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.

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Impact of Anti-Tumor Necrosis Factor and Thiopurine Medications on the Development of COVID-19 in Patients With Inflammatory Bowel Disease: A Nationwide Veterans Administration Cohort Study

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The recent outbreak of the novel coronavirus disease 2019 (COVID-19) has become a pandemic and is threatening global health.[1] The highest number of COVID-19 confirmed cases were reported in the United States, with 1.47 million confirmed cases and 89,272 deaths as of May 19, 2020.[2]

Inflammatory bowel disease (IBD) is primarily treated by immunosuppressive medications, which can put patients at risk of developing infectious complications including viral infections.[3] Therefore, it is important to evaluate the risk factors of COVID-19 in the IBD population, especially the impact of immunosuppression on incidence. Only limited data are available in the current literature on this topic.

Our aim was to evaluate the impact of anti-tumor necrosis factor (TNF) and thiopurines on the development of COVID-19 in a nationwide cohort of IBD patients in the Veterans' Affairs Healthcare System. The Veterans' Affairs Healthcare System is the largest integrated healthcare system in the United States, serving up to 9 million veterans each year.[4]

Methods

We conducted a nationwide retrospective cohort study from January 1, 2020 to May 15, 2020 using US national Veterans' Affairs Healthcare System data from the Veterans Administration (VA) Informatics and Computing Infrastructure. Eligible IBD patients were identified from the VA Informatics and Computing Infrastructure database using a previously validated algorithm[5] (see Supplementary Methods).

The main exposures were the use of thiopurines and anti-TNF agents as of January 1, 2020. For thiopurines, we looked at patients' prescription histories on and before January 1, 2020 to see whether they had an active prescription as of January 1, 2020. We assumed an anti-TNF injection can be effective for 3 months. Thus, we looked to see whether a patient had an anti-TNF injection in the 3 months before January 1, 2020. As a sensitivity analysis, we evaluated a subgroup of anti-TNF users who received the medication as an infusion (ie, Remicade, Janssen, PA; Inflectra, Celltrion, South Korea; Renflexis, Merck, PA). Because these patients had to come to the hospital every 4 to 8 weeks to get an infusion, they were theoretically more likely to undergo COVID-19 testing than other IBD patients. If the COVID-19 incidence was not higher in this group than in other groups, it would provide additional reassurance that anti-TNF use was not associated with the risk of COVID-19.

The outcome was incident cases of COVID-19 from January 1, 2020 to May 15, 2020, which was defined as meeting at least 1 of 2 criteria within the patient chart: a positive lab finding within the VA system and/or a patient note reflecting a positive test from outside the VA. Records were extracted, and then charts were reviewed individually for accuracy. Patients were considered COVID-19 negative if they were not tested or had a negative test. We performed a logistic regression using the incident COVID-19 as the outcome and the 2 medication use indicators (ie, thiopurines and anti-TNF separately) as main exposures, adjusting for patient age and the comorbid conditions based on the Charlson comorbidity index.

Results

Among 37,857 IBD patients, 36 developed incident COVID-19 during the study period. The overall mean age was 63.0 (standard deviation [SD], 15.8), and the mean Charlson comorbidity index was 1.2 (SD, 1.8). Compared with those without COVID-19, patients with COVID-19 were younger (mean age, 60.9 [SD, 17.1] vs 63.0 [SD, 15.8]; $P = .4$) and had higher Charlson comorbidity index scores (mean, 2.2 [SD, 3.3] vs 1.2 [SD, 1.8]; $P < .001$). Among the 2391 IBD patients who were on thiopurines on January 1, 2020, 2 had incident COVID-19. Among the 4920 patients who were on anti-TNF, 3 patients developed COVID-19. Table 1 shows the cumulative incidence in the overall study cohort and the respective exposure groups. Among the 1759 patients who were on an infusible anti-TNF at

Abbreviations usedin the paper: **COVID-19, coronavirus disease 2019; IBD, inflammatory bowel disease; SD, standard deviation; TNF, tumor necrosis factor; VA, Veterans Administration.**

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Table 1. Characteristics of the Cohort and Incident Rate of COVID-19

	Incident COVID-19		Incidence Rate per 1000 IBD Patients	
	Yes	No		*P*
Overall	36	37,821	0.95	
Thiopurine yes	2	2389	0.84	>.999
Thiopurine no	34	35,432	0.96	
Anti-TNF yes	3	4917	0.61	.618
Anti-TNF no	33	32,904	1	

baseline, there was 1 case of COVID-19, yielding an incidence (0.57/1000 patients) numerically lower than that in the anti-TNF nonusers.

