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

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

aThe Henry D. Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, USA
bDepartment 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

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

Vedolizumab [VDZ], a monoclonal antibody against α4β7 integrin, blocks the interaction between α4β7 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 blocking of lymphocyte trafficking into gut-associated lymphoid tissue [GALT].3 VDZ is approved for the treatment of moderate–severe ulcerative colitis [UC] and Crohn’s disease [CD] in adult patients.1,6 Given its gut-specific mechanism of action, VDZ does not impact systemic immunity significantly and has a favourable safety profile.5 However, VDZ is associated with an increased risk of Clostridium difficile and other intestinal infections.3 Recent data report that VDZ may modulate ACE2 expression in the GI tract.7

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.18 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.19

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 ≤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 ≤ 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, ≥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 ≤ 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 ≥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 0.93; 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 | All patients on ≥1 medication and ≥18 years of age | Vedolizumab | Other IBD therapy | p-value |
|---------------|-----------------------------------------------|-------------|-------------------|---------|
|               | N | %       | N | %       | N | %       |         |         |
| Total number of patients | 3647 | 100% | 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 | | | | | | | | |
| 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 | | | | | | | | |
| Yes | 524 | 14.4% | 50 | 10.9% | 474 | 14.9% |         | <0.001 |
| 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% | 3.48% | <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 | 138 | 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: | | | | | | | <0.001 |         |
| Crohn's disease | 2049 | 56.2% | 201 | 44.0% | 1848 | 57.9% |         |         |
| 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$^d$ | | | | | | | | |
| Remission | 1982 | 54.3% | 228 | 49.9% | 1754 | 55.0% |         | | |
| Mild | 792 | 21.7% | 104 | 22.8% | 688 | 21.6% | | | |
Table 1. Continued

| Characteristic \( ^{b} \) | All patients on \( \geq 1 \) medication and \( \geq 18 \) years of age | Vedolizumab | Other IBD therapy | \( p \)-value \( ^{c} \) |
|--------------------------|--------------------------------|-------------|-----------------|-----------------|
|                         | N     | %    | N     | %    | N     | %    |     |
| Moderate/severe          | 720   | 19.7% | 103   | 22.5% | 617   | 19.3% | 0.114 |
| Smoking                  | 145   | 4.0%  | 12    | 2.6%  | 133   | 4.2%  | 0.194 |
| Comorbidity summary score|       |       |       |       |       |       |     |
| 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%  |     |
| \( \geq 3 \)            | 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                      |       |       |       |       |       |       |     |
| BMI < 30                 | 2440  | 66.9% | 320   | 70.0% | 2120  | 66.5% |     |
| BMI \( \geq 30 \)        | 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.

\( ^{a} \)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.

\( ^{b} \)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.

\( ^{c} \)\( p \)-values for tests comparing variables between vedolizumab and other medication groups.

\( ^{d} \)By physician global assessment [PGA] at the time of COVID-19 infection.
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, \( \text{Table 2} \)] after adjusting for age, number of comorbidities, and Asian and Other race/ethnicity category. 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 \( [p > 0.05], \text{Table 3} \). 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 \( [p < 0.05 \text{ for each comparison} ] \). 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 \( [p \leq 0.001 \text{ for each comparison except vomiting and other} ] \).

### 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 reported 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.15 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.12 Given the selective mechanism of action of VDZ and lack of significant systemic adverse effects,7 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-aminosalisylic acid, corticosteroids, immunomodulators, biologics and combination therapies, each of which can have varying impact on COVID-19 outcomes.15

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 registry13 and other emerging studies.5,15 Data on mucosal gene expression suggest downregulation of ACE2 in UC patients who respond to TNFi, but not in patients treated with VDZ.16 Furthermore, VDZ-mediated attenuation of lymphocyte aggregates in the GI tract may explain these findings, at least in part.17

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 | VDZ monotherapy vs anti-TNF monotherapy | p value | p value |
|--------------------------|---------------------|----------------------------------------|---------|---------|
|                          | VDZ                | All other IBD therapies                |         |         |
|                          | N [%]              | N [%]                                  |         |         |
| Abdominal pain           | 37 [8.1%]          | 250 [7.8%]                             | 0.847   |         |
| Diarrhoea                | 89 [19.5%]         | 616 [19.3%]                            | 0.934   |         |
| Nausea                   | 32 [7.0%]          | 167 [5.2%]                             | 0.120   |         |
| Vomiting                 | 14 [3.1%]          | 86 [2.7%]                              | 0.653   |         |
| Other                    | 10 [2.2%]          | 88 [2.8%]                              | 0.481   |         |
| Any GI symptom           | 116 [25.4%]        | 770 [24.1%]                            | 0.822   |         |
|                         | Any GI symptom     | 99 [29.6%]                             | 0.026   |         |
| Among patients with active IBDa |                |                                        |         |         |
| Abdominal pain           | 18 [8.7%]          | 148 [11.3%]                            | 0.258   |         |
| Diarrhoea                | 41 [19.8%]         | 289 [22.1%]                            | 0.449   |         |
| Nausea                   | 12 [5.8%]          | 84 [6.4%]                              | 0.726   |         |
| Vomiting                 | 6 [2.9%]           | 43 [3.3%]                              | 0.765   |         |
| Other                    | 4 [1.9%]           | 41 [3.1%]                              | 0.341   |         |
| Any GI symptom           | 49 [23.7%]         | 353 [27.0%]                            | 0.556   |         |
| Among patients with IBD in remissiona |                 |                                        |         |         |
| Abdominal pain           | 18 [7.9%]          | 93 [5.3%]                              | 0.109   |         |
| Diarrhoea                | 46 [20.2%]         | 292 [16.6%]                            | 0.183   |         |
| Nausea                   | 20 [8.8%]          | 77 [4.4%]                              | 0.004   |         |
| Vomiting                 | 8 [3.5%]           | 38 [2.2%]                              | 0.205   |         |
| Other                    | 5 [2.2%]           | 39 [2.2%]                              | 0.977   |         |
| Any GI symptom           | 64 [28.1%]         | 374 [21.3%]                            | 0.027   |         |

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.

*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, Janssens, 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 receiving research grants 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, Janssens, 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, Janssens, Pfizer and Takeda, is a shareholder in Johnson & Johnson, and receives research support from AbbVie, Janssens, Abbvie, Lilly, Genentech, Boehringer Ingelheim, Bristol Myers Squibb, Celtrion and ArenaPharm. J.F.C. reports receiving research grants from AbbVie, Janssens 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, Celigene Corporation, Celtrion, Eli Lilly, EnteroMed, Ferring Pharmaceuticals, Genentech, Janssens 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; 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, MChB, PhD, FRACP, Dr Gilad G. Kaplan, MD, MPH, FRCP, Michele Kissous-Hunt, PA-C, DFAAPA, Dr Sieve C. Ng, MD, PhD, Dr Jean-Francois Rahier, MD, PhD, Dr Walter Reimisch, 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. Kirchgesner J, Lemaitre M, Carrat F, Zureik M, Carbonnel 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, Yokoyama 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, Sharaha RZ, Scherl EJ, Longman RS; Jill Roberts Center Study Group Study Group; Weill Cornell Medicine-Gastrointestinal Study Group. Baseline disease activity and steroid therapy towards the SECURE-IBD registry. Writing assistance: none.
1884 M. Agrawal et al.

11. Agrawal M, et al. 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. *Inflamm Bowel Dis* 2021;27:662–6.

13. Ungaro RC, Brenner EJ, Gearry 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-α4β7-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:eaaa4711.