Low Rates of Breakthrough COVID-19 Infection After SARS-CoV-2 Vaccination in Patients With Inflammatory Bowel Disease

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Lay Summary

We demonstrate low rates of breakthrough coronavirus disease 2019 (COVID-19) infection and mild course of illness following severe acute respiratory syndrome coronavirus 2 vaccination in a large cohort of inflammatory bowel disease patients. Residence in southern United States and lower median anti-receptor binding antibody level were associated with development of COVID-19.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination is highly effective at preventing coronavirus disease 2019 (COVID-19). Immunosuppressive medications, commonly used to treat patients with inflammatory bowel disease (IBD), may diminish vaccine response, predisposing to breakthrough infection. Prior studies of patients with IBD found low short-term (within 30 days of vaccination) rates of breakthrough infection, with a majority occurring before receipt of second messenger RNA (mRNA) vaccine dose.[1-3] However, longer-term data are needed to better understand vaccine effectiveness and durability in this vulnerable population. We aimed to describe the incidence and severity of, and risk factors for, COVID-19 infection in the 6 months following SARS-CoV-2 vaccination in a large, geographically diverse population of patients with IBD.

The PREVENT-COVID (Partnership to Report Effectiveness of Vaccination in populations Excluded from iNitial Trials of COVID) trial is a prospective, observational

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Table 1. Comparison of Clinical and Demographic Factors Among Participants Who Developed COVID-19 Infection ≥1 Month After Completion of SARS-CoV-2 Vaccine Series vs Participants Who Did Not Develop COVID-19 Infection ≥1 Month After Vaccination

	All Patients n	COVID-19 Infection	No COVID-19 Infection	*P* Value
Total number of patients	2849	48	2801	—
COVID infection prior to vaccination	128	0 (0)	128 (5)	.130
COVID infection after starting vaccine series or <1 mo after completing vaccine series	18	0 (0)	18 (1)	.577
Age, y	44.5	43.6 ± 15.2	44.5 ± 14.9	.672
<18 y	22	1 (2)	21 (1)	
18–39 y	1189	23 (48)	1166 (42)	
40–64 y	1288	17 (35)	1271 (45)	
≥65 y	350	7 (15)	343 (12)	
Female	2070	32 (67)	2038 (73)	.348
Current smoker	50	0 (0)	50 (2)	.350
Region				.028
Northeast	675	6 (13)	669 (24)	
South	851	22 (46)	829 (30)	
Midwest	699	14 (29)	685 (24)	
West	623	6 (13)	617 (22)	
Highest grade				.407
>12th grade	36	1 (2)	35 (1)	
12th grade or GED	60	2 (4)	58 (2)	
Some college	328	7 (15)	321 (11)	
College	1169	24 (50)	1145 (41)	
Graduate school	1255	14 (29)	1241 (44)	
Unknown	1	0 (0)	1 (0)	
Disease type				.670
Crohn's disease	1921	32 (67)	1889 (67)	
Ulcerative colitis	886	16 (33)	870 (31)	
Missing/IBD-U	42	0 (0)	42 (1)	
Type of vaccine (first dose)				.483
BNT162b2	1639	28 (58)	1611 (58)	
mRNA-1273	1068	16 (33)	1052 (38)	
Ad26.COV2.S	138	4 (8)	134 (5)	
Unknown	4	0 (0)	4 (0)	
IBD medication at baseline vaccination[a]				
No medical therapy	239	1 (2)	238 (8)	.112
Systemic steroids	128	4 (8)	124 (4)	.196
Anti-TNF monotherapy	1018	20 (42)	998 (36)	.387
Anti-TNF combination therapy[b]	286	6 (13)	280 (10)	.567
Thiopurine	225	4 (8)	221 (8)	.910
Methotrexate	16	0 (0)	16 (1)	.600
Mesalamine or sulfasalazine	632	13 (27)	619 (22)	.410
Budesonide	114	3 (6)	111 (4)	.423
Vedolizumab	324	5 (10)	319 (11)	.833
Ustekinumab	406	9 (19)	397 (14)	.368
Tofacitinib	42	0 (0)	42 (1)	.393
Participants with antibody level	2006	31	1975	—
Anti-RBD antibody level	30.4	7.1 (2.7-21.0)	17.0 (7.1-33.0)	.004

