GI symptoms appear to occur in about 10% of cases.[29] The most

common GI symptoms for all patients from COVID-19 illness are diarrhea, nausea, vomiting, and abdominal discomfort.[30] IBD patients did show a higher tendency to exhibit GI symptoms. Recently, Singh *et al.* published a meta-analysis of the clinical manifestations of COVID-19 in IBD patients and reported that diarrhea (8.19% *versus* 5.14%), nausea and vomiting (10.77% *versus* 4.31%), and abdominal pain (7.75% *versus* 2.70%) all occurred more often in IBD patients than their non-IBD counterparts.[18] However, a major challenge with these data, and in clinical practice, is deciphering which GI symptoms are manifestations of COVID-19 *versus* that due to increased IBD disease activity.[18] Careful evaluation is required by clinicians to demarcate what are symptoms of COVID-19 and what is related to active disease so that flares do not go untreated.

Pathophysiologic connection between COVID-19 and IBD

High levels of SARS-CoV-2 viral RNA have been found in the stool of over 50% of patients with active infection.[29,31] This led many researchers to suspect a pathway of SARS-CoV-2 infection via enterocytes in the intestines. Hoffman *et al.* discovered that SARS-CoV-2 utilizes the angiotensin-converting enzyme-2 (ACE2) receptor for cell entry and the transmembrane serine protease (TMPRSS) two to prime the SARS-CoV-2 S spike protein.[32] ACE2 is a carboxypeptidase that converts angiotensin I to angiotensin, as well as angiotensin II into angiotensin.[31,33,34] ACE2's mechanism of action effectively inhibits the renin-angiotensin-aldosterone system (RAAS) leading to downstream vasodilation.[34] While ACE2 is found in numerous tissues throughout the body, there are particularly high levels of expression in the ileum, colon, and lung.[15,31,35] Upon infection with SARS-CoV-2 ACE2 is downregulated in the lungs, causing unopposed RAAS activation.[31] Meanwhile in enterocytes attachment of the viral spike protein to ACE2 is followed by cleavage of the S protein by TMPRSS2 thus facilitating cell entry.[15,31,33,34]

Studies indicate that ACE2 levels are upregulated in the setting of mucosal inflammation associated with IBD.[36,37] Within the intestinal tract, ACE2 is prominent on the surface of the terminal ileum and colon, commonly affected by CD and UC.[36,37] Suárez-Farinas *et al.*[31] studied large IBD cohorts and found inflammation in IBD altered ACE2 levels within the different levels of the GI tract, especially in the ileum and rectum. The changes in expression of the ACE2 receptor seen in IBD could potentially impact SARS-CoV2 binding and infectivity. IBD medications such as corticosteroids, thiopurines or 5-ASA agents were not associated with altered expression of TMPRSS2.[31] Notably, Anti-TNF therapy attenuated ACE2 and TMPRSS2 activity in inflamed large intestine and rectum, but did not show a difference in the ileum compared with other biologics.[31] The complex interactions and immunomodulation between COVID-19 and the gut in IBD may be region-specific and much is left to uncover regarding these observations.

IBD medications and COVID-19 risk

Systemic corticosteroids

Systemic corticosteroids have consistently been shown to increase risk for the development of severe COVID-19 in the IBD population.[5,12,13,22,23,25] Analysis from the SECURE-IBD database revealed that patients using corticosteroids were subject to a 6.9-fold risk of severe COVID-19 and 11.6-fold risk of death from COVID-19 illness.[12,25] Several studies have supported the observation that systemic steroids use in IBD worsens outcomes from COVID-19.[16,17,38] However, this data has been appropriately contextualized in a recent review by Lin *et al.* citing unmeasured confounding variables between IBD activity, the severity of COVID-19 infection, and subsequent steroid administration.[12] It is beyond reasonable to assume that patients receiving enteral or parenteral steroids are in heightened states of systemic inflammation related to their underlying IBD activity. Additionally, the RECOVERY trial in 2021 found reduced mortality from COVID-19 in hospitalized patients receiving respiratory support.[39] Studies in other immune-meditated disease also suggest an increased risk with steroids. In a cohort of hospitalized COVID-19 patients, being on steroids at the time of viral infection was associated with an 8-fold increased risk of severe COVID-19 in people with autoimmune and chronic inflammatory conditions.[40] Moreover, researchers have proposed corticosteroids to be associated with delayed clearance of viral RNA from the respiratory system.[5,40,41] It seems the harmful effects of steroids in COVID-19 may be related to timing and stage of infection with steroids impeding viral

