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.

RESEARCH LETTERS

Impact of Medications on COVID-19 Outcomes in Inflammatory Bowel Disease: Analysis of More Than 6000 Patients From an International Registry

The Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) database, an international, collaborative database created to monitor COVID-19 outcomes in patients with inflammatory bowel disease (IBD), has previously reported that corticosteroids and mesalamine or sulfasalazine are associated with an increased risk of severe COVID-19 and tumor necrosis factor (TNF) antagonists do not impact risk.[1] A follow-up report observed that patients on combination therapy with TNF antagonists and thiopurines appeared to be at higher risk of severe COVID-19.[2] However, at that time, the number of reported cases was too low to fully evaluate the risk of other IBD therapies. As the cases reported to SECURE-IBD have increased substantially, more granular analyses evaluating other IBD medication classes (including combination therapies) and adjusting for more covariates are possible. In this study, we compared associations between multiple medication classes and adverse COVID-19 outcomes in the SECURE-IBD database.

We analyzed reports to SECURE-IBD from inception (March 13, 2020) through May 21, 2021. Details regarding data and analysis are provided in the Supplementary Material.

Demographic and clinical characteristics of 6144 included reports stratified by medication type are provided in Supplementary Table 1. Figure 1 summarizes the independent associations of medication classes on adverse COVID-19 outcomes among all cases reported to SECURE-IBD. Systemic corticosteroids were associated and methotrexate was marginally associated with an increased odds of hospitalization or death or both. Medications associated with a decreased odds of COVID-19–related hospitalization or death or both included TNF, interleukin-12/23, and integrin antagonists. Systemic corticosteroids were significantly associated with increased odds of severe COVID-19, and TNF and interleukin-12/23 antagonists were associated with a decreased odds of severe COVID-19. Systemic corticosteroids were associated with increased odds of death due to COVID-19, and biologics were not. Notably, there were no statistically significant associations between mesalamine or sulfasalazine and any adverse COVID-19 outcome. We also observed that TNF antagonist and thiopurine combination therapy was associated with a significantly increased risk of hospitalization or death (adjusted odds ratio [aOR], 1.82; 95% confidence interval [CI], 1.26–2.62), but not severe COVID-19 (aOR, 1.63; 95% CI, 0.87–3.10). In contrast, a combination of TNF antagonist and methotrexate was not significantly associated with risk of either adverse COVID-19 outcome (aOR, 0.82; 95% CI, 0.42–1.60 and OR, 2.44; 95% CI, 0.55–10.74).

Lastly, we restricted our analyses to only patients on biologics (Supplementary Table 2). There was no statistically significant difference in the odds of severe COVID-19 across biologic classes. The proportion of patients who experienced death was similar across biologics. When we included a covariate for mesalamine or sulfasalazine use in models of patients treated with biologics, there was no difference in outcomes with mesalamine or sulfasalazine use compared with nonuse (hospitalization or death: aOR, 1.11; 95% CI, 0.82–1.50; severe COVID-19: aOR, 0.94; 95% CI, 0.48–1.82).

Using a global registry of patients with IBD who developed COVID-19, we evaluated associations between IBD medications and COVID-19 outcomes. The robust number of cases now reported to SECURE-IBD enabled us to perform more granular analyses than before. Reassuringly, biologics were not associated with more severe COVID-19 outcomes and may have protective effects. Importantly, mesalamine or sulfasalazine does not appear to be associated with worse COVID-19 outcomes. Combination of TNF antagonists with thiopurines was associated with an increased risk of adverse COVID-19 events, but combination with methotrexate was not.

