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.

reporter activity when compared with cells with FXR-1GG wild type expression.

In conclusion, this study's authors identify an SNV at FXR-1 that may aid in predicting women with CD at highest risk for progression to surgery and provide an in vitro model that suggests that estradiol signaling through ERs may contribute to the suppression of FXR-1 activity. Clinically, they postulate that the identification of women with CD who are carriers of the FXR-1G>T variant could allow clinicians to focus efforts on aggressive, and early, medical therapy for these patients.

Comment. Sex differences are present in the prevalence and incidence of Crohn's disease (Gastroenterology 2018;155:1079–1089.e3). Epidemiologic studies have also found more CD within families of female patients (specifically, inheritance patterns involving female-to-female transmission) and higher rates of IBD in patients with Turner syndrome (XO genotype) (Pediatrics 1980;66:63–67), which suggests that an X-linked driver may play a role in observed sex differences in rates of disease.

Data regarding sex differences in disease activity, phenotype, and complication rates have been conflicting, with some studies showing increased severity in males and other studies among females. With regard to the extraintestinal manifestations of CD, a higher incidence was noted among females in associated skin, pulmonary, joint, and ophthalmologic conditions (Am J Gastroenterol 2001;96:1116–1122). Major differences have been found in the postdiagnostic course of disease: women are initiated on biologic therapy later and less frequently with anti–tumor necrosis factor alpha medications, report more side effects from biologics, have lower overall compliance than males, and report increased rates of depression, fatigue, and lower quality of life than their male counterparts (Digestion 2020;101(Suppl 1):98-104). Female patients with CD have also been found to suffer from diagnostic delay, which may also contribute to higher rates of CD-related surgery and other complications seen in women (Am J Gastroenterol 2013;108:1744–1753). Thus, advances in the study of sex differences have the potential to have broad impact on disease management in IBD.

FXR has been implicated in the mucosal immune response, gut permeability, bile acid diarrhea via epithelial transport processes, and the development of colon cancer (Cell Mol Gastroenterol Hepatol 2006;2:725–732). However, FXR polymorphisms have not been found to serve as clinically meaningful predictors of CD location or disease type in previous human studies (BMC Res Notes 2012;5:12). Similarly, despite interest in identifying a nuclear bile acid receptor that predicts IBD severity, location, or behavior, other targets, including PRX, NR1I2, and MDR1, have not been found to be of meaningful clinical use in forecasting CD behavior or patient outcomes (Gut 2006;55:1676–1677; Inflamm Bowel Dis 2012;18:562–572). Wilson et al have made the observation that prior studies of FXR, MDR1, and PXR have not investigated sex-based outcome differences among cohort populations and have sought to address this in their cohort of patients with IBD.

The study's authors identify a gene variant FXR-1G>T that may be a sex-based determinant for risk for surgery in CD patients. They also show that in vitro FXR activity may be inhibited in the presence of estradiol-induced ER signaling. Certainly, whether this underlies the pathogenesis leading to the risk for surgery in CD patients remains to be proven. Moreover, because the study's in vitro model used a hepatocellular carcinoma cell line, more studies are needed to determine whether the findings these authors noted in hepatocytes are at play in other cell types that express FXR in intestinal tissues. Of note, frequency of the studied gene was also low (5.9% of the cohort) when compared with frequency of other studied nuclear bile acid receptors, and the cohort was "largely Caucasian," which may limit the genetic marker's usefulness among non-White patients. A larger cohort may be needed to further elucidate the impact of genetic variation on clinical outcomes.

The study does, however, demonstrate the importance of sex-based differences in the genetics, pathophysiology, and clinical management of patients with IBD. There may well be an intricate cell-type–specific crosstalk between genetic variants and hormone signaling that lead to sex-based differences in IBD. Interestingly, although the FXR-1G>T variant was associated with time to and risk of surgery, it did not predict other indicators of disease severity, including medication failure rates or the risk of hospitalization, which could indicate variations in molecular and cellular disease pathways that ultimately require surgery versus pathways that result in medication failure alone. Larger clinical studies are needed, as are further genetic and laboratory-based investigations on the interplay among genetic variants and sex-based hormonal drivers.

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The authors disclose no conflicts.

Steering a Course through the COVID-19 Pandemic: Should the SECURE-IBD Registry Influence Prescribing for Patients with Inflammatory Bowel Disease?

Effect of IBD medications on COVID-19 outcomes: results from an international registry; Gut. 2020 Oct 20 [Epub ahead of print].

The global pandemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, which causes the associated illness, coronavirus disease-2019 [COVID-

19]) rapidly became an unprecedented health care challenge. It represents a particular concern for patients with inflammatory bowel disease (IBD), many of whom require treatment with immunosuppressive medication which may be associated with an increased risk of both viral and bacterial infections (Gastroenterology 2018;155:337–346.e10). Moreover, because IBD is a lifelong condition, patients are frequently older with comorbidities, further increasing the potential risks of a more severe COVID-19 disease course. This has led to considerable uncertainty over appropriate treatment of IBD in the COVID-19 era, and has brought safety considerations into the focus of the patients and physicians.

The Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) registry is an international registry that was launched in March 2020 as cases of COVID-19 first increased rapidly around the world. The overarching aim of SECURE-IBD has been to characterize the clinical course of COVID-19 among patients with IBD, and identify factors associated with worse outcome including the potential impact of IBD medication.

An initial report of the first 525 cases from 33 countries found that older age, $\geq$2 comorbidities, systemic corticosteroid therapy, and sulfasalazine/mesalamine therapy were associated with severe COVID-19, whereas tumor necrosis factor (TNF) antagonist use was not (Gastroenterology 2020;159:481–491). However, relatively small study numbers together with concerns over possible reporting bias and unmeasured confounding factors potentially limited interpretation, and updated results in a larger cohort have been eagerly awaited. In the present study, incorporating data from March to June 2020, the authors describe 1439 cases from 47 countries with 112 patients (7.8%) developing severe COVID-19, defined as intensive care unit admission, ventilator use, and/or death. The mean age was 44.1 $\pm$ 17.6 years, 82.1% were White, and 51.4% male, with 34.5% from the United States. More than one-third (37.2%) had $\geq$1 comorbidity, most commonly hypertension, lung disease, or cardiovascular disease. TNF antagonist therapy was the most common medication and prescribed in 38.5% of patients, with 30.6% on mesalamine/sulfasalazine therapy. Strikingly, there was a continued association after multiple regression analysis with any mesalamine/sulfasalazine therapy and increased risk of severe COVID-19, when compared both with no mesalamine/sulfasalazine therapy (adjusted odds ratio [aOR], 1.70; 95% confidence interval (CI), 1.26–2.29) or with TNF antagonist monotherapy (aOR, 3.52; 95% CI,1.93–6.45). When compared with TNF antagonist monotherapy, both thiopurine monotherapy (aOR, 4.08; 95% CI, 1.73–9.61) and combination therapy with TNF antagonist (aOR, 4.01; 95% CI, 1.65–9.78) were associated with an increased risk of severe COVID-19. Conversely, IL-12/23 and integrin antagonists were associated with a similar risk to TNF antagonist monotherapy. Similar to the first report, corticosteroid use remained significantly associated with severe COVID-19 (aOR, 3.24; 95% CI, 1.78–5.90).

Comment. The SECURE-IBD registry provides novel and valuable data on the risks of IBD medications in the current pandemic, and this international collaboration should be applauded for their rapid and innovative approach, providing data and updates in a regular basis from its inception, allowing for informed decision-making for the prescribing physicians. There are, however, important limitations to the reported data, as acknowledged by the study authors. These limitations include concerns about generalizability, with $<$20% of non-White ethnicity, and of reporting bias, with particular risk of overrepresentation for those on intravenous medication or biologics who have frequent health care interactions. Also, it is plausible that those patients on mesalamine developing more severe infection would be more likely reported in the registry, raising the possibility of reporting bias. As with any observational study, association does not imply causality and the results must be interpreted as such.

Nonetheless, several issues arise from the current publication that merit discussion with respect to their impact on patient management during the ongoing pandemic. Thiopurines are associated with a significantly increased risk of severe COVID-19 when used as monotherapy or in combination with TNF antagonists. This finding is in keeping with previous data demonstrating an association between thiopurines and viral infection, with the risk greatest in those receiving combination therapy (United Eur Gastroenterol J 2020;8:303–313). It is also biologically plausible, given that thiopurines inhibit T-cell activation, which forms a critical part of the host antiviral response (J Pharmacol Exp Ther 2005;312:537–545). Furthermore, lymphopenia, which commonly results from thiopurine therapy, has been associated with worse COVID-19 outcomes (JAMA Intern Med 2020;180:934–943).

The replication of the association between sulfasalazine/mesalamine and severe COVID-19 is much harder to explain. Although the multivariable regression analysis adjusted for multiple established risk factors for severe COVID-19 including age, ethnicity, corticosteroids, comorbidities, IBD diagnosis, and disease activity, unmeasured confounding factors such as differing socioeconomic status must still be a plausible explanation for this unexpected result, particularly because no dose effect was seen. Importantly, patients on mesalamine/sulfasalazine had more frequently active disease based on physician's global assessment. Even if this covariate was adjusted for, no objective markers of inflammation that could allow a more granular distinction on disease severity were captured in the registry, which could have limited analysis. It has been shown the that inflammation associated with IBD enhances the expression of angiotensin-converting enzyme 2 and TMPRSS2 in the rectum and colon (Gastroenterology 2021;160:287–301), which could at least theoretically promote viral entry and COVID-19 disease severity. Further, there is as yet no biological basis to explain this proposed association, although it is important to keep an open mind with much still to learn about this novel virus.

