REVIEW

Management of patients with Intestinal Bowel Disease and COVID-19: A review of current evidence and future perspectives

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Abstract   The COVID-19 pandemic has been a challenge for countries and health professionals worldwide. Viral entry by ACE-2 receptor and an excessive activation of the immune system are key to understand both incidence and severity of disease. Inflammatory Bowel Disease (IBD) represents a special condition associated with an inordinate response of the immune system to external agents. IBD treatments have been associated to an increased risk of bacterial and viral infections. This has raised the question of possible higher incidence and severity of COVID-19 infection in IBD patients. Several papers have been published during this year of pandemic to answer that question. Moreover, COVID-19 vaccination offers great promise in controlling infection in patients with IBD. Based on current evidence, patients with IBD do not have a higher incidence of COVID-19 than the general population, and they do not have worse disease evolution. Advanced age and presence of a greater number of comorbidities have been associated with worse outcomes, similar to the general population. Corticosteroids are associated to an increased risk of COVID-19 infection, higher hospitalization rate and higher risk of severe COVID-19. 5-ASA/Sulfasalazine and Thiopurines have a possible increased risk of severe COVID-19, although studies are lacking. On the other hand, Anti-TNF may have a possible protective effect. It is recommended to maintain the treatment. Anti-IL-12/23, anti-integrins and tofacitinib have results comparable to anti-TNF. Based on the efficacy, expert recommendations, and the absence of other evidence, it is recommended that patients with IBD be vaccinated.

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Manejo de pacientes con enfermedad inflamatoria intestinal y COVID-19: revisión de la evidencia actual y perspectivas futuras

Resumen   La pandemia por COVID-19 ha supuesto un reto para los países y sus profesionales sanitarios. La entrada viral en el hospedador a través del receptor ACE-2 y una activación excesiva del sistema inmunológico son claves para comprender tanto la incidencia como la gravedad de la enfermedad. La enfermedad inflamatoria intestinal (EII) representa una condición especial asociada con una respuesta descontrolada del sistema inmunológico a agentes externos. Los tratamientos para la EII se han asociado con un mayor riesgo de infecciones bacterianas y virales, lo que ha planteado la cuestión de una posible mayor incidencia y gravedad de la infección por COVID-19 en pacientes con EII. A lo largo del año 2021 se han publicado varios artículos que tratan de responder esta cuestión. La vacunación contra la COVID-19 ofrece una gran promesa para controlar la infección en pacientes con EII. Según la evidencia actual, los pacientes con EII no tienen mayor incidencia de COVID-19 ni peor evolución de la enfermedad en comparación con la población general. La edad avanzada y la presencia de un mayor número de comorbilidades se han asociado con peores resultados. Los corticosteroides están asociados con un mayor riesgo de infección por COVID-19, una mayor tasa de hospitalizaciones y un mayor riesgo de enfermedad grave. La mesalazina/sulfasalazina y las tiopurinas presentan un posible aumento del riesgo de COVID-19 grave, aunque se requieren más estudios para demostrar esta asociación. Dentro de los fármacos biológicos, los anti-TNF pueden tener un posible efecto protector. Los anti-IL-12/23, anti-integrinas y tofacitinib presentan resultados comparables con anti-TNF. Se recomienda mantener el tratamiento con agentes biológicos. Con base en la eficacia, las recomendaciones de los expertos y la ausencia de otra evidencia, se recomienda la vacunación de pacientes con EII.
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Introduction

The COVID-19 pandemic has been a challenge for health professionals worldwide. In December 2019, several pneumonia cases of unknown aetiology were reported in China, progressing to acute respiratory distress syndrome (ARDS). A new RNA virus from the *corona viridae* family, called SARS-CoV-2, was later confirmed to be the causative agent. The set of clinical manifestations derived from its infection is encompassed under the term COVID-19. It includes the participation of various body systems, of which the respiratory system is the most frequently affected. Data up to 12th March 2021 has reported approximately 118,867,662 cases of infections and 2,634,979 deaths worldwide.[1]

