Turkish IBD Organization's Position Statement on Inflammatory Bowel Disease Management Recommendations During COVID-19 Pandemic

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ABSTRACT

The COVID-19 pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2, has resulted in high mortality and morbidity worldwide and is still a growing problem. Inflammatory bowel disease (IBD) is a chronic inflammatory disease for which a substantial number of patients are treated with immunosuppressive medications, either occasionally or long-term. Despite the accumulating evidence, there is still a lack of knowledge about the impact of COVID-19 on IBD patients, especially those who are under immunosuppressive treatment. Moreover, following the emergence of several COVID vaccines, there are concerns regarding vaccine effectiveness and possible side effects in such patients. In this context, we tried to briefly summarize the accumulating evidence and recommendations for the management of IBD in the context of the COVID-19 pandemic.

Keywords: *Inflammatory bowel diseases, Crohn's disease, ulcerative colitis, COVID-19 pandemic*

COVID-19, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first described in Wuhan, China, in December 2019.[1] On January 30, 2020, the World Health Organization stated that this viral infection constituted a global public threat. Subsequently, on March 11, 2020, they declared COVID-19 to be a pandemic, as a rapid spread of the virus was observed globally.[2] By April 2021, more than 145 million people were infected by SARS-CoV-2, and more than 3 million people died as a result. [3]

The SARS-CoV-2 virus is a respiratory virus which is transmitted from person to person through respiratory droplets, aerosols, and through the conjunctiva.[4] However, since SARS-CoV-2 viral RNA was detected in stool samples, the potential for transmission through the fecal–oral route is also being questioned.[5] The main symptoms of the COVID-19 disease include shortness of breath, dry cough, fever, and myalgia.[6] Although the first reports from China revealed that only 3.8% of the patients had diarrhea,[7] recent reports from other countries showed that up to 22.1% of the patients had diarrhea as part of their clinical symptoms.[8,9] Almost 50% of the hospitalized COVID-19 patients presented with digestive tract symptoms.[10] Observations from previous reports suggest that more than 80% of the patients had a mild course, whereas up to 20% of the patients had a moderate to severe disease course.[11,12] The severity and mortality of the COVID-19 disease are associated with increasing age and underlying comorbidities such as cardiovascular diseases, obesity, diabetes, and cancer.[7,13]

Risk factors for COVID-19 disease in inflammatory bowel disease (IBD) patients are still not clear. However, we know from other cases of lower respiratory tract infections in immunocompromised patients that older age, the use of steroids, a low lymphocyte count, and neutropenia increase the risk of infection.[14,15] The combined factors of age and the effects of immunosuppressive and immunomodulator medications such as thiopurines, steroids, and anti-TNF drugs place IBD patients at great risk for infections; the risk is even higher when the medications are used as a combination therapy.[16-20] Both IBD patients and gastroenterologists are concerned that the

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COVID-19 pandemic will pose a greater risk especially for those who use such medications. Fortunately, contrary to this expectation, early reports from Italy and China showed lower COVID-19 rates in IBD patients.[21] An international database called Secure-IBD was founded in March 2020, to track SARS-CoV-19 infections in IBD patients. An initial evaluation of this database showed that the severity of COVID-19 disease in IBD patients was more or less the same as in non-IBD patients, and that the proportion of IBD patients with COVID-19 disease was not higher than in the normal population.[21] This observation was supported by a report from New York City, which showed that the incidence of hospitalization for COVID-19 disease among patients with immune-mediated conditions including IBD was similar to that among the normal population.[22] Despite the initial reports revealing low SARS-CoV-2 infection rates in IBD patients and a disease severity similar to non-IBD patients, both IBD patients and gastroenterologists are still concerned about COVID-19 and its ongoing medical management. A multinational patient survey supported by the European Federation of Crohn's and Colitis Association, in which 3815 patients from 51 countries responded, revealed that one-third of the patients believed that being an IBD patient increased the risk of contracting the COVID-19 infection, and two-thirds of the respondents stated that taking immunosuppressive medications increased the risk of infection.[23] Another survey was carried out through gastroenterology doctors supported by European Crohn's and Colitis Organization. This survey revealed that only half the doctors believe that IBD is not associated with increased risk of COVID-19 disease, while almost two-thirds of the doctors believe that IBD drugs are associated with an increased risk of COVID-19 disease.[24] Therefore, we can conclude that both the majority of IBD patients and doctors believe that IBD medications might increase the risk of COVID-19 disease in IBD patients.