A further conundrum is whether the association between severe COVID-19 and thiopurine monotherapy or sulfasalazine/mesalamine, when compared with TNF antagonist therapy, is due to the harmful effects of the former 2 classes or the protective effect of the latter class. The lack of an association on multivariable analysis between TNF antagonist therapy and a decreased risk of severe COVID-19, when compared with nonuse or other biologic therapies, argues against a clear protective effect. Nonetheless, there is biological plausibility for the benefits of TNF antagonists, with particular interest in the role of a "cytokine storm" in severe COVID-19. These patients have demonstrated higher levels of proinflammatory cells and cytokines, including anti-TNF, with potential links to endothelial cell dysfunction, severe lung disease, and disseminated intravascular coagulation (Trends Immunol 2020;41:1100–1115). It is therefore plausible that TNF antagonists might blunt this exaggerated and deleterious immune response, and studies such as AVID-CC (ISRCTN33260034) and CATALYST (ISRCTN40580903) are ongoing to address the use of these therapies in the treatment of COVID-19. Separate SARS-CoV-2 seroprevalence data also raises the possibility that these and other cytokine antagonists might reduce susceptibility even to the development of COVID-19, perhaps by dampening the initial inflammatory tissue response to infection and preventing the priming of the adaptive immune response (Nat Commun 2020;11:3774). The ICARUS and CLARITY (ISRCTN45176516) studies will provide further important seroprevalence data in patients with IBD on biologics, although this approach is inevitably vulnerable to bias in exposure risk, despite careful attempts to adjust for this.

Should the present study influence current clinical practice? The first question is whether we should consider the withdrawal of thiopurines in patients during the COVID-19 pandemic. This approach needs appropriate circumspection, given the potential implications. Weighed against this evidence of a more severe COVID-19 outcome are data showing that IBD treated with thiopurine monotherapy on remission have a significant risk of disease relapse after withdrawal (Cochrane Database Syst Rev 2018;5:CD012540). Therefore, the routine withdrawal of thiopurine monotherapy for patients in remission cannot be recommended, not least because any relapse risks corticosteroid exposure, which themselves increase the risk of severe COVID-19. Instead, a case-by-case decision must be made, taking into account patient preference, previous disease course, and other risk factors for severe COVID-19. However, when considering the withdrawal of thiopurine from combination therapy, the risk/benefit ratio may be markedly different. Combination therapy has been shown to increase the risk of severe infections and lymphoma, and according to these recent data, of severe COVID-19 as well. Additionally, withdrawal does not seem to increase the relapse rate at $\leq$2 years of follow-up on currently available evidence, although longer prospective studies are needed for both Crohn's and ulcerative colitis (Lancet Gastroenterol Hepatol 2020;5:63–79). A specific concern surrounds the effect of thiopurine withdrawal on the immunogenicity of TNF antagonist therapy; however, the concept of optimized monotherapy has recently emerged as a strategy to maintain TNF antagonist efficacy through proactive therapeutic drug monitoring and dose escalation, with similar clinical efficacy described for combination therapy (Lancet Gastroenterol Hepatol 2019;4:341–353).

The second question relates to the use of oral 5-aminosalicylate therapy. Although it is far from certain that any association with severe COVID-19 is causal, there are important subsets of patients in whom 5-aminosalicylates can be withdrawn without apparent risk to control of their IBD. Indeed, recent data suggest that 5-aminosalicylates may be safely withdrawn in patients with ulcerative colitis escalated to biologic therapy (Gut 2019;68:977–984). There is also no clear evidence supporting their use in Crohn's disease, despite 30% of patients receiving long-term therapy. However, we would not otherwise suggest stopping 5-aminosalicylate therapy based on data from the present study until further confirmation.

The third question surrounds the selection of appropriate immunosuppression in those patients who require escalation. A very important message arising from SECURE-IBD, and that has also been replicated through similar registry study in Rheumatoid Arthritis (Lancet Rheumatol 2020;2:e250–e253), is that anti-TNF based therapies seem to be safe in the context of COVID-19. The real concerns that the present study raises about the safety of thiopurines, together with the decreasing costs of TNF antagonist therapy with biosimilars, suggest that biologic monotherapy may be now preferable to thiopurine monotherapy as first-line therapy if economics allow. Further, recent data suggest that thiopurine monotherapy is considerably less effective in Crohn's disease than ulcerative colitis, lending further support to this approach in this group of patients (Gut 2020 320185; doi: 10.1136/gutjnl-2019-320185). It also seems prudent to avoid combination therapy where possible. Although considerably more costly, this study also suggests that the IL-12/23 antagonist ustekinumab and the integrin antagonist vedolizumab may be safely used. With data suggesting no benefit to the addition of an immunomodulator to these therapies, this represents a further means of circumventing the potential hazards of combination therapy. As with all therapy decisions, patient preference is central, although other factors including age and comorbidities that significantly influence risk of severe COVID-19 must be considered carefully.

In summary, although the advent of vaccines effective against COVID-19 promises an eventual end to this tumultuous era, there remains a challenging path to navigate. Indeed, a further critical question to address is the efficacy of these varied vaccines in patients on immunosuppressive medication, which may themselves all impact differently on the vaccine immune response. Although not without limitations, the SECURE-IBD registry has helped to illuminate the way forward in our use of medical therapy in patients

with IBD, and further data from this important resource will soon be available to provide further insights.

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