SARS-Cov-2 is introduced into the human host by binding its surface spike glycoprotein (S protein) with the ACE-2 receptor. SARS-Cov-2 is widely distributed in the lower respiratory tract (alveolar type-2 cells). It is also found in myocardial cells, liver cholangiocytes, proximal kidney tubules, urothelial bladder cells, and gastrointestinal epithelial cells.[2–3] This binding is followed by production of mediators that lead to the activation of cells of the immune system (monocytes/macrophages, neutrophils, effector T cells). Excessive activation may cause the release of a massive cytokine (cytokines storm syndrome) or provoke ARDS, shock, renal failure, and multi-organ failure.[4–6]

COVID-19 can produce different gastrointestinal symptoms. One early descriptive study in the province of Wuhan, which included 204 patients infected with COVID-19 confirmed by PCR, reported a frequency of digestive symptoms of 50.5%, with the most common being anorexia (78.6%) and diarrhoea (35%). If anorexia was excluded, the reported frequency was 18.6%. It was also observed that patients with digestive symptoms took longer to go to the hospital from the onset of symptoms.[7] Another study analyzed the clinical characteristics of a subgroup of patients with low severity of COVID-19 and digestive symptoms. In these patients, it was more common to present positive viral RNA in faeces, a more significant delay in viral clearance and a greater diagnostic delay for patients with only respiratory symptoms.[8] In patients with a chronic gastrointestinal disease such as IBD (Inflammatory Bowel Disease), the gastrointestinal symptoms of COVID19 (anorexia, diarrhoea, nausea, vomiting, abdominal pain, fever),[7–8] can mimic symptoms of an IBD flare, so a coronavirus infection should be ruled out in some cases. However, SARS-CoV-2 infection does not seem to increase the risk of flares in IBD patients as it has been reported in several single-centre studies.[9–10]

The term Inflammatory Bowel Disease (IBD) includes Ulcerative Colitis (UC), Crohn's Disease (CD) and unclassifiable colitis (IC).[11–13] IBD can also include a wide variety of presentations and clinical manifestations. The main characteristic of IBD is that it is a chronic inflammation of the digestive tract, in different locations, of unknown cause, associated to an excessive immune response causing lesions of variable depth and extent in the intestine. It is characterized by a difficult-to-predict evolution in which periods of more active (flares) and less active disease alternate. In many cases it is associated with the development of extraintestinal manifestations, which

is why it is considered a systemic immune-mediated disease.

This paper will assess the management of patients with IBD and COVID19, review current evidence and explore future perspectives. Responses to the following questions will be sought: Is COVID-19 more common in IBD patients? Is COVID-19 more serious in IBD patients? Is there any treatment for IBD that increases the risk of COVID-19 or its severity? What are possible future perspectives for the management of IBD patients upon the introduction of the first vaccines?

Incidence of COVID-19 in patients with IBD

The risk of transmission of the SARS-CoV-2 depends on the type and duration of exposure, the use of preventive measures and individual factors.[15] In IBD, two aspects are relevant regarding the risk of infection: the patient's intestinal and systemic pro-inflammatory state, which may make viral entry easier; and the drugs used for the treatment of IBD (corticosteroids, immunomodulators, biologics, Janus-kinase inhibitors ½), which can increase the susceptibility to viral infections.[14] Kirchgessner et al. concur that the ACE-2 receptor is the virus gateway and is widely distributed throughout the entire organism, including the intestines. Burgueño et al. studied the expression of ACE-2 and the host transmembrane serine protease 2 (TMPRSS-2, transmembrane protein in which the receptor is anchored) animal models with IBD. They observed that both ACE-2 and TMPRSS-2 are abundantly expressed in the ileum and colon, and that their expression is not affected by inflammation. Similarly, anti-tumour necrosis factor drugs, Vedolizumab, ustekinumab, and steroids were associated with a decrease in the ACE-2 expression.[16]

Muhammad Aziz et al. presented a meta-analysis of 9177 patients with IBD (data available in 6 of the 8 included studies) which included the first series of reported incidence and outcomes of patients with IBD and COVID-19. Thirty-two of these patients had confirmed COVID19 with an incidence of 0.3% (95% Confidence interval (CI) 0.1–0.5%), lower than the incidence reported at the population level (0.2–4.0%). Based on the study of Burgueño et al., the authors conclude that IBD patients are somehow protected against COVID-19 due mainly to the treatment for IBD and that this treatment should not be interrupted.[17]

