Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

a higher risk of infection with SARS-CoV-2? Do immunosuppressive drugs have an impact on the risk of complications and/or death after developing novel coronavirus disease 2019 (COVID-19)? At present, no evidence-based guidelines have been issued in this respect, and so gastroenterologists are unable to advise and reassure their patients. In contrast, it is possible that immunosuppressants might dampen the cytokine storm associated with severe COVID-19.

A recent publication in *Gastroenterology* reported on a cohort of patients with IBD in at the university hospital in Bergamo, Italy. Over a 1-month period, none of the 522 monitored patients developed COVID-19.[1] Similarly, no cases of COVID-19 had been observed in an IBD cohort in Wuhan, China, 2 months after the start of the local SARS-CoV-2 outbreak [2]. The researchers concluded—hastily, in our opinion—that IBD patients taking immunosuppressants might have a lower risk of developing COVID-19.

The provision of well-grounded answers to these questions requires complex epidemiologic risk and benefit analyses with an a priori sample size calculation and a design that takes account of confounding factors and likely sources of bias.[3] According to modelling results recently published by the Institut Pasteur (Paris, France), only 6% of the French population may have been in contact with SARS-CoV-2, and 2.6% of exposed people have been hospitalized for COVID-19.[4] Given the lack of solid epidemiologic evidence, we referred to our population-based registry (EPIMAD) of all incident cases of IBD recorded in northern France since 1988.[5] This area has around 6 million inhabitants, or approximately 10% of the whole French population. We calculate that at the time of writing, approximately 20 patients with IBD should have been hospitalized for COVID-19 in northern France. We also hypothesize that a lower than expected number of severe cases of COVID-19 might be primarily owing to tighter containment of people suffering from chronic diseases.

This low expected number of incident cases of COVID-19 among patients with IBD prevents any analysis of factors associated with severe viral disease. Our calculation highlights how difficult is it to build rigorous, robust studies designed to answer crucial questions about managing patients with chronic diseases during the SARS-CoV-2 pandemic.

The recently published, underpowered publications cannot provide answers for patients with IBD, and more generally infrequent diseases, and may even prompt misguided and possibly harmful treatment decisions.

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Conflicts of interest
The authors disclose no conflicts.

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Reply. We are grateful for the interest of Dr Kotze et al and Dr Gower-Rousseau et al in our article, and we would like to take the opportunity to respond to their interesting comments.

We totally agree with the concept elucidated by Dr Kotze, that a tailored therapeutic approach should always be maintained when caring for patients with a chronic disease facing an event such as the severe acute respiratory disease novel coronavirus-2(SARS-CoV-2) pandemic. Our main aim was focused on the importance to avoid overreacting to a possible threat before demonstrating its real risks. As the first Western epicenter of the pandemic, we felt committed to share the Bergamo experience on the uneventful course of patients with inflammatory bowel disease (IBD) during the epidemic,[1] which was followed by other papers confirming our impression,[2] endorsing our early hypothesis that, in general, immunosuppression does not increase the risk of severe novel coronavirus disease-19.[3] As also shown

by a large world registry, immunomodulators, and biologic treatments in patients with IBD do not increase the severity of SARS-CoV-2 disease.[4] All these important contributions led international societies to promptly produce recommendations meant to defend patients with IBD from the pandemic, but also from relapses caused by unnecessary treatment tapering.[5]

We also agree with the comment by Dr Gower-Rousseau that our early report could have been underpowered by the rate of exposure of our patients to SARS-CoV-2. However, we eventually produced evidence that the uneventful course previously described in our cohort of patients with IBD was not due to sheltering from the infection.[6] Indeed, for patients undergoing biologic treatment in our service, coming to the hospital several times for the infusions had a SARS-CoV-2 seroprevalence of 21%, compared with the general population in the area (the highest hit province of Italy, with a seroprevalence as high as 24%) (www.istat.it/it/files//2020/08/ReportPrimiRisultatiIndagineSiero.pdf). Furthermore, more than one-half of patients that came into contact with the virus was completely asymptomatic during the lockdown period.[5] Recently, this concept was stressed further, with the hypothesis of a possible role of anti–tumor necrosis factor-α in the treatment of novel coronavirus disease-19.[7]

In conclusion, we would like to thank Dr Kotze and Dr Gower-Rousseau for their agreeable contributions, and we are pleased to see that in ours, as well as in larger series, our preliminary finding of an uneventful course of patients with IBD during SARS-CoV-2 epidemic has been confirmed.

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The authors disclose no conflicts.

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Preclinical Inflammatory Bowel Disease: Back to the Future

Dear Editors:

In the current issue of *Gastroenterology*, we have read with great interest the results of the research conducted by Torres et al.[1] In this interesting article, the authors report their findings on the possible prediction of Crohn's disease with a panel of 1129 serum protein biomarkers with a 75% accuracy 5 years before diagnosis, and this proportion increased to 88% in the year before. New insights on the possible prediction and prevention of this disease are highly awaited and we would like to remark the potential impact of this research for the prospects of identifying high-risk individuals and early diagnosis of patients with inflammatory bowel disease (IBD).

The PREDICTS collaborative project[2] has previously demonstrated that multiple antimicrobial antibodies can be detected years before the onset of Crohn's disease.[3] A similar observation has been described in other immune-mediated diseases such as diabetes mellitus,[4] rheumatoid arthritis,[5] or systemic lupus erythematosus,[6] where a combination of genetic predisposition and environmental factors trigger an organ-specific immune response that leads to tissue damage. The interval of time between the initiation of the first immunopathologic mechanisms and the final diagnosis of the disease is defined as the preclinical period. Population-based studies and especially those focused on high-risk individuals (ie, first-degree relatives) have demonstrated that a wide range of autoantibodies may be detected before the disease onset, including ASCA, anti-OmpC, anti-Fla2, anti-FlaX, and anti-CBir1. Based on this observation, it is currently accepted that a period of months to years precede the onset of the histologic and endoscopic lesions, and its analysis will offer the opportunity to study the first immune disturbances present at the beginning of the pathophysiology of IBD.

The identification of certain immune pathways within the present study—complement cascade, lysosomes, innate immune response, and glycosaminoglycan metabolism—represents a significant step forward in the characterization of the early phases involved in the pathogenesis of the disease. However, despite an impressive collection of blood samples, the retrospective collection in this study does not allow to differentiate between those patients with or without established endoscopic lesions during the preclinical period. As the authors explain, the expansion of an altered circulating immune response will lead to subclinical intestinal lesions and gastrointestinal symptoms once a certain degree of bowel damage is present. These lesions may appear during the preclinical period months to years before the final diagnosis; it has been observed in asymptomatic patients with an incidental diagnosis of IBD in approximately 1 in every 300 patients undergoing an endoscopic examination during the colorectal cancer screening program.[7] Although we acknowledge that the sequential sampling in the study by Torres et al does provide a comprehensive overview of the early disease pathogenesis, it