



Original Article

# The Impact of Vedolizumab on COVID-19 Outcomes Among Adult IBD Patients in the SECURE-IBD Registry

Manasi Agrawal,<sup>a,○</sup> Xian Zhang,<sup>b</sup> Erica J. Brenner,<sup>b</sup> Ryan C. Ungaro,<sup>a</sup> Michael D. Kappelman,<sup>b</sup> Jean-Frederic Colombel<sup>a,○</sup>

<sup>a</sup>The Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

<sup>b</sup>Department of Pediatrics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Corresponding author: Manasi Agrawal, MD, The Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, New York, NY 10029, USA. Email: [manasi.agrawal@mountsinai.org](mailto:manasi.agrawal@mountsinai.org)

## Abstract

**Background.** The impact of immune-modifying therapies on outcomes of coronavirus disease 2019 [COVID-19] is variable. The purpose of this study was to determine the impact of vedolizumab [VDZ], a gut-selective anti-integrin, on COVID-19 outcomes in inflammatory bowel disease [IBD] patients.

**Methods.** Using data from the Surveillance of Coronavirus Under Research Exclusion for IBD [SECURE-IBD], an international registry of IBD patients with confirmed COVID-19, we studied the impact of VDZ on COVID-19 hospitalization and severe COVID-19 [intensive care unit stay, mechanical ventilation and/or death].

**Results.** Of 3647 adult patients on any IBD medication in the registry, 457 [12.5%] patients were on VDZ. On multivariable analyses using backward selection of covariates, VDZ use was not associated with hospitalization or severe COVID-19 when compared with patients on all other medications (adjusted odds ratio [aOR] 0.87; 95% confidence interval [CI] 0.71, 1.1 and aOR 0.95; 95% CI 0.53, 1.73, respectively). On comparing VDZ monotherapy to anti-tumour necrosis factor [anti-TNF] monotherapy, the odds for hospitalization, but not severe COVID-19, were higher [aOR CI 1.39; 95% CI 1.001, 1.90 and aOR 2.92; 95% CI 0.98, 8.71, respectively]. In an exploratory analysis, VDZ monotherapy, compared to anti-TNF monotherapy, was associated with new-onset gastrointestinal symptoms at the time of COVID-19, especially among patients whose IBD was in remission.

**Conclusions.** COVID-19 outcomes among IBD patients on VDZ are comparable to those on all other therapies. Hospitalization, but not severe COVID-19, is more likely with VDZ monotherapy than with anti-TNF monotherapy. Overall, VDZ appears to be safe in IBD patients with COVID-19.

**Key Words:** Inflammatory bowel disease; Crohn's disease; ulcerative colitis; coronavirus disease 2019; vedolizumab; outcomes

## 1. Introduction

The coronavirus disease 2019 [COVID-19] pandemic due to the severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] has led to an unrelenting pandemic, affecting over 85 million persons globally with 2.32 million deaths as of February 8, 2021.<sup>1</sup> Comorbid

disease is a risk factor for worse outcomes,<sup>2</sup> and medications that modulate the immune system can have varying effects on COVID-19, depending on their mechanism of action. SARS-CoV-2, in addition to infecting the respiratory epithelium, can also infect the gastrointestinal [GI] tract mucosa via angiotensin converting enzyme

2 [ACE2] and transmembrane protease, serine 2 [TRMPRSS].<sup>3</sup> In addition to upper and lower respiratory symptoms, COVID-19 can be associated with GI symptoms such as anorexia, vomiting and diarrhoea.<sup>4</sup>

Vedolizumab [VDZ], a monoclonal antibody against  $\alpha_4\beta_7$  integrin, blocks the interaction between  $\alpha_4\beta_7$  integrin on CD4+ T cells and its receptor mucosal addressin cell adhesion molecule [MAdCAM] on high endothelial venules [HEVs] in the GI tract, with downstream blockage of lymphocyte trafficking into gut-associated lymphoid tissue [GALT].<sup>5</sup> VDZ is approved for the treatment of moderate–severe ulcerative colitis [UC] and Crohn's disease [CD] in adult patients.<sup>5,6</sup> Given its gut-specific mechanism of action, VDZ does not impact systemic immunity significantly and has a favourable safety profile.<sup>7</sup> However, VDZ is associated with an increased risk of *Clostridium difficile* and other intestinal infections.<sup>8</sup> Recent data report that VDZ may modulate ACE2 expression in the GI tract.<sup>9</sup>

We aimed to determine the outcomes of COVID-19 infection among inflammatory bowel disease [IBD] patients on VDZ compared to other IBD therapies. We also determined the proportion of IBD patients on VDZ who had new-onset GI symptoms at the time of COVID-19.