A more recent multinational and multicentre study included patients with IBD and concomitant COVID 19. Out of the 23,879 patients from the different IBD units, 97 acquired the SARS-CoV-2 infection, representing a cumulative incidence of 0.406%, similar to the cumulative incidence of the general population (0.402%). It was observed that the national lockdown was effective in preventing the infection (63% of subjects were infected outside the lockdown compared to 37% during the lockdown). The authors confirm that this measure, together with the general recommendations of physical distance, hand washing and use of a face mask, is effective in reducing transmission.[18]

A limitation of previous studies is that they assess the incidence and outcomes in patients with IBD without establishing comparison groups with patients without IBD,

extrapolating the results to the epidemiological data of each country.

Lukin et al. published a case–control study conducted in two New York hospitals in which they compared the clinical characteristics and outcomes of COVID-19 patients with or without IBD. Also, they conducted an analysis of the cohort of patients with IBD to evaluate, among other aspects, the effects of IBD activity and treatments on the risk of COVID-19. The moderate-severe activity of IBD (measured by clinical and endoscopic indices) and the use of corticosteroids were associated with a higher rate of COVID-19. A higher prevalence of gastrointestinal symptoms was observed in COVID-19 patients with IBD, especially diarrhoea and abdominal pain. The authors argue that there must be a high index of suspicion for COVID-19 in patients with IBD. The latter present gastrointestinal symptoms.[19]

Severity of COVID-19 in patients with IBD

Recent evidence suggests that the severity of COVID-19 is related to the excessive activation of the immune system and IBD is associated with an excessive immune response, both at the intestinal and systemic levels. It could be hypothesized that IBD patients may be at increased risk for severe COVID-19.

Individual risk factors for severe COVID19 include advanced age and different comorbidities (cardiovascular disease, hypertension, chronic lung disease, cancer, obesity).[20–23]

In the review and meta-analysis carried out by Muhammad Aziz et al., in the first series of patients with IBD and COVID-19 who reported outcomes, a hospitalization rate of 40.3% was obtained, an ICU admission of 8.6%, the need for mechanical ventilation (invasive/no invasive) of 10.7% and a mortality of 6.4%.[17] Given that they are initial studies and that the diagnostic methods in the first months of the pandemic were not as available, and was mainly used in severe patients, this percentage may be overestimated.

The multinational cohort of Alloca et al., obtained a hospitalization rate of 24%, a pneumonia rate of 22%, an ICU admission rate of 4% and a mortality of 1%. In the multivariate analysis, age >65 years was associated with an increased risk of pneumonia and hospitalization. The increase in the Charlson comorbidity index was also associated with an increased risk of pneumonia and hospitalization in the univariate analysis. As a limitation, the authors argue the small sample size and the different mortality and incidence rates reported by the different participating countries.[18]

In the case–control study of Lukin et al., a total of 240 patients were included (80 cases and 160 controls). Among the patients admitted for COVID-19 the primary endpoint, a compound rate of ICU admission, intubation or death was comparable in both groups: 23.5% in IBD patients (4 out of the 17 patients admitted with COVID-19 and IBD) and 35.3% in patients without IBD (12 out of the 34 patients admitted with COVID-19 without IBD). In patients with IBD, advanced age was noted to be a risk factor for consultation in the emergency department or hospitalization.[19]

In August 2020, Brenner EJ and Ungaro RC published the first results of the Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel

Disease (SECURED), a multinational database in which the outcomes of adult and child patients with IBD and COVID-19 infection are monitored. The multivariate analysis showed that increasing age, ≥two comorbidities, the use of systemic corticosteroids and the use of 5-ASA/Sulfasalazine were associated with a higher risk of severe COVID-19.[24] The latest results, published in October 2020, have shown data of 1439 patients from 47 countries: 112 (7.8%) had severe COVID-19 defined by ICU admission (5.7%), the need for ventilation (4.6%) or mortality (3.4%). Most severe COVID-19 cases (88/112, 79%) and the majority of deaths (44/49, 90%), ocurred in patients 50 years of age or older.[25]

Treatment of IBD in patients with COVID-19 infection

Treatments used to control inflammation in IBD – corticosteroids, immunosuppressant's and biological agents – have all been noted to have an increased risk of bacterial and viral infections as adverse events, which include pneumonia due to Influenza virus, among others.[14] Therefore, one may conclude that these drugs could increase the risk of COVID-19 or severe COVID-19.

