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.

resistance in insulin tolerance test, but hepatic miR-122 on gluconeogenesis, glucose uptake, pancreatic β cell function and insulin signaling originated from NASH was not well investigated," we wish to point out that nonalcoholic fatty liver disease is characterized by the ectopic accumulation of lipids within hepatocytes and can progress to NASH and advance to liver fibrosis; therefore, we measured hepatic lipid metabolism and fibrosis pathways. Although the metabolic syndrome and type 2 diabetes are associated with NASH in humans and are interesting to investigate, in our article, mice fed a high-fat diet exhibited liver steatosis, but were not diabetic. Therefore, type 2 diabetes and glucose dysfunction regarding miR-122 activity should be investigated in a different mouse model.

Addressing the comment: "The role of hepatic miR-122 in [brown adipose tissue] and mitochondrial functions has not been completely mentioned, and the effects of miR-122 on adipokines require more investigations to verify." Although we did not measure brown adipose tissue activity linked to thermoregulation, we did find that miR-122 is secreted to the medium upon cold exposure via RORα activity in human HCC cells. In addition, using lipidomic analysis, we detected significant increase in plasma miR-122 levels and decreased levels of TG species in humans undergoing systemic body cooling. These observations indicate that miR-122 might have a role in thermoregulation, but again, different models and approaches are needed to further investigate this interesting connection. Our findings suggest that the FFA-miR122-TG circuit regulation via RORα activity is relevant to humans, therefore, we proposed that RORα activators are promising compounds to be developed and assessed for their clinical beneficial effects in patients with nonalcoholic fatty liver disease.

We agree with Dr Chung that the induction of miR-122 by specific activators can be applied to other metabolic disorders and carcinogenesis. The regulation of lipid and glucose metabolism is complex and probably involves many metabolic hormones that participate in broad related pathways. Nevertheless, we believe that the activity of miR-122, which is regulated by RORα, is important for coordinating lipid metabolism between the liver and peripheral tissues. Therefore, we are confident that manipulating miR-122 levels by RORα agonists could have beneficial therapeutic implications.

This response was prepared together with Raymond F. Schinazi, Laboratory of Biochemical Pharmacology, Department of Pediatrics, Emory University, Atlanta, Georgia.

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Conflicts of interest
The authors disclose no conflicts.

Most current article

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Therapeutic Decisions in Inflammatory Bowel Disease in the SARS-Cov-2 Pandemic

Dear Editors:

We were very interested to read the recent report of the first formal analysis of the Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE) registry of the worldwide experience of inflammatory bowel disease (IBD) outcomes during the severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) pandemic.[1] We feel that a number of important observations worthy of discussion arise from this manuscript, each with potential implications for patient management.

The safety of anti–tumor necrosis factor (anti-TNF) therapy during the pandemic, along with other conventional therapies, is of great interest to all IBD physicians. Current international guidance has taken an appropriately cautious stance regarding the potential risks of immunosuppression and its implications for patient behavior/social distancing.[2,3] We note the large number of SECURE-IBD registry patients who have developed Coronavirus Disease 2019 (COVID-19) while taking an anti-TNF (43.4%), most (three-fourths) on monotherapy, and the absence in this group of a signal of harm. The authors demonstrate in exploratory analyses a 5-fold increase in severe complications for those on combination therapy.

Without further data from this registry, or from a case-control study, we would caution against drawing firm conclusions regarding safety. We suggest it is still possible that anti-TNF may yet be shown to increase susceptibility to COVID-19. We acknowledge that SECURE-IBD is not designed to determine this question, but it is interesting that there is a relative paucity of other biologic use represented in the registry. The impact of anti-TNF monotherapy on those with infection appears reassuring, and there is the potential for benefit perhaps dependent on the phase of the viral illness.[4] As clinicians, we are inevitably concerned by the data presented regarding combination therapy that appears to be associated with severe complications. Interestingly the proportion of patients in SECURE-IBD on combination therapy is substantially lower (23%) than that described during anti-TNF induction in the UK PANTS (Personalised anti-TNF therapy in Crohn's disease study) (adalimumab 53%, infliximab 62%),[5] and lower than in our ongoing local practice (760 patients on anti-TNF; combination therapy on adalimumab 31%, on infliximab 65%). The SECURE-IBD data suggest that treatment-naïve

patients requiring anti-TNF therapy during the pandemic may preferentially be started on the least immunogenic agent (in our practice, adalimumab over infliximab), and this emerges as an important focal point for further research.