## 2. Methods

### 2.1. Data source

The Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease [SECURE-IBD] registry is a global, web-based, collaborative database, which was established at the start of the COVID-19 pandemic in March 2020 to study characteristics and outcomes in IBD patients with confirmed COVID-19, as well as the impact of IBD therapies.<sup>10</sup> Healthcare providers voluntarily report confirmed COVID-19 cases using a REDCap [Research Electronic Data Capture] survey at our website covidibd.org, hosted at the University of North Carolina. SECURE-IBD collects only de-identified data, and the Office of Human Research Ethics at the University of North Carolina, Chapel Hill, determined that the storage and analysis of de-identified data for this project did not constitute human subjects research. Details of the data collection and quality control are described in detail in a previous publication.<sup>10</sup>

### 2.2. Statistical analysis

Using data reported up to January 26, 2021, we compared baseline and demographic characteristics, and COVID-19 outcomes of adult IBD patients on VDZ therapy to those on all other IBD medications. As VDZ is approved for treatment of adult IBD patients only, we excluded patients  $\leq 18$  years of age from this analysis. Our primary outcome was adverse COVID-19, defined as hospitalization or death due to COVID-19. Our secondary outcome was severe COVID-19 defined as a composite of intensive care unit [ICU] admission, mechanical ventilation and/or death. We compared all outcomes among adult patients on VDZ vs all other IBD therapies in the registry [VDZ vs non-VDZ]. As the category of all other medications is heterogeneous, we additionally compared VDZ monotherapy with anti-tumour necrosis factor [TNF] monotherapy, which is the largest homogeneous category of reported medications in the registry. Lastly, as an exploratory analysis, we compared the frequency of GI symptoms due to COVID-19 between VDZ and non-VDZ groups as well as between VDZ monotherapy and anti-TNF monotherapy groups.

We analysed categorical variables using chi-square or Fisher's exact tests, and continuous variables using Wilcoxon rank-sum or *t*-test when applicable. Using generalized estimating equations [GEEs] to account for clustering by country, and applying the logit link function, we estimated the odds of each of the two binary outcomes, adverse and severe COVID-19. In addition to the primary predictor variable medication group, covariates in each of the models were determined by backward selection to obtain the most parsimonious models from clinically relevant covariates determined a priori, or if associated with medication group at  $p \leq 0.10$  on bivariate analysis. Considered covariates included age, sex, race/ethnicity, IBD type, IBD activity (remission vs active disease, based on physician global assessment [PGA]) and comorbidities [0, 1,  $\geq 2$ ]. Additionally, as IBD activity may modify the association between treatment and each study outcome, and treatment and GI symptoms, we repeated all analyses stratified by IBD activity categorized as remission vs active disease. *p* values  $\leq 0.05$  were considered statistically significant for all analyses. Data preparation and analyses were conducted using SAS version 9.3 [SAS Institute].

## 3. Results

### 3.1. Cohort baseline characteristics

Of 3647 patients  $\geq 18$  years old in the SECURE-IBD registry on one or more IBD medication, 457 [12.5%] patients were reported to be on VDZ, of whom 334 [9.2%] were on VDZ monotherapy. In total, 1043 [28.6%] patients were on an anti-TNF monotherapy. Of these, 536 [51.4%] patients were on an intravenous anti-TNF while the remaining 507 [48.6%] patients were on a subcutaneous anti-TNF. In total, 354 [9.7%] patients were on combination therapy with an anti-TNF and an immunomodulator. The baseline demographic and clinical characteristics of all patients in VDZ vs non-VDZ groups are reported in [Table 1](#). Compared to the non-VDZ group, patients on VDZ were slightly older [mean age 43.8 years vs 42.0 years,  $p = 0.03$ ], more likely to be white [86.0% vs 81.2%,  $p = 0.01$ ] and less likely to be Asian or Hispanic [1.8% vs 5.0%,  $p = 0.002$  and 10.9% vs 14.9%,  $p < 0.001$ , respectively]. Of patients on VDZ, 209 [45.7%] were from the USA, whereas of those on other therapies, 1110 [34.8%] were from the USA [ $p < 0.001$ ]. Compared to the non-VDZ group, more patients in the VDZ group had UC [53.8% vs 40.2%,  $p < 0.001$ ]. Other baseline and clinical characteristics were similar between the two groups. Baseline characteristics of VDZ monotherapy compared to anti-TNF monotherapy are reported in [Supplementary Table 1](#).

