Inflammatory Bowel Diseases, XXXX, **XX**, 1–9
https://doi.org/10.1093/ibd/izab302
Advance access publication 6 December 2021
Original Research Articles - Clinical

Impact of SARS-CoV-2 Vaccination on Inflammatory Bowel Disease Activity and Development of Vaccine-Related Adverse Events: Results From PREVENT-COVID

Kimberly N. Weaver, MD,[*,] Xian Zhang, PhD,[†] Xiangfeng Dai, PhD,[*] Runa Watkins, MD,[§] Jeremy Adler, MD, MSc,[¶] Marla C. Dubinsky, MD,[‖,] Arthur Kastl, MD,[**] Athos Bousvaros, MD, MPH,[††] Jennifer A. Strople, MD,[‡‡] Raymond K. Cross, MD, MS,[§§,] Peter D.R. Higgins, MD, PhD,[¶¶] Ryan C. Ungaro, MD, MS,[‖‖] Meenakshi Bewtra MD, PhD,[*,†††] Emanuelle Bellaguarda, MD,[‡‡‡] Francis A. Farraye, MD, MS,[§§§] Margie E. Boccieri, MA,[†] Ann Firestine, MS,[†] Michael D. Kappelman MD, MPH,[†,‡,a] and Millie D. Long, MD, MPH[*,‡,a]**

From the [*]Division of Gastroenterology and Hepatology, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA;
[†]Division of Pediatric Gastroenterology, Department of Pediatrics, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA;
[‡]Center for Gastrointestinal Biology and Disease, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA;
[§]Division of Pediatric Gastroenterology and Nutrition, University of Maryland School of Medicine, Baltimore, MD, USA;
[¶]Susan B. Meister Child Health Evaluation and Research Center and Division of Pediatric Gastroenterology, University of Michigan, Ann Arbor, MI, USA;
[‖]Susan and Leonard Feinstein IBD Center, Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY, USA;
[**]Division of Gastroenterology, Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA;
[††]Department of Pediatrics, Boston Children's Hospital, Boston, MA, USA;
[‡‡]Department of Pediatrics, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA;
[§§]Division of Gastroenterology and Hepatology, University of Maryland School of Medicine, Baltimore, MD, USA;
[¶¶]Division of Gastroenterology & Hepatology, University of Michigan, Ann Arbor, MI, USA;
[‖‖]Susan and Leonard Feinstein IBD Center, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA;
[***]Division of Gastroenterology, Perelman School of Medicine, University of Pennsylvania, Philadelphia PA, USA;
[†††]Department of Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia PA, USA;
[‡‡‡]Division of Gastroenterology and Hepatology, Northwestern University, Chicago, IL, USA; and
[§§§]Division of Gastroenterology and Hepatology, Mayo Clinic, Jacksonville, FL, USA.

[a]M.D.K. and M.D.L. contributed equally.
Address correspondence to: Kimberly N. Weaver, MD, Corresponding address: University of North Carolina at Chapel Hill, 130 Mason Farm Road, Campus Box #7080, Chapel Hill, NC 27599, USA (kim_weaver@med.unc.edu).

Background. Severe acute respiratory syndrome coronavirus 2 vaccination is recommended for all individuals with inflammatory bowel disease (IBD), including those on immunosuppressive therapies; however, little is known about vaccine safety and efficacy in these patients or the impact of vaccination on IBD disease course.

Methods. We evaluated coronavirus disease 2019 (COVID-19) vaccine–related adverse events (AEs) and the effect of vaccination on IBD disease course among participants in the PREVENT-COVID (Partnership to Report Effectiveness of Vaccination in populations Excluded from iNitial Trials of COVID) study, a prospective, observational cohort study. Localized and systemic reactions were assessed via questionnaire. Disease flare was defined by worsening IBD symptoms and change in IBD medications. Outcomes were stratified by vaccine type and IBD medication classes.

Results. A total of 3316 individuals with IBD received at least 1 COVID-19 vaccine. Injection site tenderness (68%) and fatigue (46% dose 1, 68% dose 2) were the most commonly reported localized and systemic AEs after vaccination. Severe localized and systemic vaccine-related AEs were rare. The mRNA-1273 vaccine was associated with significantly greater severe AEs at dose 2 (localized 4% vs 2%, systemic 15% vs 10%; $P < .001$ for both). Prior COVID-19 infection, female sex, and vaccine type were associated with severe systemic reactions to dose 1, while age <50 years, female sex, vaccine type, and antitumor necrosis factor and vedolizumab use were associated with severe systemic reactions to dose 2. Overall rates (2%) of IBD flare were low following vaccination.

Conclusions. Our findings provide reassurance that the severe acute respiratory syndrome coronavirus 2 vaccine is safe and well tolerated among individuals with IBD, which may help to combat vaccine hesitancy and increase vaccine confidence.