As in previous SECURE-IBD publications, corticosteroids were associated with increased odds of severe COVID-19 outcomes.[1,2] Although we adjusted for physician global assessment in our models, it is an imperfect disease activity measure, and separating the impact of corticosteroids from uncontrolled disease remains challenging. However, the strength and consistency of this signal across immune-mediated inflammatory diseases suggest a true harmful association.[3–5]

Our biologic medication analyses substantiate previous studies among patients with immune-mediated inflammatory diseases, which found that these therapies are safe to continue during the COVID-19 pandemic.[1,2,4,5] The current findings reinforce prior observations that biologics are not associated with an increased risk of severe COVID-19 outcomes.[1,6] We also observed that combination therapy of TNF antagonists with thiopurines was associated with higher risk of adverse COVID-19 events compared with TNF antagonist monotherapy. In contrast, a combination of TNF antagonists

Abbreviations used in this paper: **aOR, adjusted odds ratio; CI, confidence interval; IBD, inflammatory bowel disease; SECURE-IBD, Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease; TNF, tumor necrosis factor.**

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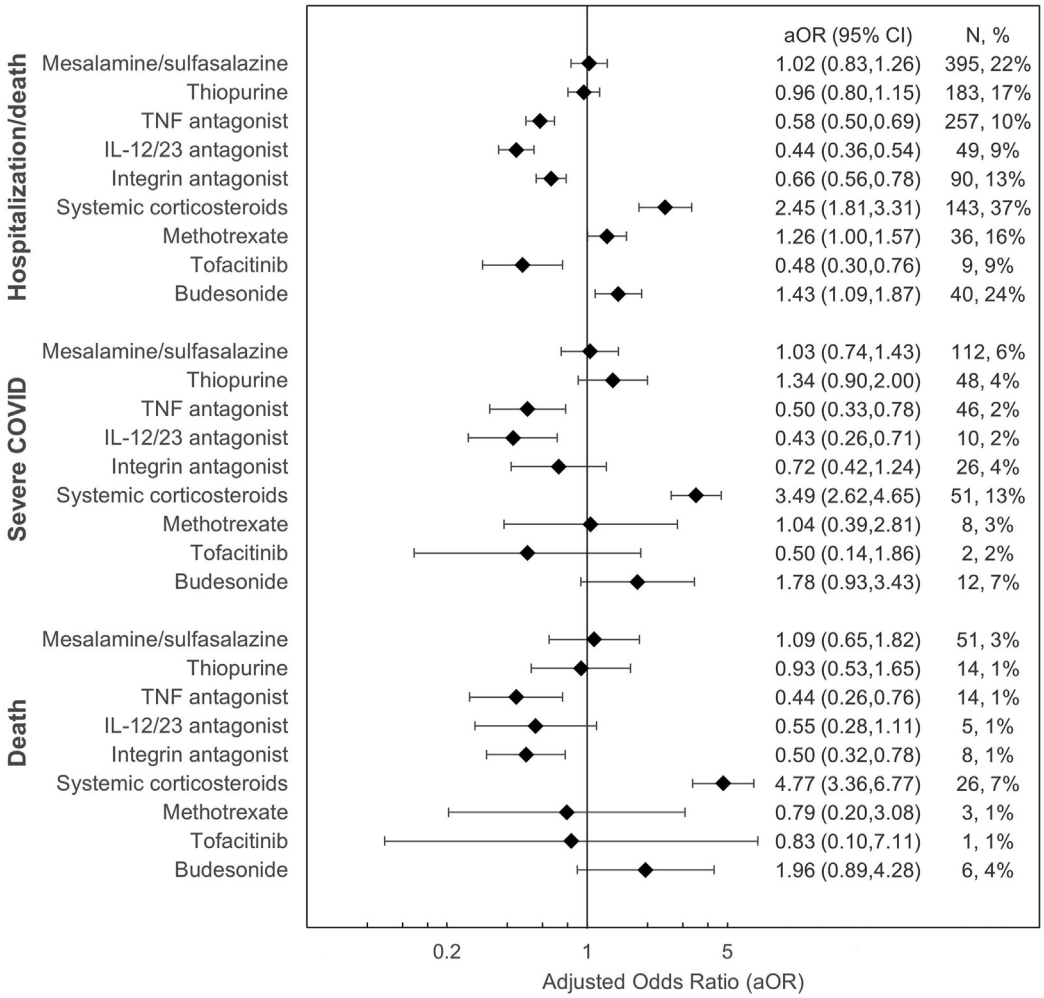