### 3.2. COVID-19 outcomes in adult IBD patients on VDZ compared with other therapies

In total, 664 hospitalization and 166 severe COVID events occurred in the cohort. Compared to non-VDZ use, VDZ use was not associated with hospitalization (adjusted odds ratio [aOR] 0.87; 95% confidence interval [CI] 0.71, 1.1, [Table 2](#)) after adjusting for age, Asian and Other race/ethnicity groups compared to non-Hispanic White group, IBD type, sex and number of comorbidities. Similarly, compared to non-VDZ use, VDZ use was not associated with severe COVID-19 [aOR 0.95; 95% CI 0.53, 1.73] on adjusting for age, IBD type, comorbidities and IBD activity. Upon stratifying by IBD activity [active disease vs remission], the results were not significantly altered. In the stratum of active IBD, compared to non-VDZ use, VDZ use was not associated with hospitalization [aOR 0.95; 95% CI 0.72, 1.25] or severe COVID-19 [aOR 0.91; 95% CI 0.46, 1.81]. Similarly, in the stratum of IBD

**Table 1.** Demographic and clinical characteristics of IBD patients on vedolizumab compared with other IBD therapies in the SECURE-IBD registry

Characteristic <sup>a,b</sup>	All patients on ≥1 medication and ≥18 years of age		Vedolizumab		Other IBD therapy		p-value <sup>c</sup>
	N	%	N	%	N	%	
Total number of patients	3647		457	12.5%	3190	87.5%	
Age							
Mean [SD]	42.2	16.4	43.8	17.82	42.0	16.12	0.031
Median [IQ range]	40	29.0, 53.0	40	29.0, 55.0	40	29.0, 53.0	0.137
Female sex	1847	50.6%	239	52.3%	1608	50.4%	0.450
Race							
Reported at least selected one race	3620	99.3%	454	99.3%	3166	99.2%	1.000
White	2983	81.8%	393	86.0%	2590	81.2%	0.013
Black or African American	175	4.8%	22	4.8%	153	4.8%	0.987
American Indian/Native Alaskan	8	0.2%	0	0.0%	8	0.3%	0.607
Asian	167	4.6%	8	1.8%	159	5.0%	0.002
Native Hawaiian/Pacific Islander	1	0.0%	0	0.0%	1	0.0%	1.000
Other	205	5.6%	18	3.9%	187	5.9%	0.095
Unknown	184	5.0%	20	4.4%	164	5.1%	0.485
Hispanic/Latino							<0.001
Yes	524	14.4%	50	10.9%	474	14.9%	
No	2493	68.4%	349	76.4%	2144	67.2%	
Unknown	403	11.1%	31	6.8%	372	11.7%	
Missing	227	6.2%	27	5.9%	200	6.3%	
Reporting country							
USA	1319	36.2%	209	45.7%	1110	34.8%	<0.001
Spain	279	7.7%	24	5.3%	255	8.0%	0.039
Russian Federation	261	7.2%	37	8.1%	224	7.0%	0.405
UK	156	4.3%	16	3.5%	140	4.4%	0.380
France	106	2.9%	10	2.2%	96	3.0%	0.328
Italy	150	4.1%	23	5.0%	127	4.0%	0.290
Brazil	101	2.8%	9	2.0%	92	2.9%	0.265
Iran, Islamic Republic of	51	1.4%	0	0.0%	51	1.6%	0.006
Belgium	136	3.7%	22	4.8%	114	3.6%	0.191
Argentina	59	1.6%	4	0.9%	55	1.7%	0.179
Germany	99	2.7%	20	4.4%	79	2.5%	0.019
Turkey	73	2.0%	7	1.5%	66	2.1%	0.443
Netherlands	158	4.3%	13	2.8%	145	4.5%	0.095
Canada	63	1.7%	7	1.5%	56	1.8%	0.731
Other	636	17.4%	56	12.3%	580	18.2%	0.002
Disease type:							
Crohn's disease	2049	56.2%	201	44.0%	1848	57.9%	<0.001
Ulcerative colitis	1527	41.9%	246	53.8%	1281	40.2%	
IBD unspecified	57	1.6%	8	1.8%	49	1.5%	
IBD disease activity <sup>d</sup>							
Remission	1982	54.3%	228	49.9%	1754	55.0%	0.149
Mild	792	21.7%	104	22.8%	688	21.6%	