clearance earlier but potentially helping with cytokine storm in more advanced and severe COVID-19.[22] In conclusion, IBD patients currently using corticosteroids (especially prednisone >20 mg per day) appear to still be at increased risk of severe COVID-19. A more detailed discussion regarding the current management of patients receiving steroids will be discussed later in this review *(See IBD management in patients with COVID-19)*.

5-ASA (Mesalamine/Sulfasalazine)

5-aminosalicylic acid (5-ASA) agents, primarily mesalamine, are helpful agents in mild to moderate UC. In the early days of the pandemic, many gastroenterology societies, including Crohn's & Colitis UK and Crohn's and Colitis Canada recommended continuing these agents as prescribed, regardless of COVID-19 status.[4] Early in the pandemic there were conflicting reports in the literature regarding their deleterious effect in IBD patients diagnosed with COVID-19 infection. Initial studies from the SECURE-IBD registry reported that mesalamine and sulfasalazine increased the risk of severe COVID-19 (13.9%) compared to no 5-ASA (5.2%) (aOR 1.70, 95% CI 1.26–2.29) and to anti-TNF agents (aOR 3.52, 95% CI 1.93–6.45).[23] These reports were surprising as 5-ASA had generally not been associated with risks related to infections. However, this risk with 5-ASA did not appear to be accurate as more research emerged. Attauabi *et al.* published two studies focusing on Danish-population cohorts that revealed no association between 5-ASA medications and worsened COVID 19 outcomes.[12,42,43] Updated data from SECURE-IBD observed that 5-ASA mesalamines did not lead to worse outcomes.[22] To explain these discrepancies, researchers referenced inherent reporting bias, as patients on 5-ASAs may have participated in less social distancing precautions than patients on immunosuppressive agents and milder COVID-19 symptoms may have been less likely identified earlier in the pandemic due to less frequent encounters with their doctors than those on immunosuppression.[12,22]

Budesonide

There are limited clinical data concentrating on the safety of budesonide use in IBD patients infected with COVID-19. Although no obvious signal has been observed, the SECURE-IBD registry had insufficient numbers of patients on budesonide to fully evaluate its effect on COVID-19 outcomes.[5,23] However, the wide consensus amongst experts in the field is that these agents are widely accepted as safe. The British Society of Gastroenterology supported the continued use of budesonide during COVID-19 pandemic, citing no increased risk of adverse COVID-19 outcomes.[4] IBD patients with asymptomatic or mild COVID symptoms on systemic corticosteroids are recommended to be transitioned to budesonide if feasible.[5,23,44] More studies are needed regarding their effect on outcomes, but as of now these agents should be continued as clinically indicated.[5–7,23,44]

Anti-TNFs, immunomodulators, and combination therapy

The most recent analysis from SECURE-IBD found anti-TNF monotherapy was associated with decreased odds of COVID-19-related hospitalization (aOR 0.58, 95% CI 0.50–0.69), severe COVID-19 (aOR 0.50, 95% CI 0.33–0.78) and death (aOR 0.44, 95% CI 0.26–0.76).[22] Additionally, the study reported an increased risk of hospitalization or death (aOR 1.82, 95% CI 1.26–2.62) with anti-TNF and thiopurine (azathioprine/6-mercaptopurine) combination therapy.[22] This was consistent with prior studies that similarly found an increased risk for serious infection in IBD patients on thiopurine and anti-TNF combination therapy.[2,25] In contrast, methotrexate (MTX) and TNF antagonist combination therapy was not associated with severe COVID-19, hospitalization, or death.[22] MTX monotherapy was not associated with increased risk of severe COVID-19 or death but did trend toward higher odds of hospitalization.[5] Recently published pooled analysis has reinforced the lower rates of hospitalization and death from COVID-19 in patients with immune-mediated inflammatory diseases on anti-TNF monotherapy compared with MTX monotherapy, thiopurine monotherapy, and anti-TNF and thiopurine combination therapy.[45] Many studies have proposed a protective effect against COVID-19 with anti-TNF agents for IBD patients.[5,12,15,22,46] Bamias *et al.*[46] observed favorable COVID-19 disease course in IBD patients on TNF antagonism (OR 0.4, 95% CI 0.16–0.99). Impressively, Tripathi *et al.* found a lower risk of hospitalization and ICU admission for patients on TNF antagonists *versus* both corticosteroids and 5-ASA