Values are n, n (%), mean ± SD, or median (interquartile range).
Abbreviations: COVID-19, coronavirus disease 2019; IBD-U, inflammatory bowel disease–unclassified; RBD = receptor binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF, tumor necrosis factor.
[a]Numbers do not add to total n as patients may be taking more than 1 medication class.
[b]Including azathioprine, 6-mercaptopurine, or methotrexate.

cohort of patients with inflammatory bowel disease (IBD) in the United States who have received any SARS-CoV-2 vaccine granted emergency use authorization or approval, including BNT162b2 (Pfizer-BioNTech), mRNA-1273 (NIH-Moderna), and Ad26.COV2.S (Johnson & Johnson). Eligibility criteria have been previously described.[4,5] Participants completed baseline and 30-day follow-up surveys that assessed demographics, IBD characteristics, immunization date(s) and lot number(s), and history of COVID-19 infection. A 6-month follow-up survey ascertained development of COVID-19, method of diagnosis, severity of infection, requirement for hospitalization, and treatment with monoclonal antibodies. Optional quantitative measurement of anti-receptor binding domain (RBD) immunoglobulin G antibodies specific to SARS-CoV-2 (LabCorp Cov2Quant IgG assay) was offered approximately 8 weeks after completion of the primary vaccine series.[4,5]

Participants included in this analysis completed SARS-CoV-2 vaccination and the 6-month follow-up survey prior to December 7, 2021. We used descriptive statistics to characterize the study population and bivariate statistics to evaluate associations between patient characteristics and COVID-19 infection ≥1 month after receipt of the Ad26.COV2.S vaccine or second dose of an mRNA vaccine. Variables included prior COVID-19 infection, age, sex, disease type (Crohn's disease vs ulcerative colitis vs IBD–unspecified or missing), vaccine type, IBD medication at time of initial vaccination, geographical region of residence, and anti-RBD antibody level where applicable.

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). *P* values <.05 were considered significant. The study was approved by the University of North Carolina at Chapel Hill Institutional Review Board.

Of 3157 total participants, 2849 (90%) participants completed their SARS-CoV-2 vaccine series and 6-month follow-up survey by December 7, 2021, and were included in this analysis. Forty-eight (1.7%) reported COVID-19 infection ≥1 month after complete vaccination (Table 1). Mean and median times from vaccination to infection were 4.6 and 5 months, respectively. Of these 48 patients, 41 (85%) were diagnosed via nasal polymerase chain reaction or antigen testing, and 42 (88%) reported symptomatic infection. Nine (19%) received monoclonal antibody treatment and 1 (2%) required hospitalization. No deaths were reported. Only 2 (4.1%) of 48 patients had received a third dose of an mRNA vaccine prior to COVID-19 infection.

Individuals in the South were more likely to develop COVID-19 infection following vaccination compared with those in other regions (*P* = .028). Although not statistically significant, the AD26.COV2.S vaccine was numerically less effective at preventing infection compared with mRNA vaccines. Age, sex, and IBD medication class at time of initial vaccination were not associated with breakthrough infections (Table 1).

Of 2006 participants who underwent anti-RBD antibody measurement, median antibody levels were lower in individuals who developed breakthrough infection compared with those who did not (median 7.1 μg/mL vs 17.0 μg/mL; *P* = .004).

Our findings demonstrate low rates of breakthrough COVID-19 infection and a relatively mild course of illness after completion of SARS-CoV-2 vaccination in a large U.S. IBD cohort. These data correlate well with real-world surveillance data from Israel, where vaccine effectiveness within 4 months of receiving 2 doses of BNT162b2 was estimated to be 95.3%.[6] Similarly, 6-month postimmunization follow-up data from the BNT162b2 multinational phase 1-2-3 clinical trial found that 2 doses of BNT162b2 were 91.1% effective at preventing COVID-19 infection and 97% effective at preventing severe disease from 7 days to 6 months after second vaccine dose.[7]

As in the initial clinical trials of the SARS-CoV-2 vaccines, these real-world data in patients with IBD reaffirm that vaccination was highly effective at preventing severe disease and death, even among patients on immunosuppression. In our cohort, lower anti-RBD antibody levels following primary vaccine series were associated with breakthrough infections. Additionally, lower vaccination rates in the southern United States and the emergence of delta as the predominant COVID-19 variant by summer 2021 may have contributed to increased breakthrough infections in this group. It is also possible that waning immunity among those vaccinated >6 months prior played a role in breakthrough cases as was seen in a large Israeli study.[8]

Interestingly, only 9 participants were treated with monoclonal antibodies, which are indicated for nonhospitalized patients with mild-moderate COVID-19 infection at high risk of developing severe disease. Educating patients and providers about emerging COVID-19 treatments is essential.