The data presented in the manuscript implicating sulfasalazine/5-aminosalicylate (5-ASA) therapy with poor outcomes are worrying, counterintuitive, and surprising based on the lack of immune-modulatory activity. Many possible explanations require exploration. We propose that the observed association with 5-ASA may partly be a surrogate marker for underlying IBD activity, and note that the record of disease activity in the registry, for pragmatic reasons, is based on a physician global assessment. We observe the elevated (12%) intensive care unit/ventilator/death rate in those patients with reported moderate to severely active IBD, and that other studies have also reported a detrimental association between all IBD activity and COVID-19 outcomes.[6] Similarly, it is possible that the more serious COVID-19 outcomes in patients on steroids may at least be partly confounded by an association with active IBD. Recent data have implicated active colitis as associated with increased colonic expression of the angiotensin-converting enzyme 2 epithelial cellular receptor for SARS-Cov-2,[7] providing a possible mechanistic link. Of note neither 5-ASA nor steroids are reported to independently alter intestinal mucosal angiotensin-converting enzyme 2 expression.[8]

Overall, we congratulate the authors for their timely establishment of a critically important resource during the pandemic, and for addressing important issues. We point to the need for further data to substantiate these initial observations, and for detailed case-control and cohort-based studies to address the key issues in patient management. As data accrue, evidence-based alterations to current clinical guidelines will be of additional benefit to our patients, not only in relation to therapy decisions, but also to social distancing guidelines and their ability to safely perform their roles within society. At present these, and other, published data suggest that in the COVID-19 era, we should closely monitor for objective IBD activity so as not to delay effective management, using where possible biologic monotherapy and avoiding systemic steroids. Importantly, we feel these data should not negatively affect the appropriate use of 5-ASA in management algorithms.

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Conflicts of Interest
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Aminosalicylates and COVID-19: Facts or Coincidences?

Dear Editors:

It was with great interest that we read the paper of Brenner et al[1] published recently in *Gastroenterology*. In the setting of Coronavirus Disease 2019 (COVID-19), the authors defined severity as the need for intensive care unit admission and ventilator use, and/or death. The paper reports that tumor necrosis factor (TNF) antagonists do not appear to be associated with severe COVID-19, but sulfasalazine or 5-aminosalicylate (5-ASA) use adjusted for age, comorbidities, inflammatory bowel disease (IBD) disease characteristics, and corticosteroids were positively associated with the outcome of hospitalization or death (adjusted odds ratio 3.1; 95% CI, 1.3–7.7).[1] These findings are surprising and unexpected, because neither immunomodulators nor TNF antagonists have been associated positively with the composite outcome. Oral delayed-release mesalamine is a pH-dependent drug; the formulation allows delayed release from the terminal ileum to the colon, resulting in local topical activity on the mucosa and low systemic concentration.[2] Depending on the dose and type of formulation, only 15% to 67% of the drug is absorbed and excreted in the urine (mostly in the acetylated form), whereas 24% to 67% passes to the stool (approximately 50% in acetylated form). Colonic epithelial cells acetylate 5-ASA rapidly, however N-acetyl 5-ASA is poorly absorbed by epithelial cells.[3] Therefore, how can we explain that aminosalicylates with low bioavailability are associated with poor outcomes in patients with IBD with COVID-19? Two explanations occur: one relates to methodological aspects, and the other with mechanistic pathways of 5-ASA. To guarantee that we are following the right path, we suggest a complementary analysis to the work of Brenner et al.[1]:

1. In the multivariate regression, the group of 5-ASA should analyze patients on monotherapy with aminosalicylates (without other concomitant drugs to treat IBD).
2. Comorbidities like hypertension, diabetes, and cardiovascular conditions were reported to be associated with worst prognosis in patients with COVID-19, and to have different weight from that of history of stroke, asthma, NAFLD, or cirrhosis. In this work, the authors considered all comorbidities as having similar influence. From our point of view, this can be a potential