agents, but not death.[13] It is thought that by diminishing TNF activity, the risk of cytokine cascade seen in severe COVID-19 disease and acute respiratory distress syndrome (ARDS) may be lessened on anti-TNF therapy.[12,23,25] Data from Israel supports this theory, as COVID-19 disease severity appears to be considerably lower in IBD patients on anti-TNF therapy.[1] Recent meta-analysis by Kokkotis *et al.*[47] confirmed anti-TNF therapy is associated with a decrease in the risk for hospitalization (OR 0.53, 95% CI 0.42–0.67) and severe COVID-19 (ICU admission or death) (OR 0.63, 95% CI 0.41–0.96) in patients with immune-mediated diseases compared to no anti-TNF therapy in the general population after controlling for validated risk factors.

Notably, some studies have not appreciated an increased risk of COVID-19 with combination therapy. Alrashed *et al.*[48] conducted a meta-analysis of 18 studies from multiple countries including, the United States, Italy, and the UK, and found combination therapy of anti-TNF and immunomodulators did not heighten the risk of COVID-19 hospitalization (RR 0.98, 95% CI 0.81–1.18). These findings were supported in a large retrospective national cohort study of over 30,000 IBD patients that reported immunomodulators were not associated with an increased risk of COVID-19, as either monotherapy or in combination with an anti-TNF.[17]

Anti-IL 12/23

Anti-interleukin therapy has become an exciting new therapy in the world of biologics for IBD patients, as new studies examining ustekinumab and risankizumab emerged prior to the start of the pandemic. Both ustekinumab and Risankizumab are human IgG monoclonal antibodies targeted at interleukin (IL) − 23 receptor, with ustekinumab also having IL-12 activity, leading to inhibition of proinflammatory cytokines on T cells, natural killer cells, and antigen presenting cells (APC).[49] The cytokine storm associated with COVID-19 has been shown to involve IL-6 and IL-12; however, it is still unclear if IL-23 has a role.[50] Overall, IL-12/23 antagonism appears to be safe during COVID-19, with several studies suggesting a beneficial effect. Data from SECURE-IBD revealed that the use of ustekinumab in IBD patients decreased risk of hospitalization from COVID-19 (aOR 0.44, 95% CI 0.36–0.54) and developing severe COVID-19 (aOR 0.43, 95% CI 0.26–0.71).[5,12,22,23] When compared with other biologics, IL-12/23 and integrin blockers were not associated with significantly different risk as TNF monotherapy (aOR 0.98, 95% CI 0.12–8.06 and aOR 2.42, 95% CI 0.59–9.96, respectively).[22,23] Moreover, IL-12/23 antagonists appear to have similar effect as anti-TNF agents on the risk of severe COVID-19.[22,23] In a small Israeli study, 12 IBD patients received ustekinumab and not a single patient advanced to severe COVID-19.[1] Kridin *et al.* (2021)[51] and Hansel *et al.*[52] found a similar decrease in hospitalization rate for patients with Psoriasis currently on IL-12/23 blockade. Researchers have proposed that by hindering the cell signaling pathways from the IL-12/23 receptor, the severe inflammatory response and cytokine storm produced by SARS-CoV-2 infection is stifled in patients on these medications.[53] The AGA recommended IBD patients who do not test positive for COVID-19 to continue these medications during the pandemic.[6] As the pandemic has progressed, these collective results are very reassuring that use of interleukin antagonists for IBD patients is safe during the COVID pandemic.