MAIN POINTS

- *The COVID-19 pandemic is still a growing problem globally.*
- *So far, no increased risk of COVID-19 disease has been shown in IBD patients.Immunosuppressive/immunomodulatory medications are believed to be safe in IBD patients except high-dose prednisolone (>20 mg/day).*
- *If a patient contracts COVID-19, all immunosuppressive medications should be stopped until full recovery. The decision on resuming such medications depends on the severity of both IBD and COVID-19 disease. Recent reports showed a possible increased risk of COVID-19 in IBD patients receiving combined immunosuppressive medications such as anti-TNF+thiopurines.*
- *Vaccines against COVID-19 are believed to be safe for IBD patients.*
- *There are no increased side effects due to COVID-19 vaccines in IBD patients when compared to the general population.*
- *Following COVID-19 vaccinations, anti-SARS-CoV-2 antibody responses are lower in patients receiving immunosuppressive medications regardless of vaccination type.*

Since it is known that there is an association between IBD medications and infections in IBD, the issue of major concern is identifying which drugs might increase the risk of the SARS-CoV-2 infection in IBD patients. However, since there are still no prospective data evaluating the effect of immunosuppressive medications on increased risk for COVID-19, clinicians act depending on published observational data, comments, and published recommendations from the medical fraternity.

Sulfasalazine and mesalazine, formulations which are widely used in IBD management, are believed to be safe during the pandemic. A panel study from China, on behalf of the Chinese Society of IBD, the Chinese Elite IBD Union, and the Chinese IBD Quality Care Evaluation Center Committee reported that the use of mesalazine should be continued, and that it does not increase the risk of COVID-19 disease and SARS-CoV-2 infection.[25] Further, the British Society of Gastroenterology (BSG) classified patients under mesalazine treatment as patients with the lowest risk, and they stated that that there is no evidence that treatment with mesalazine increases risk for SARS-CoV-2 infection.[26] The American Gastroenterology Association's Clinical Practice Update and The Asian Pacific Association of Gastroenterology (APAGE) IBD Working Party guidelines in IBD management stated that 5-aminosalycylic acid (5-ASA) compounds such as mesalazine are safe to be used in IBD patients during the pandemic.[27,28] In contrast, findings from a multinational database which records COVID-19 cases in IBD patients (SECURE-IBD) showed that 5-ASA formulations are surprisingly associated with increased ventilator need, ICU admission, and death rates.[29] However, while evaluating the results of this study, the absence of details defining the vulnerability of patients, like age distribution, IBD flare-ups in response to cessation of immunosuppressants during the COVID-19 pandemic should be further analyzed.

Data in the Secure-IBD database reveal that systemic corticosteroids are associated with a 6-fold increased ventilator need, ICU admissions, and death rates.[29] The

BSG and APAGE guidelines[26,27] recommend that the dose of corticosteroids should not exceed 20 mg/day, and in patients who are receiving a higher dose of corticosteroids, the dose should be tapered quickly. The BSG also recommended the use of budesonide and budesonide Multi-matrix system (MMX) in patients with flaring ulcerative colitis and in ileocecal Crohn's disease.

Thiopurines are believed to be safe for use in IBD patients during the pandemic. Published recommendations and guidelines have indicated that the use of thiopurines and methotrexate is not associated with increased risk of COVID-19 disease. However, a recent report from an international registry revealed that especially when used in combination with anti-TNF medications, use of thiopurines increased the risk of COVID-19 by approximately 4-fold when compared to the anti-TNF monotherapy.[30] In general, patients receiving thiopurines were not recommended to stop their medications unless they had COVID-19 disease.