**Table 1. Continued**

Characteristic <sup>a,b</sup>	All patients on ≥1 medication and ≥18 years of age		Vedolizumab		Other IBD therapy		p-value <sup>c</sup>
	N	%	N	%	N	%	
Moderate/severe	720	19.7%	103	22.5%	617	19.3%	
Smoking	145	4.0%	12	2.6%	133	4.2%	0.114
Comorbidity summary score							0.194
0	2517	69.0%	320	70.0%	2197	68.9%	
1	772	21.2%	83	18.2%	689	21.6%	
2	208	5.7%	33	7.2%	175	5.5%	
≥3	150	4.1%	21	4.6%	129	4.0%	
Cardiovascular disease	206	5.6%	25	5.5%	181	5.7%	0.860
Diabetes	178	4.9%	23	5.0%	155	4.9%	0.872
Asthma	177	4.9%	29	6.3%	148	4.6%	0.112
COPD	50	1.4%	7	1.5%	43	1.3%	0.752
Other chronic lung disease	50	1.4%	5	1.1%	45	1.4%	0.586
Hypertension	378	10.4%	41	9.0%	337	10.6%	0.296
Cancer	56	1.5%	9	2.0%	47	1.5%	0.420
History of stroke	33	0.9%	3	0.7%	30	0.9%	0.791
Chronic renal disease	71	1.9%	13	2.8%	58	1.8%	0.137
Chronic liver disease	105	2.9%	17	3.7%	88	2.8%	0.250
Other comorbidity	412	11.3%	58	12.7%	354	11.1%	0.314
BMI							0.280
BMI < 30	2440	66.9%	320	70.0%	2120	66.5%	
BMI ≥ 30	609	16.7%	72	15.8%	537	16.8%	
Missing	598	16.4%	65	14.2%	533	16.7%	

Abbreviations: COVID-19 = Coronavirus Disease 2019; ICU = intensive care unit; COPD = chronic obstructive pulmonary disease; IBD = inflammatory bowel disease; PSC = primary sclerosing cholangitis; NAFLD = non-alcoholic fatty liver disease.

<sup>a</sup>Unless otherwise specified, percentages do not include missing values or 'unknown'. For all characteristics, unless noted above, less than 4% of data were missing and unknown, respectively, for each category.

<sup>b</sup>Percentages and *n* from each subcategory may not add up to the exact number of total reported cases due to missing values and/or non-mutually exclusive variables.

<sup>c</sup>p-values for tests comparing variables between vedolizumab and other medication groups.

<sup>d</sup>By physician global assessment [PGA] at the time of COVID-19 infection.

**Table 2.** Multivariable regression analyses with backward selection of covariates for COVID-19 outcomes by medication class from adult cases in the SECURE-IBD registry

Outcome	Adjusted OR [95% CI]	<i>p</i> value
<i>Hospitalization</i>		
VDZ vs all other IBD therapies <sup>a</sup>	0.87 [0.72, 1.06]	0.17
<b>VDZ monotherapy vs anti-TNF monotherapy<sup>b</sup></b>	<b>1.38 [1.001, 1.90]</b>	<b>0.049</b>
<i>Severe COVID-19</i>		
VDZ vs all other IBD therapies <sup>c</sup>	0.95 [0.53, 1.73]	0.88
<b>VDZ monotherapy vs anti-TNF monotherapy<sup>d</sup></b>	<b>2.92 [0.98, 8.71]</b>	<b>0.055</b>

Abbreviations: COVID-19 = coronavirus disease 2019; SECURE-IBD = Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease; VDZ = vedolizumab; TNF = tumor necrosis factor; OR = odds ratio.