Anti-Integrins

Anti-integrin agents such as vedolizumab (VDZ) are unique in that they are the gut-selective class of biologics. Many studies have shown their high safety profile with low incidence of serious infections, crediting anti-integrins lack of systemic effect.[54] However, integrin antagonism's role in COVID-19 outcomes has been less than clear. Early studies reported increased risk of COVID-19 in patients on VDZ. A large case series from Italy by Ardizone *et al.* found a lower incidence of symptomatic SARS-CoV-2-infection in non-gut-selective treatments compared to gut-selective agents.[55] A large national cohort from the Veterans Affairs Healthcare System showed VDZ increased risk of COVID-19 infection relative to 5-ASA derivatives (HR 1.70, 95% CI 1.16–2.48, $p = 0.006$).[17] Furthermore, using data from SECURE-IBD, Agrawal *et al.* revealed that patients on VDZ monotherapy were 38% more likely to be hospitalized from COVID-19 compared to those on anti-TNF monotherapy.[56] Moreover, researchers from this same study found a higher rate new-onset GI symptoms in the VDZ group (29.6%) compared to anti-TNF monotherapy (19.2%).[56] However, as time has progressed and more data is collected, we have

seen a shift in our understanding of VDZ and COVID-19. More recent findings from the SECURE-IBD registry support VDZ to be correlated with a decreased risk of COVID-19-related hospitalization or death (aOR 0.66, 95% CI 0.56–0.78) and no association with a risk of severe COVID-19.[5,12,22] Other studies around the world have supported this result.[1] Many have attributed the disappeared risk of VDZ to be a result of earlier studies being underpowered.[12,22] Overall, these conclusions reinforce that the anti-integrin class of biologics are safe for IBD patients and do not increase the risk of worse outcomes from COVID-19.

JAK inhibitors

Tofacitinib is a Janus kinase inhibitor (JAKi), predominately JAK1 and JAK3 with functional selectivity for JAK2, that was recently approved for the treatment of UC in 2018 by the Food and Drug Administration (FDA).[57–59] Regarding risk of infections, Sandborn *et al.* showed tofacitinib use increases the risk of herpes zoster infection.[58] A major concern for gastroenterologists with using JAKi agents during COVID-19 is the risk for thromboembolic events, as safety trials have reported an increased incidence of thromboembolic events with tofaticinib.[59–61] Notably, SARS-CoV-2 infection raises the risk for thrombotic events, which carries over a fivefold higher risk for all-cause mortality in ICU patients.[62,63] Interestingly, when compared to other IBD medications, Agrawal *et al.* reported on a subgroup from the SECURE-IBD database that found tofacitinib to not be associated with an elevated risk for severe COVID-19, hospitalization, or death.[5,12,63] Although this analysis was a small sample size, with only 37 patients receiving tofacitinib, none developed thrombotic events.[63] In their guidelines, the AGA has recommended the continued use of JAKi in IBD patients during the COVID-19 pandemic.[5,6] Recently, JAKi agents have become an area of growing research regarding their potential therapeutic benefit in the management of COVID-19. Guimarães *et al.* published findings showing tofacitinib to decrease the risk of respiratory failure and death from COVID-19 pneumonia in hospitalized patients.[64] Targeting the JAK/STAT pathway has been linked to the pathogenesis of the hyperimmune response seen in SARS-CoV-2 infection. Inhibition of the intracellular transduction pathways has been suggested to decrease the release of cytokines, effectively blunting the hyperinflammatory state leading to ARDS.[48,59,63,64] Bronte *et al.* designed an observational, longitudinal trial of 20 patients infected with COVID-19 treated with baricitinib, a JAK1/JAK2 inhibitor.[65] Patients treated with baricitinib were associated with significant fall in serum IL-6, IL-1β, and TNF-α levels that clinically resulted in a reduction in the need of oxygen therapy and prevented progression to severe COVID-19 disease.[63,65] A recent meta-analysis found that tofacitinib did not increase the risk of COVID-19-related hospitalization in IBD patients (RR = 0.81, 95% CI 0.49–1.33, $p = 0.40$).[48] As of now, there are limited data on JAK inhibitors though the available results are reassuring.