Received for publication: September 30, 2021. Editorial Decision: October 31, 2021

Lay Summary

The severe acute respiratory syndrome coronavirus 2 vaccine is safe and well tolerated among individuals with inflammatory bowel disease (IBD). Severe localized and systemic vaccine-related adverse events were rare, and rates of IBD flare were low (2%) following severe acute respiratory syndrome coronavirus 2 vaccination in a cohort of 3316 participants with IBD.

Key Words: Crohn's disease, COVID-19, preventive care, ulcerative colitis, vaccination

Introduction

The clinical trials that led to emergency use authorization (EUA) of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines showed low rates of serious adverse events (AEs) among participants but did not include individuals with Crohn's disease (CD) or ulcerative colitis (UC).[1-3] Thus, little is known about the safety and the efficacy of these vaccines in patients with inflammatory bowel disease (IBD), many of whom are treated with immunosuppressive medications. A recent survey of patients with IBD indicated that although a vast majority of individuals felt that the coronavirus disease 2019 (COVID-19) vaccine was important for their health and the health of others, many participants had concerns about the unknown safety of the vaccine, preferred to see how others tolerated the vaccine first, and desired specific data regarding vaccine safety and effectiveness in IBD patients.[4]

There is no evidence to date that other vaccinations trigger flares of IBD. Prior studies of IBD patients who received the 23-valent polysaccharide pneumococcal, H1N1 influenza, trivalent influenza vaccines, or recombinant zoster vaccine did not show increased risk of serious AEs, and there were no significant changes in IBD clinical activity scores postimmunization.[5-9] Additionally, a small study of IBD patients (n = 246) suggested that individuals with IBD experience similar frequencies of AEs after SARS-CoV-2 vaccination compared with the healthy participants studied in the initial vaccine clinical trials.[10]

Despite this early reassuring data, larger real-world studies are needed to evaluate COVID-19 vaccine safety and tolerability in IBD patients. This study aimed to evaluate SARS-CoV-2 vaccine–related AEs in patients with IBD and the effects of vaccination on IBD disease activity.

Methods

Partnership to Report Effectiveness of Vaccination in populations Excluded from iNitial Trials of COVID (PREVENT-COVID) is a prospective, observational, cohort study of patients with IBD in the United States who have received any COVID-19 vaccine granted EUA including BNT162b2 (Pfizer-BioNTech), mRNA-1273 (NIH-Moderna), and Ad26.COV2.S (Johnson & Johnson). Eligibility criteria have previously been described and include (1) diagnosis of IBD, (2) receipt of 1 or more doses of any COVID-19 vaccine approved under the EUA within the prior 90 days, (3) age 12 years or older, (4) residence in the United States, (5) access to the internet and ability to complete surveys in English, and (6) willingness to remain in this study for 18 months.[11] Participants were recruited through education, social media, and other outreach efforts in collaboration with the Crohn's & Colitis Foundation and by referral at selected clinical sites and will be followed through Internet surveys for up to 18 months to ascertain outcomes of COVID-19 infection and safety events. Baseline surveys assessed type of immunization, date and lot numbers of immunization(s), patient demographics and IBD characteristics, and detailed data regarding IBD medication use around the time of vaccination. IBD disease activity was measured via the Manitoba index.[12] The 30-day follow-up survey collected data on the second immunization, including the specific timing of this vaccination in relation to the first, and ascertained whether participants developed COVID-19, the method of diagnosis, and the severity of infection. Both surveys collected data on vaccine AEs and clinical course of IBD following vaccination. Vaccine AEs were classified as injection site (localized) or systemic reactions. Adverse localized reactions included pain, redness, itching, swelling, tenderness, or warmth at the injection site. Systemic adverse reactions included fever, chills, fatigue, headache, joint pain, muscle aches, nausea, allergic reaction, rash, or other. If individuals reported an adverse reaction to the SARS-CoV-2 vaccine, they were asked to rate the severity of reaction as mild (did not interfere with daily activity), moderate (interfered with daily activity), severe (prevented daily activity, required medications), or requiring emergency room visit or hospitalization. Participants were also assessed for flare of IBD, which was defined as (1) worsening of at least 1 of the symptoms of abdominal pain, bowel frequency, rectal bleeding, and extraintestinal manifestation after vaccine 1 or 2; and (2) a need to add or change IBD medication due to symptoms within 1 month of vaccination.

This analysis included all participants who completed baseline and 30-day post-enrollment surveys prior to July 8, 2021. We used descriptive statistics to characterize the study population, vaccine-related AEs, IBD disease activity, and development of COVID-19 infection after vaccination. Outcomes were stratified by vaccine type and by IBD medication classes. We used bivariate analyses to identify factors associated with severe localized or systemic AEs to SARS-CoV-2 vaccination.