As discussed above, the SECURE-IBD's first outcomes reported a greater risk of severe COVID-19 (primary endpoint) in patients treated with systemic corticosteroids and 5-ASA/Sulfasalazine. It was seen that the use of Anti-TNF was not associated with more severe COVID-19 and even a global protective effect was observed (Odds Ratio 0.9 95% IC (0.37–2.17)). The authors conclude that it is important to obtain the remission of the disease with steroid-sparing treatments and that patients should continue with anti-TNF as maintenance therapy.[24]

In the previous study of the SECURE-IBD registry, the use of anti-TNF monotherapy was compared to the use of thiopurines monotherapy or combined thiopurines and anti-TNF therapy. The last two regimes were associated with an increased risk of severe COVID-19 compared to monotherapy with anti-TNF. The authors suggest discontinuing thiopurines in selected patients (for instance, elderly patients or patients with multiple comorbidities) with stable remission in combination therapy with anti-TNF. On the other hand, the treatment with mesalamine/sulfasalazine was associated with a higher risk of severe COVID-19 than anti-TNF. However, no dose-response association was seen, which is why the authors consider that more studies are needed to reproduce these results and demonstrate biological plausibility to establish a causal relationship. In clinical practice, they recommend not to discontinue treatment except in certain situations with limited benefit (for example Crohn's disease), especially in older patients. Finally, no significant differences were found in the risk of severe COVID-19 with the use of IL-12/23 and the integrin antagonist compared with the use of anti-TNF monotherapy as a reference group.[25]

Similar results to the SECURE-IBD registry were reported in the multinational cohort study performed by Alloca et al. In the multivariate analysis, the use of corticosteroids was associated with a higher hospitalization rate, whereas the use of monoclonal antibodies was associated with a lower risk of hospitalization and pneumonia. Nevertheless, no statistically significant associations were found between the use of immunomodulators, mesalazine, or different therapies in combination with the main outcomes.

There are mixed results regarding the relationship between 5-ASA and COVID-19 outcomes. As mentioned above in SECURE-IBD resgitry treatment with 5-ASA was associated with a higher risk of severe COVID-19 than anti-TNF. Attaubi M et al. published the results of two Danish population-based cohort studies demonstrating no association between COVID-19 outcomes and 5-ASA in patients with IBD and other immune-mediated inflammatory diseases.[26,27] More recently they updated their database and made an analysis of 320 patients with IBD to investigate such association. They did not observe any association between COVID-19 outcomes and the use of 5-ASA even after stratifying the results by several factors like type of IBD and dosing of 5-ASA. The authors conclude that further analysis is needed to confirm the association between 5-ASA and COVID-19 related outcomes.[28]

The results of 37 patients with IBD receiving tofacitinib treatment have recently been reported in the SECURE-IBD registry. No differences were found in the outcomes in comparison with other IBD treatments. There was also no increased risk of thromboembolism, a potentially serious complication that can be found in patients with COVID-19 and an adverse effect of treatment with tofacitinib.[29]

Future perspectives

In December 2020, the vaccination process of the population began after the approval of the first vaccines by different drug regulatory agencies. In Europe, the first commercialized vaccine was BNT162b2 produced by BioNTech & Pfizer, an RNA vaccine that encodes the complete protein S of SARS-CoV-2 in a lipid nanoparticle. In the Phase 3 trial published in the *New England Journal of Medicine*, a 95% efficacy seven days after the second dose was reported.[30] ChAdOx1 nCoV-19 (Oxford/AstraZeneca), and mRNA-1273 (Moderna) vaccines reported overall vaccine efficacy of 70.1% and 94.1% respectively.[31,32] Patients with immunosupressive treatments were excluded from the three trials and therefore important unanswered questions remain, especially in patients with pre-existing conditions. There is currently no evidence against vaccinating IBD patients. Based on evidence from studies looking at the effect of immunosuppression on the immunogenicity of vaccines used for other infectious diseases it could be hypothesized that immunosuppresive drugs could reduce the effectiveness of SARS-CoV-2 vaccines. However benefit of vaccination outweighs the eventual loss of inmune response. In Spain, different organizations and medical societies, such as the Spanish Working Group on Crohn's Disease and Ulcerative Colitis (GETECCU), recommend vaccinating all patients with IBD regardless of the treatment they are on. The high risk of contagion and the significant morbidity and mortality caused by SARS-CoV-2 infection, the high efficacy and safety of vaccines against the virus and the absence of evidence suggesting a greater risk in patients with IBD are the three pillars that support the basis for establishing this recommendation. In the same direction the British Society of Gastroenterology Inflammatory Bowel Disease (IBD) section