Figure 1. Associations between medication class and COVID-19 outcomes. Each multivariable model included country (as a random effect), days from first case reported, age, sex, race (White vs non-White), ethnicity (Hispanic vs non-Hispanic), disease type (Crohn's disease vs ulcerative colitis or inflammatory bowel disease-unclassified), disease activity by physician global assessment (active vs nonactive), smoking, body mass index ($\geq$30 kg/m^2 vs others), number of comorbidities, and calendar month. Final model was selected using backward selection. IL, interleukin. *Right column:* N and % represent number and proportion of patients with outcome within specified medication class. There were 6105 patients in each model.

with methotrexate was not significantly associated with any adverse outcomes, which is consistent with previous literature on combination therapies and infection risk.[7,8]

Prior SECURE-IBD analyses suggested that mesalamine or sulfasalazine may be associated with increased risk of worse COVID-19 outcomes. This finding appropriately surprised the international gastroenterology community, as mesalamine is considered a low-risk medication with minimal systemic effects.[9] Our updated analysis suggests that mesalamine or sulfasalazine is not associated with worse outcomes. Earlier findings were likely due to reporting bias or reporting delays, as mild cases of COVID-19 among patients on mesalamine or sulfasalazine may have gone unreported if patients did not alert their IBD provider that they had COVID-19. In contrast, the SECURE-IBD registry may have captured a relatively higher proportion of mild cases among patients on biologics, as these medications require more frequent provider–patient contact. As the pandemic has evolved and testing for COVID-19 has become more widespread, patients with mild COVID-19 symptoms are more likely to be tested and therefore reported to SECURE-IBD. With increased reporting of mild cases among patients on mesalamine or sulfasalazine, the earlier associations may have attenuated substantially.

Strengths of this study include the global, collaborative nature of the SECURE-IBD registry, which that includes more than 6000 cases from 6 continents. However, these data are subject to reporting, confirmation, and recall biases, along with residual or unmeasured confounding. Patient self-discontinuation of medications could have introduced measurement bias, likely toward the null for higher-risk medications. Finally, although the registry now includes enough patients to adequately power many analyses, some, including those involving tofacitinib and budesonide, remain underpowered.

Overall, these results suggest that many commonly used IBD medications, including biologics and mesalamine or sulfasalazine, are not associated with severe COVID-19 outcomes,

and that some medications may even exert a protective effect. In addition, TNF antagonist combination therapy with methotrexate might confer lower risk of adverse COVID-19 outcomes than combination with thiopurines. Corticosteroids appear to increase the risk of adverse COVID-19 outcomes and providers should work with patients to wean off corticosteroids when possible. These results support maintaining IBD patients on medications that optimally treat their IBD during the COVID-19 pandemic.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://doi.org/10.1053/j.gastro.2021.09.011.

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SURVEILLANCE EPIDEMIOLOGY OF CORONAVIRUS UNDER RESEARCH EXCLUSION FOR INFLAMMATORY BOWEL DISEASE (SECURE-IBD) RESEARCH GROUP

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Data Availability Statement
Aggregate data are available on the SECURE-IBD website (covidibd.org) and patient-level data are available through an application process noted on website.

Conflicts of interest

These authors disclose the following: Ryan C. Ungaro: served as an advisory board member or consultant for AbbVie, Bristol Myers Squibb, Janssen, Pfizer, and Takeda; received research support from AbbVie, Boehringer Ingelheim, Eli Lilly, and Pfizer. Richard B. Gearry: speaker fees and Scientific Advisory Boards for AbbVie and Janssen. Gilaad G. Kaplan: Honoraria for speaking or consultancy from Abbvie, Janssen, Pfizer, and Takeda; received research support from Ferring, Janssen, Abbvie, GlaxoSmith Kline, Merck, and Shire; ownership of a patent (Treatment of Inflammatory Disorders, Autoimmune Disease, and PBC. UTI Limited Partnership, assignee. Patent WO2019046959A1. PCT/CA2018/051098. September 7. 2018). Michele Kissous-Hunt: speaker/consultant for AbbVie, Janssen, Takeda. James D. 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Supplementary Materials and Methods

The SECURE-IBD database is an international, collaborative effort created to monitor COVID-19 outcomes in patients with IBD. Physicians and other health care providers voluntarily reported cases of polymerase chain reaction–confirmed, antibody-confirmed, or rapid antigen–confirmed COVID-19 occurring in patients with IBD. We instructed health care providers to report cases, regardless of severity, after a minimum of 7 days from symptom onset with sufficient time having passed to observe the disease course through resolution of acute illness or death.