All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). *P* values <.05 were considered statistically significant. The study protocol was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

Results

Baseline Characteristics

A total of 3316 participants with IBD (71.7% female, mean age 43.7 years, 54.6% Crohn's disease) completed the baseline survey and were included in the study population as of July 8, 2021. A total of 160 (4.8%) participants reported a history of COVID-19 infection before SARS-CoV-2 immunization. Vaccine distribution included 1908 (57.5%) BNT162b2 (Pfizer-BioNTech), 1247 (37.6%) mRNA-1273 (NIH-Moderna), and 161 (4.9%) Ad26.COV2.S (Johnson & Johnson). A majority of participants were taking biologic or small molecule therapies at baseline. Full details regarding medication distribution, demographics, and IBD clinical characteristics are presented in Table 1.

Table 1. Demographics and Clinical Characteristics of the Study Population

	Total (N = 3316)	BNT162b2 (n = 1908)	mRNA-1273 (n = 1247)	Ad26.COV2.S (n = 161)
Age, y	43.7 ± 15.1	42.8 ± 15.2	45.1 ± 15.0	43.4 ± 14.5
Sex				
Male	919 (27.7)	543 (28.5)	331 (26.5)	45 (28)
Female	2378 (71.7)	1355 (71.0)	909 (72.9)	114 (70.8)
Other	19 (0.6)	10 (0.5)	7 (0.6)	2 (1.2)
Race				
White	3115 (93.9)	1791 (93.9)	1174 (94.1)	150 (93.2)
Black/African American	39 (1.2)	23 (1.2)	11 (0.9)	5 (3.1)
Asian	62 (1.9)	33 (1.7)	27 (2.1)	2 (1.2)
Native Hawaiian/Pacific Islander	2 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)
Multiple	59 (1.8)	39 (2.0)	17 (1.4)	3 (1.9)
Other	39 (1.1)	21 (1.1)	17 (1.4)	1 (0.6)
Hispanic				
Yes	107 (3.2)	66 (3.5)	33 (2.6)	8 (5.0)
No	3198 (96.5)	1836 (96.2)	1209 (97.0)	153 (95.0)
Unknown	11 (0.3)	6 (0.3)	5 (0.4)	0 (0.0)
BMI, kg/m^2	26.1 ± 7.7	25.8 ± 8.4	26.5 ± 6.7	26.5 ± 6.4
Current Smoker				
Yes	69 (2.1)	41 (2.1)	24 (1.9)	4 (2.5)
No	3247 (97.9)	1867 (97.9)	1223 (98.1)	157 (97.5)
Region				
Northeast	784 (23.7)	451 (23.7)	292 (23.5)	41 (25.5)
South	996 (30.0)	559 (29.3)	394 (31.6)	43 (26.7)
Midwest	811 (24.5)	494 (25.9)	277 (22.2)	40 (24.8)
West	722 (21.8)	402 (21.1)	283 (22.7)	37 (23.0)
Highest grade				
<12th grade	76 (2.3)	71 (3.7)	5 (0.4)	0 (0.0)
12th grade or GED	87 (2.6)	61 (3.2)	23 (1.8)	3 (1.9)
Some college	405 (12.2)	202 (10.6)	169 (13.6)	34 (21.1)
College	1339 (40.4)	747 (39.2)	525 (42.1)	67 (41.6)
Graduate school	1408 (42.5)	826 (43.3)	525 (42.1)	57 (35.4)
Disease duration, y	17.7 ± 12.4	17.3 ± 12.3	18.2 ± 12.6	17.5 ± 11.7
0-9 y	956 (28.8)	574 (30.1)	332 (26.7)	50 (31.1)
10-19 y	1154 (34.8)	664 (34.8)	439 (35.2)	51 (31.7)
20-29 y	678 (20.5)	386 (20.2)	253 (20.3)	39 (24.2)
30-39 y	289 (8.7)	157 (8.2)	122 (9.8)	10 (6.2)
40+ y	238 (7.2)	127 (6.7)	100 (8.0)	11 (6.8)
IBD hospitalization (ever)				
Yes	2050 (61.8)	1169 (61.3)	775 (62.1)	106 (65.8)
No	1266 (38.2)	739 (38.7)	472 (37.9)	55 (34.2)
IBD hospitalization (past 6 mo)				
Yes	129 (3.9)	69 (3.6)	52 (4.2)	8 (5.0)
No	3187 (96.1)	1839 (96.4)	1195 (95.8)	153 (95.0)
IBD activity 6 mo before vaccine				
Constantly active (daily sxs)	189 (5.7)	103 (5.4)	79 (6.3)	7 (4.3)
Often active (sxs most days)	365 (11.0)	190 (10.0)	158 (12.7)	17 (10.6)
Sometimes active (sxs 1-2 d/wk)	602 (18.1)	319 (16.7)	242 (19.4)	41 (25.5)
Occasionally active (sxs 1-2 d/mo)	526 (15.9)	317 (16.6)	185 (14.8)	24 (14.9)
Rarely active (sxs on a few days)	557 (16.8)	328 (17.2)	203 (16.3)	26 (16.1)
Well/remission	1077 (32.5)	651 (34.1)	380 (30.5)	46 (28.6)
Oral/parenteral steroids				
Yes	153 (4.6)	93 (4.9)	54 (4.3)	6 (3.7)
No	3163 (95.4)	1815 (95.1)	1193 (95.7)	155 (96.3)