Statistically significant associations are in bold.

<sup>a</sup>Adjusted for age, sex, Asian and other race/ethnicity category [reference: non-Hispanic White], IBD type, active IBD (reference: remission; based on Physician Global Assessment [PGA]) and number of comorbid conditions [1, ≥2; reference: 0].

<sup>b</sup>Adjusted for age and IBD activity, Asian and other race/ethnicity category and number of comorbid conditions.

<sup>c</sup>Adjusted for age, IBD type, IBD activity and number of comorbid conditions.

<sup>d</sup>Adjusted for age and number of comorbid conditions.

remission, compared to non-VDZ use, VDZ was not associated with hospitalization [aOR 0.84; 95% CI 0.61, 1.15] or severe COVID-19 [aOR 1.40; 95% CI 0.53, 3.67].

Upon comparing to anti-TNF monotherapy, VDZ monotherapy was associated with a higher odds of hospitalization [aOR 1.38; 95% CI 1.001, 1.90, Table 2] after adjusting for age, number of comorbidities, and Asian and Other races compared with non-Hispanic White group and IBD activity. The magnitude and direction of the association of VDZ monotherapy, compared to anti-TNF monotherapy, with severe COVID-19 outcomes were similar but not statistically significant after adjusting for age and number of comorbidities [aOR 2.92; 95% CI 0.98, 8.71]. Upon stratifying by IBD activity, results remained similar in magnitude and direction. The association of VDZ monotherapy with hospitalization was not significant in the stratum of active IBD [aOR 1.32; 95% CI 0.75, 2.33], but it was significant in the stratum of IBD in remission [aOR 1.54; 95% CI 1.05, 2.25]. The number of severe COVID-19 outcomes in the VDZ and anti-TNF monotherapy groups were too few for stratified analyses.

### 3.3. GI symptoms due to COVID-19

All GI symptoms [nausea, vomiting, abdominal pain, diarrhoea and 'other'] were comparable between VDZ and non-VDZ groups [ $p > 0.05$ ], Table 3]. On stratifying by IBD activity, all GI symptoms were comparable in both strata except nausea, which was more common with VDZ in those with IBD in remission [8.8% vs 4.4%,  $p = 0.004$ ].

On comparing VDZ monotherapy with anti-TNF monotherapy, all GI symptoms except other symptoms were more common with VDZ monotherapy [ $p < 0.05$  for each comparison]. When we stratified these comparisons by IBD activity, among patients with

active IBD, all GI symptoms were similar in frequency with VDZ and anti-TNF monotherapies. Among IBD patients in remission, all GI symptoms, except vomiting and other, were more common with VDZ monotherapy [ $p \leq 0.001$  for each comparison except vomiting and other].

## 4. Discussion

In this analysis of 3647 adult patients from 63 countries in the SECURE-IBD registry, we report COVID-19 outcomes among 457 patients on VDZ therapy compared to other IBD therapies. Overall, we observed comparable COVID-19 outcomes among IBD patients on VDZ vs those on all other therapies. New-onset GI symptoms were reported in 29.6% of patients on VDZ monotherapy and 19.2% of patients on anti-TNF monotherapy. Hospitalization and the development of GI symptoms were more frequently observed with VDZ monotherapy than with anti-TNF monotherapy.

Hospitalization and severe COVID-19 outcomes were comparable among VDZ and non-VDZ users, unchanged upon stratification by IBD activity. These findings are consistent with other data on COVID-19 outcomes among IBD patients on VDZ, although there are few such patients in each of these analyses. Lukin et al. reported in a case-control study that COVID-19 outcomes of patients on all biologic therapies, including VDZ [ $n = 10$ ], were comparable, although VDZ was not studied individually.<sup>11</sup> Similarly, Axelrad et al. reported in a descriptive case series that there were no differences in outcomes among patients on VDZ [ $n = 5$ ] compared to other IBD therapies.<sup>12</sup> Given the gut-selective mechanism of action of VDZ and lack of significant systemic adverse effects,<sup>7</sup> its safety in patients with COVID-19 is reassuring. It is important to note that the comparator, non-VDZ group is heterogeneous and includes patients on all other medications such as 5-aminosalicylic acid, corticosteroids, immunomodulators, biologics and combination therapies, each of which can have varying impact on COVID-19 outcomes.<sup>13</sup>

