Inflammatory Bowel Diseases, 2022, **28**, 1126–1129
https://doi.org/10.1093/ibd/izab337
Advance access publication 3 March 2022
Brief Report - Clinical

Outcomes of COVID-19 Infections in Vaccinated Patients with Inflammatory Bowel Disease: Data From an International Registry

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Key Words: Crohn's disease, ulcerative colitis, vaccine, breakthrough infection

Introduction

Coronavirus disease 2019 (COVID-19) vaccines are highly effective,[1–3] including in patients with inflammatory bowel disease (IBD).[1,4] However, infections among vaccinated patients still occur. Patients with IBD on immunosuppressive therapies may have blunted humoral responses to COVID-19 vaccines, and antibody levels may wane over time.[5,6] Currently, data on COVID-19 infections in vaccinated patients with IBD are limited. We aimed to describe outcomes of COVID-19 infections in this population using an international registry.

Methods

The Surveillance Epidemiology of Coronavirus Under Research Exclusion in Inflammatory Bowel Disease (SECURE-IBD) database is an international registry of patients with IBD and confirmed COVID-19 infection previously described.[7] Reports with data on vaccination prior to COVID-19 infection, including vaccine type (Pfizer, Moderna, AstraZeneca, Sputnik, Sinovac, Sinopharm, CanSino, or "other," such as Janssen), doses administered, and time from last dose to COVID-19 infection (<30 days, 30-90 days, or ≥90 days) between December 12, 2020, and October 1, 2021, were included. Patients were excluded if vaccine type, number of doses, and/or COVID-19 outcomes were missing.

Cases were patients with complete vaccination, defined as the required number of doses for the vaccine type (at least 2 doses of Moderna, Pfizer, Sinopharm, Sinovac, AstraZeneca, or Sputnik, or 1 of CanSino or Janssen). Partial vaccination status was assigned to those not receiving a full complement of doses. Vaccine mechanism was categorized as mRNA (Pfizer and Moderna), adenovirus vector (CanSino, AstraZeneca, Sputnik, and Janssen), or inactivated SARS-CoV-2 (Sinopharm and Sinovac). Inflammatory bowel disease medications at time of COVID-19 infection were mesalamine/sulfasalazine, thiopurines (eg, 6-mercaptopurine or azathioprine), methotrexate (MTX), tumor necrosis factor (TNF) antagonists, interleukin 12/23 antagonists, integrin antagonists, systemic corticosteroids, and tofacitinib. Biologic monotherapy was defined as use of a biologic without an immunomodulator. Immunomodulator monotherapy was defined as methotrexate, thiopurine, or an unspecified immunomodulator without use of a biologic. Combination therapy was considered concurrent use of any biologic with an immunomodulator.

COVID-19 infection adverse event outcomes were (1) hospitalization due to COVID-19 or related complications; (2) severe COVID-19, defined as a composite of intensive care unit admission, mechanical ventilation, and/or death; and (3) death due to COVID-19 or related complications. Continuous data were described using means and standard deviations. Categorical data were described using proportions. Statistical comparisons were performed using Wilcoxon rank-sum, χ^2, and Fisher exact tests as appropriate. All data were analyzed using R Studio (RStudio Team [2021]. RStudio: Integrated Development Environment for R. RStudio, PBC, Boston, MA, USA, http://www.rstudio.com/).

Results

Of 2477 patients reported, 88 were fully vaccinated, and 53 were partially vaccinated. Characteristics of fully vaccinated patients are presented in Table 1. Cases were reported from 18 countries, with most from the United States (n = 39). Patients completed series with Pfizer (65.9%),

Received for publication: November 16, 2021. Editorial Decision: December 1, 2021

Table 1. Characteristics of fully vaccinated patients with IBD and COVID-19 infection.