Table 1. Continued

	Total (N = 3316)	BNT162b2 (n = 1908)	mRNA-1273 (n = 1247)	Ad26.COV2.S (n = 161)
Oral budesonide				
Yes	139 (4.2)	80 (4.2)	50 (4.0)	9 (5.6)
No	3177 (95.8)	1828 (95.8)	1197 (96.0)	152 (94.4)
Oral mesalamine				
Yes	622 (18.8)	346 (18.1)	246 (19.7)	30 (18.6)
No	2694 (81.2)	1562 (81.9)	1001 (80.3)	131 (81.4)
Sulfasalazine				
Yes	98 (3.0)	58 (3.0)	39 (3.1)	1 (0.6)
No	3218 (97.0)	1850 (97.0)	1208 (96.9)	160 (99.4)
Thiopurine				
Yes	554 (16.7)	309 (16.2)	220 (17.6)	25 (15.5)
No	2762 (83.3)	1599 (83.8)	1027 (82.4)	136 (84.5)
Methotrexate				
Yes	179 (5.4)	114 (6.0)	60 (4.8)	5 (3.1)
No	3137 (94.6)	1794 (94.0)	1187 (95.2)	156 (96.9)
Infliximab				
Yes	807 (24.3)	482 (25.3)	289 (23.2)	36 (22.4)
No	2509 (75.7)	1426 (74.7)	958 (76.8)	125 (77.6)
Adalimumab				
Yes	626 (18.9)	376 (19.7)	218 (17.5)	32 (19.9)
No	2690 (81.1)	1532 (80.3)	1029 (82.5)	129 (80.1)
Certolizumab				
Yes	57 (1.7)	29 (1.5)	25 (2.0)	3 (1.9)
No	3259 (98.3)	1879 (98.5)	1222 (98.0)	158 (98.1)
Golimumab				
Yes	25 (0.8)	18 (0.9)	6 (0.5)	1 (0.6)
No	3291 (99.2)	1890 (99.1)	1241 (99.5)	160 (99.4)
Vedolizumab				
Yes	402 (12.1)	219 (11.5)	163 (13.1)	20 (12.4)
No	2914 (87.9)	1689 (88.5)	1084 (86.9)	141 (87.6)
Ustekinumab				
Yes	489 (14.7)	273 (14.3)	195 (15.6)	21 (13.0)
No	2827 (85.3)	1635 (85.7)	1052 (84.4)	140 (87.0)
Tofacitinib				
Yes	59 (1.8)	30 (1.6)	25 (2.0)	4 (2.5)
No	3257 (98.2)	1878 (98.4)	1222 (98.0)	157 (97.5)
Cyclosporine				
Yes	2 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)
No	3314 (99.9)	1907 (99.9)	1246 (99.9)	161 (100.0)
Tacrolimus				
Yes	15 (0.5)	5 (0.3)	6 (0.5)	4 (2.5)
No	3301 (99.5)	1903 (99.7)	1241 (99.5)	157 (97.5)
COVID-19 infection prior to vaccine				
Yes	160 (4.8)	83 (4.4)	67 (5.4)	10 (6.2)
No	3156 (95.2)	1825 (95.6)	1180 (94.6)	151 (93.8)
COVID-19 infection since first vaccine				
Yes	10 (0.3)	7 (0.4)	3 (0.2)	0 (0.0)
No	3306 (99.7)	1901 (99.6)	1244 (99.8)	161 (100.0)

Values are mean ± SD or n (%).
Abbreviations: Ad26.COV2.S, Johnson & Johnson; BMI, body mass index; BNT162b2, Pfizer-BioNTech; COVID-19, coronavirus disease 2019; d, day; IBD, inflammatory bowel disease; mo, month; mRNA-1273, NIH-Moderna; sxs, symptoms; wk, week.

