COVID-19 and IBD drugs

COVID-19 and IBD drugs: should we change anything at the moment?

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The COVID-19 pandemic has raised questions about the management of people with inflammatory bowel disease (IBD).[1] To date, there have been over 43 million confirmed cases of COVID-19 globally, including over 1.1 million deaths (https://COVID-19.who.int). What have we learnt about the risks of SARS-CoV-2 infection in patients with IBD and is there any evidence to support a change in IBD management?

Established risk factors for poor COVID-19 outcomes are older age, male sex, obesity, non-white ethnicity, type 2 diabetes, social deprivation and a range of comorbidities (respiratory disease, cardiovascular disease, stroke, malignancy and liver disease).[2] Based on prior knowledge and early observations from China and Italy, patients with IBD felt to be at higher risk included older patients with comorbidities, patients on higher doses of systemic corticosteroids and patients with active disease.[1 3] However, they were generally advised not to stop IBD treatment in order to minimise the risk of flare, steroid prescription and hospitalisation during the pandemic.[1]

The SECURE-IBD Registry was set up to collect data on confirmed SARS-CoV-2 infections in people with IBD to address the urgent need for information guiding decisions about drug therapy during a time of great uncertainty. This physician-reported registry has accrued over 2700 cases to date (https://covidibd.org/current-data/). An initial analysis of 521 patients reported an association between corticosteroids and adverse COVID-19 outcomes.[4] Ungaro and colleagues now report an expanded analysis on the first 1439 cases.[5] These cases were 34.5% from the USA, 51.4% male individuals and 82.1% white. Overall, 38.5% of patients were on anti-tumour necrosis factor (TNF) therapy and 30.6% were taking a 5-ASA preparation. The primary outcome measure of severe COVID-19 disease was a composite of intensive care unit (ICU) admission, mechanical ventilation or death. This endpoint was met in 112 of 1439; 79% of those with a severe COVID-19 outcome were over 50 years of age. With only 24 events in those under 50 years of age, it is difficult to draw too many conclusions about younger adults.

The major finding was of an increased risk of severe COVID-19 outcomes in patients taking thiopurines.[5] Using anti-TNF monotherapy as a reference arm, thiopurine monotherapy and anti-TNF plus thiopurine combination therapy were both associated with worse outcomes (ORs of 4.08 and 4.01, respectively). On face value, these are clinically impactful results. However, there are several important limitations that require detailed exploration.

The most important consideration is around the physician-reporting nature of the registry. This may introduce over-reporting of cases in closer follow-up (biologic-treated patients with IBD), memory bias (over-reporting of serious outcomes) and confirmation bias (over-reporting of cases that fit a predefined viewpoint: eg, thiopurines are bad; biologics are good). There is also a risk of under-reporting some cases due to a lack of notification; it is possible that gastroenterologists are less likely to be made aware of patients with stable IBD who are not on biologics with non-severe COVID-19, compared with a patient who is taking a biologic or is admitted to the ICU.

In addition, specific to COVID-19, there is a danger of testing bias. This cohort was accumulated exclusively during the first wave when testing for SARS-CoV-2 was limited (13 March to 9 June 2020). Patients in the community with mild symptoms were unlikely to be tested. It is possible that stable patients taking 5-ASA or thiopurines would only have attended hospital if they had severe COVID-19, at which point they would be tested. However, patients with active IBD (who are more likely to be taking steroids) or attending for the administration of a biologic, who had mild COVID-19 symptoms would likely have been tested.

It is established that thiopurines are known to increase the risk of viral infections more than anti-TNFs do.[6] In particular, they promote severe forms of primary infection/reactivation of Epstein-Barr virus (EBV),[7 8] cytomegalovirus (CMV)[7] and varicella zoster virus[9] infection. However, there is less evidence that thiopurines also promote severe infections of the upper respiratory tract. In a tertiary cohort with 15 000 patient-years of follow-up, no case of fatal or hospitalisation-requiring influenza was reported.[7] Furthermore, in the nationwide Danish database, while patients with IBD were more prone than matched controls to develop influenza and serious influenza requiring hospitalisation, exposure to thiopurines did not increase this risk.[10] However, the lack of any prior immunity to SARS-CoV-2, a completely novel respiratory virus, requires caution in extrapolating any further from the influenza data.

While the increased risk of severe COVID-19 in patients exposed to monotherapy with thiopurines versus those exposed to monotherapy with anti-TNFs may be explained by a deleterious effect of thiopurines, it may also relate to a beneficial effect of anti-TNFs. In a randomised controlled trial by Abraham *et al*,[11] patients with severe sepsis were randomly assigned to receive an infusion of placebo, infliximab 7.5 mg/kg or infliximab 15 mg/kg. There was a significant reduction in mortality (40%) at day 3 in the subgroup of patients with septic shock. Indeed, phase 2 trials of infliximab and adalimumab in COVID-19 are planned/ongoing (https://www.clinicaltrials.gov, NCT04425538).[12]

Risks and/or benefits of drug therapy may also be confounded by disease activity. Both systemic and intestinal inflammation in IBD promote the replication of EBV and CMV,[13] and clinically active IBD at the onset of viral infection is a strong and independent risk factor for serious infections.[7] It is possible that patients exposed to combination therapy represent a more severe cohort who are more prone to have uncontrolled IBD (particularly severe perianal Crohn's disease) compared with patients treated with anti-TNF monotherapy. If this is real, the particular severity of COVID-19 in patients receiving the combination of thiopurines and anti-TNF compared with those given monotherapy with anti-TNFs could be at least partially attributed to the severity of inflammation.

The findings reported by Ungaro and colleagues are valuable and welcomed.

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However, we need robust data to confirm or disprove the authors' conclusions based on the SECURE-IBD registry. Nationwide medico-administrative databases can provide complete data on the incidence of severe COVID-19 and drug exposures, although the adjustment for disease activity is partial. Publications derived from such databases are expected soon.

Based on the currently available data, we do not advocate withdrawing thiopurines in younger adults without other risk factors. In older and higher risk patients, the totality of risk and benefit of thiopurine therapy should be considered. This requires taking into account not only COVID-19 but also well-known risks such as lymphoma, as well as the limited benefit of thiopurine monotherapy in Crohn's disease.[14 15] It is important, however, to remember that there is a significant risk of disease flare on withdrawal of thiopurine monotherapy and an increased risk of immunogenicity and hence drug failure where patients are on combination therapy. Our recommendation, therefore is not to deviate substantially from current guidance based on these new data alone and to continue to consider combination therapy, especially for high-risk phenotypes such as fistulising Crohn's disease, while we await other studies.

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