Fully vaccinated patients (N)	88
Age, mean (SD)	40.1 (16.7)
Race, *n* (%)	
White	70 (89.7)
Black/African American	1 (1.3)
Asian	3 (3.8)
Other	4 (5.1)
Ethnicity, *n* (%)	
Hispanic/Latino	15 (20.8)
Not Hispanic/Latino	57 (79.2)
Sex, *n* (%)	
Male	39 (45.3)
Female	47 (54.7)
WHO Region, *n* (%)	
Americas	55 (64.0)
United States	39 (45.3)
Europe	28 (32.6)
Western Pacific	2 (2.3)
Eastern Mediterranean	1 (1.2)
Vaccine Type, *n* (%)	
Moderna	12 (13.6)
Pfizer/BioNTech	58 (65.9)
Sinovac	6 (6.8)
AstraZeneca	7 (8.0)
Sputnik	3 (3.4)
CanSino	1 (1.1)
Janssen	1 (1.1)
IBD diagnosis, *n* (%)	
Crohn's Disease	52 (59.1)
Ulcerative Colitis	34 (38.6)
Unspecified IBD	2 (2.3)
Disease Activity of IBD, *n* (%)	
Remission	53 (66.3)
Mild	16 (20.0)
Moderate	11 (13.8)
Severe	0 (0)
IBD Medications at time of infection, *n* (%)	
Mesalamine/sulfasalazine	19 (21.6)
Corticosteroids	5 (5.7)
Tofacitinib	1 (1.1)
Immunomodulator monotherapy[a]	3 (3.4)
Biologic monotherapy	51 (58.0)
TNF antagonist monotherapy	34 (38.6)
Integrin antagonist monotherapy	6 (6.8)
Anti-IL12/23 monotherapy	10 (11.4)
Monotherapy with unspecified biologic	1 (1.1)
Combination Therapy	19 (21.6)
Other	4 (4.5)
None	6 (6.8)
COVID-19 Treated with mAb	9 (10.2)

Abbreviations: 6MP, 6-mercaptopurine; AZA, azathioprine; IBD, inflammatory bowel disease; IL, interleukin; mAb: monocolonal antibodies; MTX, methotrexate; SD, standard deviation; TNF, tumor necrosis factor; WHO, World Health Organization
[a]Includes MTX, AZA, or 6MP, and 1 participant on an unspecified immunomodulator

Moderna (13.6%), AstraZeneca (8.0%), Sinovac (6.8%), Sputnik (3.4%), CanSino (1.1%), and Janssen (1.1%) vaccines. Slightly more than half (59.1%) of fully vaccinated patients had Crohn's disease (CD). At time of COVID-19 infection, 58.0% of fully vaccinated patients were on biologic monotherapy, and 21.6% were on combination therapy. Nine fully vaccinated patients were treated with monoclonal antibodies.

COVID-19 outcomes are presented in Table 2. Out of 88 fully vaccinated patients, 5 (5.7%) were hospitalized. Of these, 3 (3.4%) had severe COVID-19, 1 of whom died (1.1%). In comparison, among unvaccinated patients reported during the same time period, 9.3% were hospitalized, 1.9% had severe COVID-19, and 1.2% died. Among partially vaccinated, rates were 13.2% (n = 7), 1.9% (n = 1), and 0%, respectively. No hospitalizations were observed in the 3 patients who received third vaccine doses or in those who received COVID-19 monoclonal antibodies.

All fully vaccinated hospitalized patients on biologics were on TNF antagonists. Fully vaccinated patients on combination therapy had numerically higher proportion of hospitalizations (15.8%) compared with those on biologic (2.0%) or immunomodulator (0%) monotherapy (P = .08). A lower proportion requiring hospitalization was observed with mRNA vaccines (2.9%) than non-mRNA vaccines (16.7%; P = .06). Fully vaccinated patients requiring hospitalization were older (mean age 53 vs 39 years; P = .04).

Among 3 cases with severe COVID-19, 1 occurred with each vaccine mechanism, resulting in lower event frequencies in the mRNA (1.4%) than non-mRNA groups (8.3% and 16.7%, P = .11). Among fully vaccinated patients, only those receiving combination therapy prior to infection had severe COVID-19. Fully vaccinated patients with severe COVID-19 were older (mean age 59 vs 39 years; P = .03).