Adverse Reactions to SARS-CoV-2 Vaccination

Participants were asked to report localized and systemic AEs within 7 days after receiving SARS-CoV-2 vaccine dose 1 (D1) and vaccine dose 2 (D2). When considering localized reaction to D1, 13.0% reported no reaction, 69.7% reported mild reaction, 15.8% reported moderate reaction, and 1.1% reported severe reaction (Table 2). For D2, 13.2% reported no reaction, 64.0% reported a mild reaction, 19.7% reported a moderate reaction, and 2.8% reported a severe reaction (Table 3). Systemic reactions were more commonly seen after D2, with 21.5% reporting no reaction, 28.0% reporting a mild reaction, 37.8% reporting a moderate reaction, and 11.6% reporting a severe reaction to D2 compared with 41.7% reporting no reaction, 36.5% reporting a mild reaction, 17.9% reporting a moderate reaction, and 2.9% reporting a severe reaction to D1. There were 10 (0.3%) participants after D1 and 6 participants after D2 who required a visit to emergency room or hospitalization due to vaccine-related adverse effects (Tables 2 and 3).

The most common injection site reactions included tenderness (68% D1, 68% D2) or pain (66% D1, 65% D2). Fatigue (46% D1, 68% D2), headache (32% D1, 51% D2), and myalgias (20% D1, 43% D2) were the most frequently reported systemic reactions. Allergic reactions including anaphylaxis were rare, occurring in 0.7% after D1 and 0.5% after D2 (Tables 2 and 3).

Prior COVID-19 infection was positively associated with severe localized and systemic AEs to D1, but this same trend was not seen for D2. Female sex and vaccine type were also found to be positively associated with severe systemic reactions at D1. Treatment with ustekinumab was negatively associated with severe localized reaction at D1, while anti-tumor necrosis factor (TNF) therapy was positively associated with severe systemic reaction at D1 (Table 4).

Vaccine type was positively associated with severe injection site reaction to D2 with more localized reactions occurring with mRNA-1273 compared with BNT162b2. Age <50 years, female sex, mRNA-1273 vaccine, anti-TNF use, and

Table 2. Reported Adverse Reactions Within 7 Days After SARS-CoV-2 Vaccine Dose 1

	Total (N = 3316)	BNT162b2 (n = 1908)	mRNA-1273 (n = 1247)	Ad26.COV2.S (n = 161)
Adverse reaction injection site				
Pain	2183 (66)	1218 (64)	888 (71)	77 (48)
Redness	385 (12)	147 (8)	219 (18)	19 (12)
Itching	216 (7)	85 (4)	125 (10)	6 (4)
Swelling	383 (12)	153 (8)	218 (17)	12 (7)
Tenderness	2249 (68)	1251 (66)	905 (73)	93 (58)
Warmth	535 (16)	257 (13)	263 (21)	15 (9)
Injection site reaction severity				
None	435 (13)	271 (14)	118 (9)	46 (29)
Mild	2311 (70)	1373 (72)	842 (68)	96 (60)
Moderate	524 (16)	241 (13)	265 (21)	18 (11)
Severe	36 (1)	16 (1)	20 (2)	0 (0)
Required ED visit vs hospitalization	1 (0)	1 (0)	0 (0)	0 (0)
Systemic adverse reactions				
Fever	204 (6)	86 (5)	84 (7)	34 (21)
Chills	329 (10)	137 (7)	142 (11)	50 (31)
Fatigue	1532 (46)	817 (43)	608 (49)	107 (66)
Headache	1054 (32)	564 (30)	395 (32)	95 (59)
Joint pain	412 (12)	192 (10)	178 (14)	42 (26)
Muscle aches	673 (20)	328 (17)	283 (23)	62 (39)
Nausea	308 (9)	157 (8)	117 (9)	32 (21)
Allergic reaction	24 (1)	15 (1)	7 (1)	2 (1)
Rash	50 (2)	23 (1)	24 (2)	3 (2)
Other	220 (7)	115 (6)	89 (7)	16 (10)
Systemic reaction severity				
None	1382 (42)	853 (45)	493 (40)	36 (22)
Mild	1211 (37)	714 (37)	443 (36)	54 (34)
Moderate	595 (18)	292 (15)	247 (20)	56 (35)
Severe	86 (3)	30 (2)	41 (3)	15 (9)
Required ED visit vs hospitalization	9 (0)	5 (0)	4 (0)	0 (0)

Values are n (%).
Abbreviations: Ad26.COV2.S = Johnson & Johnson; BNT162b2 = Pfizer-BioNTech; ED = emergency department; mRNA-1273 = NIH-Moderna; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 3. Reported Adverse Reactions Within 7 Days After SARS-CoV-2 Vaccine Dose 2