Until now, biologic medications including anti-TNFs and anti-integrins were not found to be associated with increased risk of COVID-19, and were believed to be safe for use in IBD patients during pandemics. Maintenance therapy with either infliximab or vedolizumab in IBD was not associated with increased SARS-CoV-2 seroprevalence.[31] However, as mentioned, a recent report indicated that, when used in combination with thiopurines, risk of COVID-19 is increased 4-fold when compared to monotherapy. Patients on thiopurine receiving biologic agents were not recommended to stop their medications unless they either had a positive test for SARS-CoV-2 virus or had clinical COVID-19 disease. Another recent report from an international registry indicated that vedolizumab monotherapy is associated with more hospitalization due to COVID-19 when compared to anti-TNF monotherapy. However, no difference was found in COVID-19 disease incidence between groups receiving anti-TNF monotherapy and vedolizumab monotherapy.[32] The same report also indicated that the vedolizumab-treated group experienced more new-onset gastrointestinal symptoms with COVID-19 disease when compared to IBD patients on anti-TNF medication.

In summary, as mentioned above, there is almost a consensus that except high-dose steroids, all systemic and topical treatments are believed to be safe during the COVID-19 pandemic, and all immunosuppressive drugs should be stopped in case of a positive test result for SARS-CoV-2 virus or during a clinical COVID-19 disease. However, since evidence-based data is still insufficient, it is not clear when it is safe to resume medication after recovery from COVID-19. According to a recent publication from the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD), the decision to resume the IBD medication should be based on the clinical severity of both IBD and COVID-19 disease in combination with the results of SARS-CoV-2 testing. It is recommended that treatment can be resumed in patients who pass at least 3 days without fever and show an improvement in symptoms like cough and shortness of breath. In addition, there should be a gap of at least 10 days from the day of first symptom appearance. If possible, they also recommended two consecutive negative polymerase chain reaction tests which are at least 24 hours apart.[33]

With the successful emergence and use of vaccines developed against SARS-CoV-2, questions have been raised regarding the mode of vaccination and the prospect of effective protection post-vaccine for IBD patients. In addition, it is also a unclear whether the use of immunomodulator and/or immunosuppressive drugs might possibly alter the result of vaccination against COVID-19. Several studies have investigated the effects of such medications on other vaccinations such as the pneumococcal vaccine and influenza vaccine.[34-39] It was found that immunomodulator medications and anti-TNFs impair the protective immunity following vaccinations.[37,40] This impairment is even higher in patients treated with a combination of immunomodulators and anti-TNFs.[41,42] Vedolizumab, an anti-integrin, which is a gut-selective biologic, does not impair the Hepatitis B Virus (HBV) or influenza vaccine. However, it was found to be associated with impaired immune response to the cholera vaccine, which is administered orally.[43] A recent cohort study comparing antibody responses to COVID vaccinations in patients receiving either vedolizumab or infliximab showed that seroprevalence was lower in infliximab-treated patients when compared to vedolizumab-treated patients. Moreover, impairment in seroprevalence is much higher if anti-TNFs are combined with immunomodulators.[44] In contrast, another recent study showed that there is no difference in the formation of antibodies against SARS-CoV-2 following mRNA-based vaccines, between patients receiving vedolizumab and infliximab.[45] The BSG recommended that IBD patients, regardless of their IBD treatments, should get COVID vaccinations, and stated that theoretical risk factors due to vaccination in such patients remain very low.[46] Recommendations from an international consensus meeting also stated that IBD patients should be

vaccinated against COVID-19 at the earliest. The same report also stated that mRNA vaccines, replication-incompetent vector vaccines, and inactivated vaccines are safe to administer to IBD patients, irrespective of their IBD medications.[47]

In summary, the COVID-19 pandemic is still rapidly growing since November 2019. Knowledge about the mechanistic and long-term effects of COVID-19 disease on IBD patients is still limited. The effect of IBD medications on risk of contracting COVID-19, the efficacy of vaccinations in IBD patients, and the possible effects of IBD medications on seroprevalence, are also unclear. However, in light of the information we have, IBD patients should not withdraw their medications unless they contract the COVID-19 disease. Moreover, it appears that COVID-19 prognosis in IBD patients is not different from that for the general population, and that IBD medications do not affect either the prognosis of COVID-19 or the effect of vaccinations.

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