IBD management in patients with COVID-19

Medical management

The COVID-19 pandemic has brought with it an ever-changing climate, with new lessons constantly developing. Consequently, this state of flux provides a difficult context for providers to guide patients without a wealth of available data. The optimal medical management of IBD patients found to be infected with SARS-CoV-2 must be personalized depending on a variety of factors. To accommodate a personalized approach, multiple societies and experts provided consensus recommendations regarding a framework to approach COVID-19 in the IBD patient. The IOIBD, AGA, and European Crohn's and Colitis Organization (ECCO) have recommended that infusions and therapy should be continued, with the exception of corticosteroids.[6,7,12,24,66,67] Ungaro *et al.* provided updated data from over 6000 patients finding biologics to have no association with an increased risk of worsened COVID-19 outcomes and are safe to continue during the pandemic.[22,23] Switching from intravenous formulations of anti-TNF therapy to subcutaneous routes is not recommended.[6,24,66] Systemic corticosteroids (especially prednisone >20 mg/day) have steadily been associated with severe-COVID19 in the IBD population, and expert consensus suggests that when appropriate, patients should be tapered off or switched to budesonide.[6,7,12,22–25,66,68] However, the treatment of hospitalized patients with severe COVID-19 includes high dose steroids to combat the progression to ARDS. The RECOVERY trial found patients treated with dexamethasone to have a

lower mortality compared to standard care in mechanically ventilated patients (29.3% *versus* 41.4%; rate ratio 0.64, 95% CI 0.51–0.81).[39] The effect of steroids is most likely related to the phase of the COVID-19 disease course. Early in infection, during viral replication, steroids appear to be harmful compared to a potentially beneficial impact later in severe COVID-19 when a more inflammatory response is present. Patients who present with an acute severe UC (ASUC) flare are typically also treated with parenteral steroids.

Currently, the guidelines from the IOIBD state for patients who test positive for SARS-CoV-2 on PCR immunosuppressive therapy should be held for a minimum of 10 days from symptom onset and restarted at least 3 days (72 h) after symptoms have resolved.[7,12,24,66] Regardless of disease severity, patients are advised to hold thiopurines, methotrexate, and tofacitinib.[12,66] In addition, 5-ASA agents, rectal therapies, and budesonide are all safe to continue throughout the course of the infection.[6,12] However, there is recent evidence that suggests continued biologic use in stable patients does not worsen COVID-19 outcomes. Khan *et al.* recently published a retrospective cohort study from the Veteran Affairs Health System database that concluded no evidence of exacerbation of COVID-19 symptoms in a 2-week post-infusion follow-up period.[69] Stable IBD outpatients infected with SARS-CoV-2 did not require medications, oxygen, emergency room visit, or hospitalization.[69] These findings suggest the current guidelines may appear too strict, and in fact due to the half-lives of many of these agents, detectable drug levels are still present during this hold period. Moreover, multiple studies have identified IBD activity to be an independent risk factor for developing severe COVID-19.[16,24] Therefore, it is imperative not to delay biologic therapy longer than is absolutely necessary. This is often dictated by local infection control policies if patients are going to a healthcare facility, for example for biologic infusions. As more data becomes readily available, the approach to immunosuppression in IBD patients may continue to change, and a personalized approach is always favored. Recently, Hashash *et al.* published findings from a small retrospective cohort revealing after propensity-score matching, IBD patients who received nirmatrelvir and ritonavir (Paxlovid® Pfizer. Freiburg, Germany) were at lower risk for hospitalization (aOR 0.35, 95% CI 0.17–0.74) compared to IBD patients who did not receive the drug.[70] No patients in the treatment arm required admission to an ICU, were intubated, or died compared to a mortality rate of 1.8% of the control IBD group.[70] While the sample size was relatively small, targeting high-risk IBD patients to receive antiviral therapy early in the disease course could potentially improve COVID-19 outcomes.