	Total (n = 3080)	BNT162b2 (n = 1868)	mRNA-1273 (n = 1212)
Adverse reaction injection site			
Pain	1995 (65)	1143 (61)	852 (70)
Redness	442 (14)	182 (10)	260 (21)
Itching	275 (9)	115 (6)	160 (13)
Swelling	458 (15)	198 (11)	260 (21)
Tenderness	2086 (68)	1216 (65)	870 (72)
Warmth	562 (18)	287 (15)	275 (23)
Injection site reaction severity			
None	408 (13)	291 (16)	117 (10)
Mild	1970 (64)	1223 (65)	747 (62)
Moderate	606 (20)	310 (17)	296 (24)
Severe	84 (3)	34 (2)	50 (4)
Required ED visit vs hospitalization	1 (0)	1 (0)	0 (0)
Systemic adverse reactions			
Fever	776 (25)	349 (19)	427 (35)
Chills	999 (32)	484 (26)	515 (42)
Fatigue	2085 (68)	1174 (63)	911 (75)
Headache	1570 (51)	903 (48)	667 (55)
Joint pain	822 (27)	430 (23)	392 (32)
Muscle aches	1318 (43)	680 (36)	638 (53)
Nausea	552 (18)	313 (17)	239 (20)
Allergic reaction	18 (1)	11 (1)	7 (1)
Rash	63 (2)	37 (2)	26 (2)
Other	286 (9)	178 (10)	108 (9)
Systemic reaction severity			
None	662 (21)	475 (25)	187 (15)
Mild	863 (28)	573 (31)	290 (24)
Moderate	1163 (38)	623 (33)	540 (45)
Severe	352 (11)	174 (9)	178 (15)
Required ED visit vs hospitalization	5 (0)	4 (0)	1 (0)

Values are n (%).
Abbreviations: BNT162b2, Pfizer-BioNTech; ED, emergency department; mRNA-1273, NIH-Moderna; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

vedolizumab use were all positively associated with severe systemic reactions to D2 (Table 4).

Gastrointestinal Symptoms and IBD Activity Surrounding SARS-CoV-2 Vaccination

When asked about IBD activity in the 6 months leading up to COVID-19 vaccination, 32.5% described IBD in remission, 16.8% described IBD as rarely active, 15.9% described IBD as occasionally active, 18.2% described IBD as sometimes active, 11.0% described IBD as often active, and 5.7% described IBD as constantly active (Table 1). The most commonly reported gastrointestinal symptoms that worsened after SARS-CoV-2 vaccination included fatigue, bowel frequency, extraintestinal manifestations, and abdominal pain in 29%, 12%, 12%, and 11% of participants, respectively. However, we found that only 71 (2.1%) individuals met criteria for IBD flare following vaccination. Vaccine breakdown of those with IBD flare included 48 (2.5%) of 1908 from BNT162b2, 22 (1.8%) of 147 from mRNA-1273, and 1 (0.6%) of 161 from Ad26.COV2.S.

Change in Timing of IBD Medications Around SARS-CoV-2 Vaccination

A total of 456 (13.8%) participants reported changing the timing of their IBD therapy due to receiving SARS-CoV-2 D1 or D2. The medication with greatest proportion of users reporting a change in timing of dosing surrounding vaccination was methotrexate, with 32% adjusting timing of administration at D1 or D2, holding methotrexate for a median of 7 days before and after each immunization (Table 5). In comparison, only 8% and 4% of those on small molecules tofacitinib and thiopurines, respectively, reported change in timing of these medications around the time of SARS-CoV-2 vaccination.

Of the biologics, the largest proportion of individuals on certolizumab changed medication timing surrounding COVID-19 vaccination, with 22% of participants on certolizumab altering medication timing followed by adalimumab (20%), ustekinumab (14%), infliximab (10%), vedolizumab (9%), and golimumab (9%). Additional details regarding median length of time medications were held pre- and postvaccination are found in Table 5.

Table 4. Predictors of Severe Local and Systemic Reactions to SARS-CoV-2 Vaccine D1 and D2

	Severe Local Reaction D1			Severe Systemic Reaction D1			Severe Local Reaction D2			Severe Systemic Reaction D2		
	No (%)	Yes (%)	*P* Value	No (%)	Yes (%)	*P* Value	No (%)	Yes (%)	*P* Value	No (%)	Yes (%)	*P* Value
Age <50 y	99	1	.808	98	2	.148	98	2	.219	92	8	<.001
Female	99	1	.130	97	3	.015	97	3	.056	87	13	<.001
Anti-TNF use	99	1	.569	98	2	.013	98	2	.269	90	10	.008
Anti-IL-12/23 use	99	1	<.001	97	3	.934	99	1	.116	91	9	.106
Anti-integrin use	99	1	.942	95	5	.098	96	4	.392	82	18	<.001
Small molecule[a] use	99	1	.438	97	3	.686	97	3	.983	90	10	.154
Systemic steroid use	98	2	.464	99	1	.566	96	4	.585	90	10	.726
Prior COVID-19 infection	95	5	<.001	90	10	<.001	96	4	.563	87	13	.662
BNT162b2 vaccine	99	1	.068	98	2	<.001	98	2	<.001	90	10	<.001
mRNA-1273 vaccine	98	2		96	4		96	4		85	15	
Ad26.COV2.S vaccine	100	0		91	9							

Abbreviations: Ad26.COV2.S, Johnson & Johnson; BNT162b2, Pfizer-BioNTech; COVID-19, coronavirus disease 2019; D, dose; IL, interleukin; mRNA-1273, NIH-Moderna; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF, tumor necrosis factor.
[a]Methotrexate, thiopurine, or tofacitinib.