We used REDCap (Research Electronic Data Capture), a secure, web-based electronic data capture tool hosted at the University of North Carolina at Chapel Hill to collect and manage study data. Health care providers recorded the following information: age, country of residence, state of residence (if applicable), year of COVID-19 diagnosis, sex, race, ethnicity, height, weight, patient's diagnosis (Crohn's disease, ulcerative colitis, or IBD-unclassified), disease activity (as defined by physician global assessment), medications at time of COVID-19 diagnosis, whether the patient was hospitalized, gastrointestinal symptoms related to COVID-19, and whether the patient died of COVID-19 or related complications. For hospitalized patients, the name of hospital, length of stay, need for intensive care unit, and need for mechanical ventilation were also recorded. For the current analyses, we used SECURE-IBD data collected from inception (March 13, 2020) through May 21, 2021.

Quality Control

We identified potential duplicate records by matching age, sex, IBD disease type, country, and state (United States only), and confirmed duplicates were excluded. Reports from nonvalid e-mail addresses were flagged as potential errors and we performed a Google search of reporters and practice locations to confirm legitimacy of reports (confirmed as being health care providers). If we could not confirm the reporter was a health care provider, reports from nonvalid e-mail addresses were excluded.

Statistical Analysis

Continuous variables were summarized using means (standard deviations) and categorical variables using proportions. Our outcomes were as follows: hospitalization or death due to COVID-19 or related complications; severe COVID-19, defined as a composite of intensive care unit admission, mechanical ventilation, or death; and death due to COVID-19 or related complications. Medication classes of interest at the time of COVID-19 infection included mesalamine or sulfasalazine, thiopurine (6-mercaptopurine or azathioprine), TNF antagonists, interleukin-12/23 antagonists (ustekinumab), integrin antagonists (vedolizumab), systemic corticosteroids, methotrexate, tofacitinib, and budesonide. Crude data are provided for the overall study population, as well as stratified by medication class. Bivariate comparisons comparing exposure to medication class of interest vs no exposure were assessed using χ^2 or Fisher exact tests, as appropriate.

We first performed multivariable regression modeling with a generalized estimating equation accounting for country as a random effect to analyze the independent effects of each medication class. We included the medication classes of interest listed above as dichotomous variables (yes vs no exposure at time of COVID-19 infection). We considered the following covariates as potential confounders: age, sex, race (White vs non-White), ethnicity (Hispanic vs non-Hispanic), disease type (Crohn's disease vs ulcerative colitis or IBD-unspecified, disease activity by physician global assessment (moderate/severe vs remission/mild), smoking, body mass index, number of comorbidities, and calendar month. We then used backward selection for covariates to obtain the most parsimonious models, using a P value of .1 as a significance cutoff, with all medication classes of interest being forced into the models. Using an otherwise identical model, we also evaluated interaction terms between TNF antagonists and methotrexate and between TNF antagonists and thiopurines, respectively, using a P value of .1 as a significance cutoff.

To further examine the association of different classes of biologic agents with COVID-19 outcomes using an active comparator design, we then restricted our data set to only patients on a biologic (any TNF, interleukin-12/23, or integrin antagonist) at the time of COVID-19 infection. We excluded patients on tofacitinib, cyclosporine, and tacrolimus from this analysis. For the outcomes of severe COVID-19 and hospitalization or death, we then performed multivariable regression modeling with a generalized estimating equation accounting for country as a random effect. Our primary exposure was a 3-level variable including TNF antagonist use (referent group), interleukin-12/23 antagonist use, and integrin antagonist use. For this model, we considered the above covariates as potential confounders, in addition to mesalamine or sulfasalazine use, thiopurine use, systemic corticosteroid use, methotrexate use, budesonide use, and calendar month. Again, we used backward selection to obtain a parsimonious model forcing in biologic medications. For the outcome of death, we only performed unadjusted comparisons between patients on different biologic classes due to low event rates and risk of model overfitting.