In order to characterize the impact of VDZ in more homogeneous medication groups, we additionally compared COVID-19 outcomes among patients on VDZ monotherapy to those on anti-TNF monotherapy. In adjusted analyses, hospitalization was 38% more likely to occur with VDZ monotherapy compared to anti-TNF monotherapy. There was no difference in severe COVID-19 between the two groups, but the direction of the effect was consistent with that of hospitalization. These findings may reflect a potentially protective effect of anti-TNF therapy, as demonstrated in previous data from our registry<sup>13</sup> and other emerging studies.<sup>14,15</sup> Data on mucosal gene expression suggest downregulation of ACE2 in UC patients who respond to TNFi, but not in patients treated with VDZ.<sup>16</sup> Furthermore, VDZ-mediated attenuation of lymphocyte aggregates in the GI tract may explain these findings, at least in part.<sup>17</sup>

As an exploratory analysis, we also noted that new-onset GI symptoms in IBD patients with COVID-19, while reported in a minority of patients, were similar in frequency in patients on VDZ, when compared to other therapies overall. With stratification by IBD activity, nausea, but not other symptoms, was more common among patients in remission and on VDZ. However, compared to patients on anti-TNF monotherapy, patients on VDZ monotherapy more frequently experienced the most GI symptoms. Upon stratification by IBD activity, GI symptoms tended to be more common among patients on VDZ who were in remission. However, the number of patients reporting GI symptoms due to COVID-19 in each subgroup is few, making clinically meaningful interpretation difficult. The higher frequency of GI symptoms in

**Table 3.** Gastrointestinal symptoms due to COVID-19 in adult patients on VDZ compared to those on other IBD therapies, and on VDZ monotherapy compared to anti-TNF monotherapy, in the SECURE-IBD registry, overall and stratified by IBD activity

Gastrointestinal symptom	VDZ use vs non-use			All other IBD therapies			VDZ monotherapy vs anti-TNF monotherapy			p value	
	VDZ		p value	All other IBD therapies		p value	VDZ monotherapy vs anti-TNF monotherapy		p value		
	N	[%]		N	[%]		N	[%]			N
<b>Overall</b>											
Abdominal pain	37	8.1%	0.847	250	7.8%	0.847	30	9.0%	58	5.6%	0.026
Diarrhoea	89	19.5%	0.934	616	19.3%	0.934	74	22.2%	167	16.0%	0.010
Nausea	32	7.0%	0.120	167	5.2%	0.120	29	8.7%	38	3.6%	<0.001
Vomiting	14	3.1%	0.653	86	2.7%	0.653	12	3.6%	18	1.7%	0.042
Other	10	2.2%	0.481	88	2.8%	0.481	9	2.7%	19	1.8%	0.325
Any GI symptom	116	25.4%	0.822	770	24.1%	0.822	99	29.6%	200	19.2%	<0.001
<b>Among patients with active IBD<sup>a</sup></b>											
Abdominal pain	18	8.7%	0.258	148	11.3%	0.258	13	10.0%	35	10.6%	0.840
Diarrhoea	41	19.8%	0.449	289	22.1%	0.449	30	23.1%	80	24.3%	0.779
Nausea	12	5.8%	0.726	84	6.4%	0.726	10	7.7%	15	4.6%	0.183
Vomiting	6	2.9%	0.765	43	3.3%	0.765	5	3.8%	8	2.4%	0.532
Other	4	1.9%	0.341	41	3.1%	0.341	3	2.3%	11	3.3%	0.766
Any GI symptom	49	23.7%	0.556	353	27.0%	0.556	37	28.5%	95	28.9%	0.875
<b>Among patients with IBD in remission<sup>a</sup></b>											
Abdominal pain	18	7.9%	0.109	93	5.3%	0.109	17	9.0%	23	3.4%	0.001
Diarrhoea	46	20.2%	0.183	292	16.6%	0.183	43	22.9%	82	12.3%	<0.001
Nausea	20	8.8%	0.004	77	4.4%	0.004	19	10.1%	23	3.4%	<0.001
Vomiting	8	3.5%	0.205	38	2.2%	0.205	7	3.7%	10	1.5%	0.072
Other	5	2.2%	0.977	39	2.2%	0.977	5	2.7%	7	1.0%	0.150
Any GI symptom	64	28.1%	0.027	374	21.3%	0.027	60	31.9%	99	14.8%	<0.001

Abbreviations: COVID-19 = coronavirus disease 2019; SECURE-IBD = Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease; VDZ = vedolizumab; TNF = tumor necrosis factor.