The role of biologics for the direct treatment of COVID-19 has had an interesting journey during the pandemic. A French case report by Michot *et al.* was the first to report the successful treatment of COVID-19 respiratory failure with tocilizumab, an anti-IL6 antibody.[71] This early report provided encouraging evidence for the potential benefit in targeting steps in the inflammatory cytokine pathway to help combat COVID-19. In response, a plea by Feldman *et al.* was published calling for clinical trials investigating anti-TNF therapy for the targeted treatment of COVID-19.[72] As a result, multiple studies have looked at this interaction, however, few targeted biologic studies have been performed in the clinical context of concurrent IBD and COVID-19 infection. Dolinger *et al.* reported a pediatric case of a 14-year-old patient recently diagnosed with CD with multisystem inflammatory syndrome in children due to an active COVID-19 infection effectively treated with infliximab.[73] Additionally, clinicians observed higher levels of pro-inflammatory cytokines, namely TNF-a and IL-6, are present in concomitant IBD and COVID-19 than in either entity alone.[73] Follow-up studies from both Bezzio *et al.*[74] and Alhalabi *et al.*[75] have demonstrated the safety and efficacy of infliximab induction in patients with ASUC and acute COVID-19 pneumonia. In the former study, researchers appreciated a resolution of pulmonary symptoms in addition to IBD remission after treatment with anti-TNF therapy.[74] The aforementioned case studies are promising for providers facing difficult clinical dilemmas and support the notion that addressing the intestinal pathology in severe IBD flares must take priority. Reports examining other classes of biologics have also yielded optimistic outcomes. Festa *et al.* recently published a case of a patient who previously failed anti-TNF therapy that presented with steroid-refractory ASUC and a positive COVID-19 PCR achieving successful remission with administration of tofacitinib.[76] Tofacitinib, as previously described, is a nonselective JAK inhibitor that has activity against IL-6 and has been shown to be effective in decreasing

the rate of respiratory failure and death in patients hospitalized with COVID-19 pneumonia.[64,76] This Italian case report is the first to describe intentional treatment with tofacitinib in ASUC and COVID-19 infection. However, a notable difference from the infliximab cases was the fact that the patient treated with tofacitinib had an asymptomatic COVID-19 infection. Lastly, Reiker *et al.*[77] recently used tacrolimus as a bridging therapy in ASUC and symptomatic COVID-19 infection in an inpatient setting. More research is needed for the safety of calcineurin inhibition in patients with IBD and COVID-19, but it may provide an effective alternative to steroid refractory disease in patients with a high risk of surgical intervention.

The concurrent presentation of ASUC and SARS-CoV-2 infection, symptomatic or asymptomatic presents a particularly challenging navigation for the care of a vulnerable subgroup. A review by Chebli *et al.* recommended the management of ASUC in patients with asymptomatic or mild-to-moderate SARS-CoV-2 infection must prioritize the intestinal inflammation related to IBD.[78] Additionally, all patients presenting with ASUC, regardless of infection severity of COVID-19, should undergo testing for superimposed infections (CMV, Clostridium difficile, etc.) and surgical consultation while admitted.[78] Gajendran *et al.* discussed the uncertainty in the field regarding patients who present with ASUC and COVID-19 pneumonia.[68] Based on the findings of the RECOVERY trial, Gajendran *et al.*, along with the ECCO and AGA, recommend that high doses of parenteral steroids should be given in this situation, followed by rescue therapy with a biologic just as they would otherwise.[66,68,78] The doses and class of steroids in these patients remains complicated and should be individualized based on the severity of symptoms from the two disease entities. Allez *et al.*[79] proposed to limit the steroid dose to under 40 mg/d when possible in mild-to-moderate COVID-19. However, in hospitalized patients with ASUC, steroids and surgery should not be delayed despite concomitant COVID-19 pneumonia.[68] Vigano *et al.* emphasized that current data supports that biologics remain the first-line treatment for induction and maintenance of remission in cases of ASUC and concurrent COVID-19.[80] Bourgonje *et al.*[81] (2021) recently described the importance of not delaying therapy in a three consecutive case series of patients with ASUC and COVID-19, in which postponement of intravenous steroids led to a poor surgical outcome. The increased surgical risk of COVID-19 infection must be considered against the risk of delaying intervention in ASUC. Surgical consultation is necessary in presentations of ASUC, as colectomy is often required (27% of cases).[82] To understand the impact of COVID-19 on the clinical practices and management of ASUC in more detail, the COVID-19 pandemic response of assessment, endoscopy, and treatment in acute severe ulcerative colitis (PROTECT-ASUC) multicentered, case-control study was designed in the UK.[83] PROTECT-ASUC confirmed that compared to pre-pandemic times, the COVID-19 pandemic saw an increase in primary and rescue therapy with biologic agents (46% *versus* 36%; $p = 0.0064$), but that colectomy rates remained consistent (16 *versus* 13%; $p = 0.26$).[83] Researchers also found the risk of infection after colectomy was low (2%) and not associated with adverse outcomes.[83] Additionally, Somashekhar *et al.* found the risk of COVID-19 infection for the healthcare team during laparoscopic or open surgeries is low, as there is little evidence of viral transmission.[84] In summary, the current recommendation from the ECCO-COVID taskforce is to perform emergency colectomy in ASUC and simultaneous COVID-19 that fails to respond to medical therapy.[66] More data are needed looking specifically at colectomy performed in COVID-19-infected patients. Discussions from a RAND panel of experts concluded that anticoagulation prophylaxis should not only be given in all hospitalized patients with ASUC and COVID-19, but also extended upon discharge given the heightened risk of venous thromboembolism.[78,80,85]