In the adjusted logistic regression model, neither thiopurines (odds ratio, 0.962; 95% confidence interval, 0.230–4.027; $P = .9577$) nor anti-TNF (odds ratio, 0.581; 95% confidence interval, 0.174–1.939; $P = .3774$) was associated with a significant increased risk of COVID-19. The Charlson comorbidity index (odds ratio, 1.240; 95% confidence interval, 1.106–1.3912; $P = .0002$) was significantly associated with the risk of contracting COVID-19.

Discussion

This study is the first report to evaluate the impact of the most commonly used immunosuppressive medications on the incidence of COVID-19 infection among IBD patients. In this large nationwide VA cohort among IBD patients, we found that the use of anti-TNFs or thiopurines was not associated with the development of COVID-19 infection.

A recent study from Spain demonstrated that IBD patients did not have an increased risk of COVID-19 infection and associated mortality.[6] Two other studies from New York and an international registry demonstrated that baseline biologics use did not cause a worse outcome of COVID-19 infection.[7,8] However, neither evaluated the impact of immunosuppression on the development of COVID-19. It is important for both gastroenterologists and IBD patients to understand the association so they can decide whether such medications should be continued during the pandemic.

Our result provides the evidence and further supports the recommendation from major guidelines (AGA and International Organization for the Study of Inflammatory Bowel Disease) that IBD patients should continue their immunosuppressant treatment while maintaining preventive measures. Other risk factors associated with COVID-19 infection among our IBD population were higher comorbidities and white ethnicity.

Major strengths of our study were the use of a nationwide study cohort and laboratory-confirmed COVID-19 infection through an individual chart review. Every patient in the VA has a COVID-19 status determination in his or her chart (ie, positive, negative, or not tested). The limitation of our study is that patients who were not tested may be positive. However, patients on immunosuppressive medications are closely followed, especially those on infusible anti-TNF who must come to the hospital for each infusion every 4 to 8 weeks, answer a COVID-19 questionnaire, and undergo a physical exam. Even patients tested outside the VA have their results documented. Furthermore, the incidence of COVID-19 among those on infusible anti-TNF was numerically similar to other anti-TNF users and lower than that among anti-TNF nonusers. Because infusible anti-TNF users were probably most likely to undergo severe acute respiratory syndrome–coronavirus-2 testing, these results provide additional support for our conclusion.

In conclusion, using a large nationwide VA database, we found that anti-TNF medications or thiopurines were not associated with an increased risk of developing COVID-19 infection. This reinforces the recommendation that IBD patients should continue to use anti-TNF medications and thiopurines.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2020.05.065.

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Conflicts of interest
These authors disclose the following: Nabeel Khan has received research funding from Pfizer, Luitpold, and Takeda Pharmaceuticals. James Lewis has served as a consultant for Merck, AbbVie, Lilly, Janssen, Johnson & Johnson Consumer Inc, and Takeda; has served on Data Safety Monitoring Boards for Pfizer, Gilead, and UCB; and has received research support from Takeda and Nestle Health Science.

Supplementary Methods

To be included in the study, patients had to meet all 4 criteria: (1) 1 inpatient or outpatient International Classification of Diseases, 9th or 10th revision, diagnosis code for ulcerative colitis (555.xx, K50.xx) and/or Crohn's disease (556.xx, K51.xx); (2) at least 1 outpatient, inpatient, or telemedicine visit in the Veterans Administration healthcare system between January 1, 2020 and May 15, 2020; (3) at least 1 outpatient pharmacy claim for any of the following inflammatory bowel disease medications: 5-amino salicylate compounds, thiopurines, anti-tumor necrosis factor agents, combination of thiopurines and anti-tumor necrosis factor, and vedolizumab); and (4) at least 2 different prescriptions of 1 distinct inflammatory bowel disease medications from criteria 3.