Statistically significant associations are in bold.

<sup>a</sup>Based on Physician Global Assessment [PGA].

VDZ-treated patients, as compared to anti-TNF-treated patients, may partially explain the higher odds of hospitalization in VDZ-treated patients.

Our study has several strengths. We have data on COVID-19 outcomes on nearly 3500 adult IBD patients in a large collaborative registry of IBD patients from 63 different countries on diverse IBD medications, of which more than 450 patients were on VDZ. This is the largest report of COVID-19 outcomes among patients on VDZ therapy. The limitations of this voluntary registry include the risk of reporting bias, which may lead to documentation of the more severe cases that come to the attention of healthcare providers, while the milder cases may remain undiagnosed or underreported. Conversely, frequently tested asymptomatic patients may be diagnosed incidentally. However, given the large sample size and representation of patients in various subgroups, this is less likely. Other limitations include unmeasured confounding, risk of misclassification of the cause of GI symptoms [IBD vs COVID-19] and missing data, although the last was <4% for all variables except ethnicity and body mass index.

In conclusion, COVID-19 outcomes among IBD patients on VDZ are comparable to those on other therapies. Hospitalization, but not severe COVID-19, is slightly more likely with VDZ monotherapy than with anti-TNF monotherapy, possibly due to a higher frequency of GI symptoms with VDZ. These findings reiterate the overall safety of VDZ in IBD patients with COVID-19.

## Funding

This work was funded by the Helmsley Charitable Trust [2003-04445], National Center for Advancing Translational Sciences [UL1TR002489], a T32DK007634 [E.J.B.] and a K23KD111995-01A1 [R.C.U.]. Additional funding was provided by Pfizer, Takeda, Janssen, Abbvie, Lilly, Genentech, Boehringer Ingelheim, Bristol Myers Squibb, Celtrion and Arenapharm.

## Conflict of Interest

The corresponding author confirms on behalf of all authors that there have been no involvements that might raise the question of bias in the work reported or in the conclusions, implications or opinions stated. M.A. receives research support from the Dickler Family Fund, New York Community Trust and the Helmsley Charitable Trust Fund for SECURE-IBD. X.Z. reports no conflict of interest. E.J.B. is supported by an Institutional Training Grant from the National Institutes of Health [T32DK007634]. R.C.U. has served as a consultant and/or advisory board member for Bristol Myers Squibb, Eli Lilly, Janssen, Pfizer and Takeda. He has received research support from AbbVie, Boehringer Ingelheim and Pfizer. He is supported by a Career Development Award from the National Institutes of Health [K23KD111995-01A1]. M.D.K. has consulted for Abbvie, Janssen, Pfizer and Takeda, is a shareholder in Johnson & Johnson, and has received research support from Pfizer, Takeda, Janssen, Abbvie, Lilly, Genentech, Boehringer Ingelheim, Bristol Myers Squibb, Celtrion and Arenapharm. J.F.C. reports receiving research grants from AbbVie, Janssen Pharmaceuticals and Takeda; receiving payment for lectures from AbbVie, Amgen, Allergan, Inc. Ferring Pharmaceuticals, Shire and Takeda; receiving consulting fees from AbbVie, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, Celgene Corporation, Celltrion, Eli Lilly, Enterome, Ferring Pharmaceuticals, Genentech, Janssen Pharmaceuticals, Landos, Ipsen, Medimmune, Merck, Novartis, Pfizer, Shire, Takeda, Tigenix and Viela bio; and holds stock options in Intestinal Biotech Development and Genfit.

## Author Contributions

M.A.: study concept and design, interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content;

X.Z.: acquisition, analysis and interpretation of data; E.J.B.: study concept and design, acquisition of data, interpretation of data, critical revision of the manuscript for important intellectual content; R.C.U.: study concept and design, acquisition of data, interpretation of data, critical revision of the manuscript for important intellectual content; M.D.K.: study concept and design, interpretation of data, critical revision of the manuscript for important intellectual content; J.F.C.: study concept and design, interpretation of data, critical revision of the manuscript for important intellectual content.