Finally, to further evaluate the association between mesalamine and COVID-19 severity, we incorporated the covariate mesalamine or sulfasalazine use (vs nonuse) into the above biologic-only models. This allowed us to estimate the independent effect of mesalamine in a more homogeneous population of biologic users, while adjusting for the specific biologic agent and other potential confounders.

All data were prepared and analyzed using SAS, version 9.3 (SAS Institute, Cary, NC). Two-sided P values $\leq$.05 were considered statistically significant. All authors had access to

the study data and reviewed and approved the final manuscript. All data collected in the SECURE-IBD database is de-identified, in accordance with the Health Insurance Portability and Accountability Act Safe Harbor De-Identification standards. The UNC-Chapel Hill Office for Human Research Ethics has determined that the storage and analysis of de-identified data for the SECURE-IBD database does not constitute human subjects research as defined under federal regulations (45 CFR 46.102 and 21 CFR 56.102) and does not require Institutional Review Board approval.

Supplementary Table 1. Patient Population Characteristics Stratified by Medication Type

Characteristics	Overall	Sulfasalazine/ mesalamine	*P* value	6-mercaptopurine/ azathioprine	*P* value	TNF antagonists	*P* value
Total no. of patients	6144	1818	—	1072	—	2620	—
Age			<.001				<.001
Mean (SD)	40.0 (17.2)	44.0 (17.7)		39.6 (15.7)	.511	35.9 (16.1)	
Median (IQR)	38.0 (26.0–52.0)	43.0 (30.0–56.0)		38.0 (28.0–50.0)		33.0 (23.0–47.0)	
Sex							
Female	3097 (50)	909 (50)	.679	515 (48)	.088	1271 (49)	.010
Disease type			<.001		.006		<.001
Crohn's disease	3514 (57)	476 (26)		657 (61)		1839 (70)	
Ulcerative colitis	2472 (40)	1287 (71)		398 (37)		735 (28)	
IBD unspecified	118 (2)	48 (3)		13 (1)		32 (1)	
IBD disease activity			<.001		.149		<.001
Remission	3385 (55)	895 (49)		616 (57)		1590 (61)	
Mild	1326 (22)	463 (25)		216 (20)		515 (20)	
Moderate/severe	1142 (19)	396 (22)		200 (19)		386 (15)	
Unknown	291 (5)	64 (4)		40 (4)		129 (5)	
Current smoker	238 (4)	52 (3)	.008	46 (4)	.436	112 (4)	.160
No. of comorbidities			<.001		.205		<.001
0	4377 (71)	1196 (66)		789 (74)		2008 (77)	
1	1229 (20)	418 (23)		193 (18)		474 (18)	
2	324 (5)	107 (6)		58 (5)		100 (4)	
3+	214 (3)	97 (5)		32 (3)		38 (1)	

Characteristic	IL-12/IL-23 antagonists	*P* value	Integrin antagonists	*P* value	Oral/parenteral steroids	*P* value
Total no. of patients	573	—	675	—	392	—
Age		.703		.004		.147
Mean (SD)	39.7 (15.7)		41.8 (17.8)		41.2 (18.4)	
Median (IQR)	39.0 (26.0–51.0)		39.0 (28.0–53.0)		39.0 (26.0–54.0)	
Sex						
Female	326 (57)	.001	337 (50)	.791	186 (47)	.226
Disease type		<.001		<.001		<.001
Crohn's disease	492 (86)		299 (44)		153 (39)	
Ulcerative colitis	70 (12)		355 (53)		224 (57)	
IBD unspecified	10 (2)		16 (2)		14 (4)	
IBD disease activity		<.001		.187		<.001
Remission	239 (42)		354 (52)		50 (13)	
Mild	148 (26)		143 (21)		68 (17)	
Moderate/severe	144 (25)		146 (22)		264 (67)	
Unknown	42 (7)		32 (5)		10 (3)	
Current smoker	24 (4)	.682	21 (3)	.276	20 (5)	.193
No. of comorbidities		.290		.196		<.001
0	393 (69)		467 (69)		232 (59)	
1	132 (23)		134 (20)		94 (24)	
2	30 (5)		45 (7)		40 (10)	
3+	18 (3)		29 (4)		26 (7)	