and IBD Clinical Research Group has published a position statement of SARS-CoV-2 vaccination for patients with IBD supporting it.[33] In the coming months, we will see the efficacy and safety of the different vaccines in clinical practice and in the particular context of IBD patients and immunosuppressive treatments.

Key Points

Incidence of COVID-19 in patients with IBD

- Patients with IBD do not have a higher incidence of COVID-19 than the general population.
- Patients with IBD should follow the basic preventive measures recommended by the authorities to reduce the risk of COVID-19.
- Physicians must have a high index of suspicion for COVID-19 in patients with IBD and *de novo* gastrointestinal symptoms.
- Minimizing the disease activity is recommended to reduce the risk of COVID-19.

Severity of COVID-19 in patients with IBD

- IBD patients infected with COVID-19 do not have worse results than the general population.
- Taking into account personal factors, advanced age and presence of a greater number of comorbidities, IBD patients have been associated with worse outcomes (higher rates of hospital admission, emergency department visits, pneumonia and severe COVID-19).

Treatment of IBD in patients with COVID-19 infection

- CORTICOSTEROIDS: higher risk of COVID-19, higher hospitalization rate and higher risk of severe COVID-19. Steroid-sparing treatments to achieve disease remission are recommended, avoiding long maintenance treatments.
- 5-ASA/SULFASALAZINE: controversial results. Possible increased risk of severe COVID-19, although studies that reproduce the results and demonstrate causality are lacking. Discontinuing treatment may be considered in limited benefit situations (*e.g.*, in CD), especially in the elderly.
- THIOPURINES: possible increased risk of severe COVID-19 either alone or in combination with anti-TNF. Discontinuing treatment in selected patients at high risk (elderly patients or patients with comorbidities) with stable disease and combined treatment with anti-TNF, may be considered.
- ANTI-TNF: possible protective effect with lower hospitalization rate, pneumonia and severe COVID-19. It is recommended to maintain the treatment.

- ANTI-IL-12/23, ANTI-INTEGRINS and TOFACITINIB: results comparable to anti-TNF. An increased risk of thromboembolism has not been seen with tofacitinib, although more studies are needed. It is recommended to maintain the treatment.

Future perspectives

- At present, based on the efficacy of SARS-CoV-2 vaccines, expert recommendations, and the absence of other evidence, it is recommended that patients with IBD be vaccinated.

Conclusions

COVID-19 has been a challenge for healthcare professionals all around the world. The severity of COVID-19 comes at the expense of the over-activation of the immune system that leads to ARDS and ultimately multi-organ failure. Patients with IBD present two particular characteristics that may increase their vulnerability to SARS-CoV-2 infection: (1) Receiving immunosuppressive treatments that may increase the risk of getting viral infections; and (2) presenting an inordinate immune response to external agents. However, studies report incidence rates and severe COVID-19 rates similar to those of the general population, with comparable individual risk factors (age and comorbidities). Corticosteroids have been associated with a higher infection rate and severe COVID-19, as well as the disease activity, so it is recommended to prioritize clinical remission using, if possible, steroid-sparing treatments. More studies are needed to check the potential risk of severe COVID-19 with 5-ASA/Sulfasalazine and thiopurines, although in the latter group, there is previously available evidence of increased risk of other viral infections. Among the biological agents, anti-TNFs do not seem to increase the risk of infection or severe COVID-19 and could even have a possible protective effect by reducing the number of ACE-2 receptors (keys for viral entry into the body) and reduce cytokine storm. More studies are required to demonstrate this effect. There seems to be no difference between the different types of biologics. The new vaccines against SARS-CoV-2 offer promising future prospects, and there is currently no evidence of lower effectiveness or greater adverse effects in patients with IBD.

Conflict of interest

The authors report no conflict of interest.

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