Study strengths include the large population size and geographic diversity, the length of follow-up to assess breakthrough infections, and the robust retention rate (>90%). We also captured participant reports of home- and clinic-based tests.

Limitations include a convenience sample that may impact external validity and reliance on patient self-report for demographic or disease characteristics and COVID-19 infection. Additionally, objective markers of IBD activity were not available in this population. As most participants who reported COVID-19 infection were symptomatic, it is possible that the rate of breakthrough infection is underestimated, as surveillance testing of asymptomatic individuals was not performed as part of our protocol. Lack of a non-IBD comparison group and the limited length of follow-up in this report are additional limitations, although longer-term follow-up is ongoing in this cohort.

Longer-term follow-up is ongoing to (1) evaluate the impact of additional vaccine or booster doses as well as omicron and other emerging variants on rates of breakthrough COVID-19 infection, (2) correlate levels of quantitative antibodies with breakthrough infections, and (3) further elucidate risk factors for breakthrough infection including vaccine type and other patient and treatment characteristics.

Author Contributions

Guarantor of the article: K.N.W. Study concept and design: M.D.L., M.D.K. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting of the article: K.N.W. Critical revision of the article for important intellectual content: all authors. Statistical analysis: X.Z., M.D.L., M.D.K. Obtained funding: M.D.L., M.D.K. Study supervision: K.N.W., M.D.L., M.D.K. Approval of final draft submitted: all authors.

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Conflicts of Interest

K.N.W. has served as a consultant for AbbVie and Bristol-Myers Squibb. J.A. has served as a consultant for Janssen and has received research support from the Gary and Rachel Glick Charitable Fund, Shaevsky Family Research Fund for Crohn's Disease, the Crohn's and Colitis Foundation, and the Leona M. and Harry B. Helmsley Charitable Trust. M.C.D. has received consulting fees from AbbVie, Arena, Bristol-Myers Squibb, Celgene, Eli Lilly, Gilead, Janssen, Pfizer, Prometheus Labs, and Takeda; grant support from AbbVie and Prometheus Labs; and license fees from Takeda. A.B. has received research support (subinvestigator on protocols) from the following companies in the past 3 years: Janssen, AbbVie, Takeda, Buhlmann, Arena, and Eli Lilly; has served as a consultant for Arena, Best Doctors, Eli Lilly, and Takeda; and received royalties from UptoDate. R.K.C. has participated in advisory boards and served as a consultant with AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, LabCorp, Pfizer, Samsung Bioepis, Sebela, and Takeda. P.D.R.H. has served as a consultant for AbbVie, Pfizer, and Takeda; and received grant support from the National Institutes of Health, Crohn's and Colitis Foundation, AbbVie, Pfizer, Takeda, Genentech, Eli Lilly, Arena, and the Rainin Foundation. R.C.U. has served on the advisory board or as a consultant for AbbVie, Bristol-Myers Squibb, Eli Lilly, Janssen, Pfizer, and Takeda; and received research support from AbbVie, Boehringer Ingelheim, and Pfizer. M.E.B. has received research funding from Janssen, GlaxoSmithKline, and Takeda; has served as a consultant for Janssen, AbbVie, Bristol-Myers Squibb, and Pfizer; and received honoraria for participation in a CME program sponsored by AbbVie. E.B. has served as a consultant for AbbVie, Pfizer and Bristol-Myers Squibb. F.A.F. has served as a consultant for Arena, Bristol-Myers Squibb, Braintree Labs, Gilead, GI Reviewers, Innovation Pharmaceuticals, Iterative Scopes, Janssen, Pfizer, and Sebela; and on a Data Safety Monitoring Board for Bacainn Therapeutics, Lilly, and Theravance. M.D.L. has received research and/or grant support from Pfizer and served as a consulted for AbbVie, Bristol-Myers Squibb, Calibr, Eli Lilly and Company, Genentech, Gilead Sciences, Janssen Pharmaceuticals, Pfizer, Roche, Takeda Pharmaceuticals U.S.A., TARGET PharmaSolutions, and Theravance Biopharma. M.D.K. has served as a consultant 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. All other authors disclose no conflicts.

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