## Data Availability Statement

The data underlying this article are available in the article and in its online supplementary material.

## Acknowledgments

We acknowledge the contributions of our advisory board members, Dr Richard B. Gearry, MBChB, PhD, FRACP, Dr Gilad G. Kaplan, MD, MPH, FRCPC, Michele Kissous-Hunt, PA-C, DFAAPA, Dr Siew C. Ng, MD, PhD, Dr Jean-Francois Rahier, MD, PhD, Dr Walter Reinisch, MD, Dr Flavio Steinwurz, MD, MSc, MACG, Fox E. Underwood, MSc, and Irene Modesto MD, PhD towards the SECURE-IBD registry. Writing assistance: none.

## Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

## References

1. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU), 2020. <https://coronavirus.jhu.edu/map.html>. Accessed July 6, 2020.
2. Cummings MJ, Baldwin MR, Abrams D, *et al.* Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet* 2020;395:1763–70.
3. Burgueño JF, Reich A, Hazime H, *et al.* Expression of SARS-CoV-2 entry molecules ACE2 and TMPRSS2 in the gut of patients with IBD. *Inflamm Bowel Dis* 2020;26:797–808.
4. Chen A, Agarwal A, Ravindran N, To C, Zhang T, Thuluvath PJ. Are gastrointestinal symptoms specific for coronavirus 2019 infection? A prospective case-control study from the United States. *Gastroenterology* 2020;159:1161–3.e2.
5. Feagan BG, Rutgeerts P, Sands BE, *et al.*; GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2013;369:699–710.
6. Sandborn WJ, Feagan BG, Rutgeerts P, *et al.*; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013;369:711–21.
7. Colombel JF, Sands BE, Rutgeerts P, *et al.* The safety of vedolizumab for ulcerative colitis and Crohn's disease. *Gut* 2017;66:839–51.
8. Kirchgessner J, Lemaitre M, Carrat F, Zureik M, Carbone F, Dray-Spira R. Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases. *Gastroenterology* 2018;155:337–46.e10.
9. Suárez-Fariñas M, Tokuyama M, Wei G, *et al.* Intestinal inflammation modulates the expression of ACE2 AND TMPRSS2 and potentially overlaps with the pathogenesis of SARS-CoV-2-related disease. *Gastroenterology* 2021;160:287–301.e20.
10. Brenner EJ, Ungaro RC, Gearry RB, *et al.* Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an International Registry. *Gastroenterology* 2020;159:481–91.e3.
11. Lukin DJ, Kumar A, Hajifathalian K, Sharaiha RZ, Scherl EJ, Longman RS; Jill Roberts Center Study Group Study Group; Weill Cornell Medicine-Gastrointestinal Study Group. Baseline disease activity and steroid therapy

- stratify risk of COVID-19 in patients with inflammatory bowel disease. *Gastroenterology* 2020;159:1541–4.e2.
12. Axelrad JE, Malter L, Hong S, Chang S, Bosworth B, Hudesman D. From the American Epicenter: Coronavirus Disease 2019 in patients with inflammatory bowel disease in the New York City metropolitan area. *Inflam Bowel Dis* 2021;27:662–6.
  13. Ungaro RC, Brenner EJ, Geary RB, et al. Effect of IBD medications on COVID-19 outcomes: results from an international registry. *Gut* 2021;70:725–32.
  14. Gianfrancesco M, Hyrich KL, Al-Adely S, et al.; COVID-19 Global Rheumatology Alliance. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis* 2020;79:859–66.
  15. Strangfeld A, Schäfer M, Gianfrancesco MA, et al. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis* 2021.
  16. Arijs I, De Hertogh G, Lemmens B, et al. Effect of vedolizumab (anti- $\alpha 4\beta 7$ -integrin) therapy on histological healing and mucosal gene expression in patients with UC. *Gut* 2018;67:43–52.
  17. Uzzan M, Tokuyama M, Rosenstein AK, et al. Anti-alpha4beta7 therapy targets lymphoid aggregates in the gastrointestinal tract of HIV-1-infected individuals. *Sci Transl Med* 2018;10:eaau4711.