Characteristic	Methotrexate	*P* value	Budesonide	*P* value	Tofacitinib	*P* value
Total no. of patients	233		168		97	
Age		.181		.196		.187
Mean (SD)	38.5 (19.2)		41.7 (17.3)		37.6 (15.9)	
Median (IQR)	38.0 (20.0–53.5		41.0 (28.0–55.0)		35.5 (23.5–48.0)	

Supplementary Table 1. Continued

Characteristic	Methotrexate	*P* value	Budesonide	*P* value	Tofacitinib	*P* value
Sex		.645		.837		0.425
Female	114 (49)		86 (51)		45 (46)	
Disease type		<.001		.514		<.001
Crohn's disease	178 (76)		104 (62)		9 (9)	
Ulcerative colitis	48 (21)		61 (36)		85 (88)	
IBD unspecified	5 (2)		3 (2)		3 (3)	
IBD disease activity		.512		<.001		.001
Remission	137 (59)		30 (18)		39 (40)	
Mild	46 (20)		57 (34)		27 (28)	
Moderate/severe	37 (16)		72 (43)		30 (31)	
Unknown	13 (6)		9 (5)		1 (1)	
Current smoker	10 (4)	.736	5 (3)	.541	2 (2)	.351
No. of comorbidities		.322		.044		.335
0	154 (66)		107 (64)		77 (79)	
1	56 (24)		44 (26)		15 (15)	
2	15 (6)		7 (4)		3 (3)	
3+	8 (3)		10 (6)		2 (2)	

NOTE. The n (%) from each subcategory may not add up to the exact number of total reported cases due to missing values or non-mutually exclusive variables. *P* values compare those taking drug class of interest with those not taking drug class.
IL, interleukin; IQR, interquartile range; SD, standard deviation.

Supplementary Table 2. Associations Between Biologic Class and COVID-19 Outcomes Among Patients Receiving Biologic Therapy

Medication classes for each outcome model	Total no. in model	Experienced outcome of interest, n (%)	aOR	Lower 95% CI	Upper 95% CI	*P* value
Total no. of patients in the model	3817	—	—	—	—	—
Hospitalization or death	3817	392 (10.2)	—	—	—	—
TNF antagonist (Ref)	2596	256 (9.9)	Ref			
IL-12/23 antagonist	565	47 (8.3)	0.73	0.61	0.89	.001
Integrin antagonist	656	89 (13.6)	1.15	0.96	1.37	.12
Severe COVID-19	3817	82 (7.6)	—	—	—	—
TNF antagonist (Ref)	2596	46 (1.8)	Ref			
IL-12/23 antagonist	565	10 (1.8)	0.85	0.56	1.28	.43
Integrin antagonist	656	26 (4.0)	1.25	0.56	2.80	.59
Death[a]	3826	27 (0.7)	—	—	—	—
TNF antagonist (Ref)	2596	14 (0.5)	—	—	—	—
IL-12/23 antagonist	565	5 (0.9)	—	—	—	—
Integrin antagonist	656	8 (1.2)	—	—	—	—

NOTE. Each model included country (as a random effect), days from first case reported, age, sex, race (White vs non-White), ethnicity (Hispanic vs non-Hispanic) disease type (Crohn's disease vs ulcerative colitis/IBD-unclassified), disease activity by physician global assessment (active vs nonactive), smoking, body mass index ($\geq$30 kg/m^2 vs others), number of comorbidities and calendar month. Final model was selected using backward selection.
IL, interleukin; Ref, referent.
[a]No adjusted models were performed for outcome of death due to low event rate.