COVID-19 triggering IBD flare

Hadi *et al.* retrospectively analyzed over 850,000 patients across various healthcare organizations in the United States and identified over 4300 IBD patients who had been diagnosed with COVID-19 infection.[14] Researchers determined those with a IBD flare at 1 month post infection to be 5.3% and at 3 months 6.8%.[14] Similar findings were reported from a Canadian cohort study that reported 9.8% of IBD patients presented with an acute flare of their disease after COVID-19 infection.[16] In a multicenter case control study, Hong *et al.* found mild to moderate COVID-19 was not associated with an increased risk of adverse IBD outcomes (i.e. IBD associated hospitalization or surgery) (aHR 2.43, 95% CI 1.00–5.86) whereas

severe COVID-19 did show an increased risk (aHR 0.84, 95% CI 0.44–1.42).[86] Whether COVID-19 infection alone can trigger an IBD flare remains unclear; current data suggests infection severity is likely the driving factor. Larger studies are needed to provide clarity.

Vaccinations

As vaccination against COVID-19 became more readily available, it provided its own set of questions and speculations amongst the population, especially those with immune-mediated inflammatory diseases. The safety and efficacy phase three trials for COVID-19 vaccines did not include patients with IBD.[87] In order to dissuade from vaccine hesitancy, numerous medical societies, including the American College of Rheumatology (ACR) and the British Society of Gastroenterology IBD section, recommended vaccinating all patients with IBD, despite a complete knowledge of the safety and efficacy in this patient population.[87–89] Results from a panel from the IOIBD recommended vaccinating all IBD patients as soon as possible regardless of immune-modifying therapy use.[90]

Historically non-live vaccines are believed to be safe in all IBD patients, no matter what therapy they are on. In terms of efficacy, certain immune modifying agents, namely anti-TNFs have been associated with a decreased immune response following vaccination.[90] Compared with immunocompetent individuals, studies have shown decreased immunity to pneumococcal (PSV-23) and hepatitis B virus in patients on immunomodulators and anti-TNF therapy.[91–93] The two current mRNA vaccines include Moderna's 1273 and Pfizer BioNtech's BNT162b2, both of which are mRNA vaccines that form neutralizing antibodies to the SARS-CoV-2 spike protein via T cells.[87] Another common vaccine that's available in the UK is an adenovirus vaccine, ChAdOx1 nCoV-19. The RECOVER study in Israel prospectively examined 258 patients (185 IBD) mRNA vaccine (BNT162b2) responses.[94] Importantly, the study showed the vaccine to be extremely safe, as IBD activity was not affected, and the rate of adverse events were similar across all groups (infection rate ~2%).[94] Moreover, all patients regardless of therapy were found to be seropositive after the second dose, although anti-TNF patients had lower antibody levels of protection.[94]