Table 5. Change in Timing of IBD Medication Due to Receiving the COVID-19 Vaccine

	Change in Medication Timing at D1 or D2	Median Length of Time Medication Held Pre-D1 (d)	Median Length of Time Medication Held Post-D1 (d)	Median Length of Time Medication Held Pre-D2 (d)	Median Length of Time Medication Held Post-D2 (d)
Prednisone	17 (12)	18	13	7	7
Budesonide	6 (5)	0	0	3	42
5-ASA	17 (3)	1	3	2	5
Sulfasalazine	7 (8)	1	1	2	2
Thiopurine	23 (4)	2	3	2	5
Methotrexate	59 (32)	7	7	7	7
Infliximab	78 (10)	3	10	7	14
Adalimumab	124 (20)	7	4	7	4
Certolizumab	13 (22)	30	25	6	5
Golimumab	2 (9)	0	0	0	1
Vedolizumab	37 (9)	11	14	7	7
Ustekinumab	68 (14)	18	13	7	7
Tofacitinib	5 (8)	2	5	2	6

Values are n (%), unless otherwise indicated.
Abbreviations: 5-ASA, 5-aminosalicylic acid; COVID-19, coronavirus disease 2019; D, dose; IBD, inflammatory bowel disease.

COVID-19 Infection After Vaccination

A total of 16 participants reported COVID-19 infection after starting their SARS-CoV-2 immunization series. This included 10 individuals who reported COVID-19 infection after D1, and 6 individuals with COVID-19 infection at least 2 weeks after completion of vaccine series. All infections were diagnosed via nasal polymerase chain reaction or antigen testing with the exception of a single participant reporting diagnosis via saliva test. Although 93.8% (n = 15 of 16) reported symptomatic COVID-19 infection, none required hospitalization.

Discussion

Our study evaluated the development of COVID-19 vaccine–related AEs and the effect of SARS-CoV-2 vaccination on IBD disease course in a large, geographically diverse U.S. cohort of individuals with IBD. Overall, severe vaccine-related AEs were rare. Importantly, very few patients reported clinically significant IBD exacerbations following immunization.

We observed that prior COVID-19 infection was associated with severe local and systemic AEs to D1; female sex and vaccine type were associated with systemic reactions to D1 and D2; and age <50 years, anti-TNF use, and vedolizumab use were associated with severe systemic reactions to D2. Overall, our findings of a more severe reaction to D1 in those with prior COVID-19 is consistent with studies in the general population in which high reactogenicity was observed after a single dose of messenger RNA (mRNA) vaccine among individuals previously infected with SARS-CoV-2.[13,14] Our main finding of relatively low vaccine-related AEs is also consistent with a prior small study of IBD patients that indicated similar

AE frequency to that of the general population.[10] Our findings differ from this prior study in that they found AEs to be less common in those on biologic therapies, whereas we found both vedolizumab and anti-TNF therapies to be positively associated with severe systemic reactions to D2.[10] Such differences may be explained by their smaller sample size of participants on biologic therapies; however, there is no consistent pattern that would warrant change in immunization recommendations in subgroups of IBD patients.

Very few participants in our study described worsening IBD disease activity requiring either a change or addition of medication following SARS-CoV-2 vaccination. This extends the findings of with Hadi et al,[15] who found no difference in new steroid prescriptions 1 month following SARS-CoV-2 vaccination in a matched cohort of vaccinated IBD and nonvaccinated IBD patients. Rates of IBD flare reported in our cohort are similar to those previously reported in prior studies evaluating the effect of influenza, pneumococcal, and shingles vaccination on IBD disease course.[5,7-9]

When examining patterns of IBD medication use surrounding SARS-CoV-2 vaccination, we found that a higher proportion of individuals taking methotrexate changed the timing of medication dosing in comparison with other small molecules or biologics. This may have been driven by the rheumatology literature in which expert opinion recommended holding methotrexate for 1 week after each of the 2 mRNA vaccine doses and 2 weeks following Ad26.COV2.S vaccination.[16] This is in comparison with guidance from the International Organization for Study of Inflammatory Bowel Disease in which it was recommended that the best time for patients to receive SARS-CoV-2 vaccination was the earliest opportunity to do so with no specific recommendations to hold or delay IBD medications around the time of immunization.[17]