The 5 fully vaccinated patients who had an adverse event tended to be older, on immunosuppression, and/or have additional comorbidities. A 34-year-old male from the United States with ulcerative colitis in remission on adalimumab who received the Pfizer vaccine and a 54-year-old female from Iran with CD on adalimumab and azathioprine who received the Sputnik vaccine were hospitalized. Severe COVID-19 occurred in a 56-year-old male from Greece with chronic lung disease and CD in remission without therapy who received the Pfizer vaccine. Severe COVID-19 also occurred in a 59-year-old female from Chile with ulcerative colitis in remission on combination therapy with infliximab and azathioprine who received the second Sinovac vaccine within 30 days of COVID-19 infection. The only death occurred in a 63-year-old woman from Mexico with moderately active CD treated with mesalamine, corticosteroids, adalimumab, and azathioprine who completed the AstraZeneca series 30-90 days earlier. Her COVID-19 course was complicated by mechanical ventilation and gastrointestinal bleeding, from which she died.

Discussion

In this series from SECURE-IBD, approximately three-quarters of patients with COVID-19 infection after complete vaccination were on biologics (primarily TNF antagonists), and one-quarter were receiving immunomodulators. Overall, the number of adverse events was low. Only 5 (5.7%) fully vaccinated patients were hospitalized, which is lower than

Table 2. COVID-19 outcomes in vaccinated patients with IBD.

Group	Total N	Hospitalization	Severe COVID-19 (requiring ICU care, ventilator, and/or death)	Death
		n (%)	*n* (%)	*n* (%)
Vaccination Status				
No vaccination	2317	216 (9.3)	43 (1.9)	29 (1.2)
Complete vaccination	88	5 (5.7)	3 (3.4)	1 (1.1)
Vaccine Mechanism[a]				
mRNA	70	2 (2.9)	1 (1.4)	0
Adenovirus vector	12	2 (16.7)	1 (8.3)	1 (8.3)
Inactivated SARS-CoV-2	6	1 (16.7)	1 (16.7)	0
Medications[a]				
Biologic monotherapy	51	1 (2.0)	0	0
TNF antagonist monotherapy	34	1 (2.9)	0	0
Immunomodulator monotherapy	3	0	0	0
Combination Therapy	19	3 (15.8)	2 (10.5)	1 (5.3)
COVID-19 mAb	9	0	0	0

[a]Analysis limited to those with complete vaccination

unvaccinated patients (9.3%) in the same timeframe. Of the 5 cases, 4 were receiving TNF antagonists (2 on combination therapy with azathioprine and 1 on triple immunosuppression with azathioprine and systemic steroids), one of whom was infected within 30 days of last vaccine dose, and 1 had chronic lung disease.

When stratified by vaccine mechanism, there were lower proportions of hospitalization, severe COVID-19, and death among those receiving mRNA vaccines. Additionally, more outcomes occurred in fully vaccinated patients on combination therapy than monotherapy, and of those on biologics, only patients on TNF antagonists had adverse outcomes. This may indicate waning vaccine response or decreased immunity against infection among those on TNF antagonists. The only death was in a patient who was receiving systemic steroids in addition to azathioprine and a TNF antagonist, which likely affected immune response and overall infectious complication risk. Although there was a limited number of cases, there were no adverse events in patients who received monoclonal antibodies to treat COVID-19 infection.

Our findings support prior studies in patients with IBD and COVID-19 vaccination. Although Ben Tov et al found that rates of COVID-19 after vaccination were similar between patients with and without IBD, of the 23 fully vaccinated patients with IBD reporting COVID-19 infection, 9 (39.1%) were symptomatic, 2 (8.7%) were hospitalized, and 1 (4.3%) died.[1] We found lower rates of hospitalization and only 1 death. Additionally, many patients in our cohort were on TNF antagonists at time of infection, which may reflect changes in vaccine response consistent with findings that patients on TNF antagonists have blunted humoral responses to COVID-19 vaccines[5] and faster waning of antibodies.[6] Lower antibody levels are also documented in patients on combination therapy,[5,6,8] which may be associated with adverse events we observed in those on combination therapy compared with monotherapy.