While vaccines appeared to be safe for IBD patients, efficacy for patients on biologics or immunomodulators remained a concern. Kennedy *et al.* published findings from a multicenter prospective, observational cohort study (CLARITY-IBD) in the UK which reported lower antibody levels in patients treated with infliximab (81% seroconversion) *versus* vedolizumab (97.1% seroconversion) after receiving the first dose of BN162b2 or ChAdOx1 nCoV-19 vaccines.[95] Additionally, patients on immunomodulators were associated with a decreased protection after vaccination.[95] Higher seroconversion rates in infliximab-treated patients after the second dose were observed, leading researchers to recommend not delaying second doses for IBD patients.[95] These findings were supported by Chanchlani *et al.* who reported higher seropositivity rates in IBD patients who had undetectable anti-TNF drug levels.[96] In the United States, the Partnership to Report Effectiveness of Vaccination in populations Excluded from the iNitial Trials of COVID (PREVENT-COVID) investigated the response of two-dose mRNA vaccine in 317n IBD patients.[97] Researchers found that 300 out of the 317 patients had detectable antibody levels after the second dose.[97] Additionally, the study appreciated a lower proportion of detectable antibodies in patients on corticosteroids (85%) *versus* not on steroids (95%).[97] Studies examining other classes of biologics have recently shed more light on the efficacy of vaccination in different subgroups of IBD patients. Alexander *et al.*[98] reported findings from the VIP study that included 483 IBD patients treated with six different immunosuppressive therapies across nine different centers in the UK. No difference was found in geometric mean antibody concentrations for ustekinumab (582.4 u/mL), vedolizumab (954.0 U/mL), or thiopurine monotherapy (1019.8 U/mL) compared to healthy controls.[98] However, significantly reduced levels were observed in patients treated with infliximab (156.8), infliximab and thiopurine combination therapy (111.1 U/mL), and tofacitinib (429.5 U/mL) compared to the healthy controls (1578.3 U/mL).[98] Consistently, anti-TNF has been shown to have a considerable impact on long-term protection from COVID-19 after vaccination. Recent data from the CLARITY-IBD patient cohort reported a significantly higher rate of breakthrough infection with infliximab (13.7%) compared to vedolizumab (7%) in IBD patients who had received three vaccine doses.[99] Reassuringly, Spiera *et al.* found that IBD patients who received

at least two vaccine doses typically had milder disease courses from breakthrough SARS-CoV-2 infection with only 5.7% hospitalized, 3.4% with severe COVID-19, and 1.1% mortality.[100] In response to these studies, the Effectiveness and Safety of COVID-19 Vaccine in Patients with Inflammatory Bowel Disease Treated with Immunomodulatory or Biological Drugs performed a prospective, case-control study assessing humoral responses to COVID-19 vaccines in IBD patients across immunomodulatory therapies compared to healthy controls. Macaluso *et al.* found similar effects of anti-TNF therapy, but also showed IBD patients without treatment or on 5-ASAs had significantly lower levels of anti-SARS-CoV-2 IgG levels compared to healthy controls [median OD 1.72 interquartile range (IQR) 1.0–4.1, $p < 0.001$].[101] This data argues that the lower response appreciated in IBD patients to the COVID-19 vaccines may be independent of immunomodulatory therapy; however, more studies are needed to confirm.[101]

Additional booster doses may be of considerable benefit in patients on anti-TNF therapy. However, very limited information regarding booster vaccines in the IBD population is available at this moment. The HERCULES trial is a multicenter, prospective study in the United States assessing total serum SARS-CoV-2 antibody concentrations following a third vaccine dose ($n = 85$) compared to a two-dose series ($n = 139$) in an IBD cohort as its primary outcome.[102] After the third dose, all patients were found to be seropositive (100%) and have significantly higher antibody concentration than those in the two-dose series.[102] This study also observed a lower antibody level in patients on corticosteroids, anti-TNF monotherapy and anti-TNF combo-therapy.[102] Overall, substantial evidence has provided reassurance that vaccines targeting the SARS-CoV-2 are safe and effective, with a caveat for certain medications. For patients on immunosuppression, in particular steroids, anti-TNF, combo-therapy and JAKi booster doses are encouraged to attain detectable antibodies.

Conclusion

In summary, IBD patients as a whole do not appear to be at increased risk for more severe disease from COVID-19. Certain risk factors such as age, steroids, comorbidities, combination immunomodulatory therapy, and IBD disease activity have been associated with worse outcomes. Most IBD medications are low risk, with the exception of immunomodulator monotherapy and combination therapy with thiopurine and anti-TNF. Vaccination remains safe and effective for all IBD patients, although additional booster doses may be necessary, particularly in patients taking anti-TNF agents.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Nicholas Scalzo: Conceptualization; Writing – original draft; Writing – review & editing.

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