Our findings expand on prior studies by providing information about real-world experiences with multiple vaccine mechanisms, including non-mRNA vaccines. Our results suggest that mRNA vaccines may provide better protection against hospitalization and severe COVID-19 infection in patients with IBD, although larger studies are needed to confirm this observation. This also may corroborate Pozdnyakova et al's findings that demonstrated lower antibody levels after vaccination in 12 patients receiving adenovirus vector vaccines compared with 341 receiving mRNA vaccines.[9]

We acknowledge several limitations, including risk of confirmation bias and potential reporting bias for sicker patients. Furthermore, our definition of complete vaccination was based on number of doses, as we did not have data on the specific number of days since last dose. We also captured medications at time of infection and not at time of vaccination. Given the number of cases, there is limited precision of estimates, particularly for rare outcomes including severe COVID-19 and death. This additionally limited the use of multivariable models to control for confounding or perform a matched analysis between vaccinated and unvaccinated patients. Lastly, as our data only reflected those with confirmed COVID-19 infection, we cannot report on vaccine effectiveness or overall rates of outcomes among all vaccinated patients with IBD.

To our knowledge, this is the largest known report of COVID-19 infections in patients with IBD with prior vaccination. Our observations highlight the importance of complete vaccination in patients with IBD. Non-mRNA vaccines and TNF antagonist use, especially in combination therapy, may be risk factors for hospitalization. Patients with these risk factors may need prioritization for extra vaccine doses.

Acknowledgments

The authors would like to acknowledge all health care providers who reported cases to the SECURE-IBD registry. A list acknowledging all reporters can be found at: https://covidibd.org/reporter-acknowledgment/

Author Contributions

E.S. and D.Y.G.: conceptualization, formal analysis, and writing original draft. X.Z.: data curation, formal analysis, writ-

ing, review, and editing. E.J.B., M.A., J.F.C., and M.D.K.: data acquisition, data interpretation, writing, review, and editing. A.K. and R.C.U.: conceptualization, formal analysis, data interpretation, and writing/editing original draft.

Funding

This work was supported by the Helmsley Charitable Trust (2003-04445), Clinical and Translational Science Awards grant number UL1TR002489, T32DK007634 (E.J.B.), K23KD111995-01A1 (R.C.U.), K23DK129762-01 (M.A.) and a Digestive Disease Research Foundation Fellowship (E.S.). Additional funding provided by Pfizer, Takeda, Janssen, Abbvie, Lilly, Genentech, Boehringer Ingelheim, Bristol Myers Squibb, Celtrion, and Arenapharm to support investigator effort (M.D.K. and J.F.C.) and data management (X.Z.).

Conflicts of Interest

E.S., D.Y.G., E.J.B., M.A., and X.Z. have no relevant conflicts of interest. M.D.K. has consulted for AbbVie, Janssen, Pfizer, Eli Lilly, and Takeda; is a shareholder in Johnson and 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; reports receiving consulting fees from AbbVie, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, BMS, Celgene Corporation, Eli Lilly, Ferring Pharmaceuticals, Galmed Research, Genentech, Glaxo Smith Kline, Janssen Pharmaceuticals, Kaleido Biosciences, Imedex, Immunic, Iterative Scopes, Merck, Microba, Novartis, PBM Capital, Pfizer, Sanofi, Takeda, TiGenix, Vifor; and holds stock options in Intestinal Biotech Development. A.K. has received consulting fees from AbbVie, Janssen, Takeda, Pfizer, Merck, Bristol Myers Squibb, Prometheus, Salix, and Shire; has received research support from AbbVie, Janssen, Takeda, Pfizer, Salix, Celgene, and Bristol Myers Squibb; and has received speaker honoraria fees from AbbVie, Janssen, Takeda, Pfizer, Bristol Myers Squibb, Merck, Salix, and Shire. R.C.U. has served as an advisory board member or consultant for AbbVie, Bristol Myers Squibb, Janssen, Pfizer, and Takeda and has received research support from AbbVie, Boehringer Ingelheim, Eli Lilly, and Pfizer.

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