COVID-19 infection after SARS-CoV-2 vaccination was rare in our cohort, occurring in <0.5% of participants, with a majority of these cases occurring before receipt of second dose of mRNA vaccine or within weeks of completing the vaccine series. A recent study that used electronic health record data to evaluate the efficacy of SARS-CoV-2 vaccination in IBD patients (n = 5561) found a similar incidence of breakthrough COVID-19 infection at 0.4% with a majority of cases occurring within 1 month of first immunization.[15] Longer-term follow-up is ongoing within our PREVENT-COVID cohort to estimate the true rate of breakthrough COVID-19 infections in the IBD population. In particular, as the delta variant becomes more prevalent across the United States, the PREVENT-COVID study will continue to have longitudinal follow-up, with the ability to capture additional vaccinations and to assess COVID-19 infection outcomes.

Our study has several limitations including lack of racial-ethnic diversity, a convenience sample that may impact external validity, and reliance on self-report owing to direct-to-patient recruitment. Additionally, the relatively infrequent occurrence of serious AEs precluded multivariable modeling, and we did not adjust for multiple comparisons. Hence, associations between clinical and treatment-related characteristics and serious vaccine-related AEs must be considered exploratory and may be subject to confounding or false discovery. Despite these limitations, our study provides highly anticipated data regarding the safety and tolerability of the SARS-CoV-2 vaccination in an IBD-specific population, which was a key area of interest among patients with IBD who were surveyed about their intent and perceptions regarding SARS-CoV-2 vaccination.[4]

Strengths of this study include the geographic diversity as well as the size of our cohort, the largest sample to date reporting on IBD patient-reported outcomes following SARS-CoV-2 vaccination. Although safety outcomes after SARS-CoV-2 vaccination in the IBD population were previously reported by Hadi et al,[15] these focused on immediate AEs within 1 day of vaccination and AEs of special interest per the Centers for Disease Control and Prevention. Our study uses the same categories of localized and systemic AEs that were described in the initial SARS-CoV-2 vaccine clinical trials, which contributes to the generalizability of this study.[1-3]

Our findings provide reassurance that the SARS-CoV-2 vaccine is safe and well tolerated among individuals with IBD, including those on immune-suppressing therapies. Although longer-term follow-up is ongoing, these data may help to combat vaccine hesitancy and increase vaccine confidence in those with IBD.

Author Contributions

K.N.W.: acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; study supervision; final approval of manuscript. X.Z.: analysis and interpretation of data; critical revision of the manuscript for important intellectual content; statistical analysis; final approval of manuscript. X.D., R.W., J.A., M.C.D., A.K., A.B., J.A.S., R.K.C., P.D.R.H., R.C.U., M.B., E.B., F.A.F., M.E.B., A.F.: acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; final approval of manuscript. M.D.K.: study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; obtained funding; study supervision; final approval of manuscript. M.D.L.: study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; obtained funding; study supervision; final approval of manuscript.

Funding

This study was supported by the Leona M. and Harry B. Helmsley Charitable Trust.

Conflicts of Interest

X.Z., X.D., R.W., A.K., J.A.S., M.E.B., and A.F. have no conflicts of interest. K.N.W. has consulted for AbbVie. J.A. has consulted 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 & Colitis Foundation, and the Leona M. and Harry B. Helmsley Charitable Trust. M.C.D. has consulted for AbbVie, Arena, Bristol Myers Squibb, Celgene, Gilead, Janssen, Pfizer, Prometheus Labs, and Takeda; and received grant support from AbbVie and Prometheus Labs; and received license fees from Takeda. A.B. has been a subinvestigator on trials for Prometheus, Janssen, AbbVie, Takeda, Buhlmann, Arena, and Eli Lilly in the past 36 months; and consulted for Arena, Takeda, Best Doctors, and Eli Lilly. R.K.C. has participated in advisory boards and consulting with AbbVie, Bristol Myers

Squibb, Eli Lilly, Janssen, LabCorp, Pfizer, Samsung Bioepis, and Takeda. P.D.R.H. has consulted for AbbVie, Pfizer, Takeda, and has received grant support from National Institutes of Health, Crohn's & Colitis Foundation, AbbVie, Pfizer, Takeda, Genentech, Eli Lilly, Arena, and the Rainin Foundation.

R.C.U. has served as an advisory board member or consultant for AbbVie, Bristol Myers Squibb, Eli Lilly, Janssen, Pfizer, and Takeda; has received research support from AbbVie, Boehringer Ingelheim, and Pfizer; and is funded by an National Institutes of Health Career Development Award (K23KD111995-01A1). M.B. discloses research funding from Janssen, GlaxoSmithKline, and Takeda; having served as a consultant for Janssen, AbbVie, BMS, and Pfizer; and having received honorarium for participation in a continuing medical education program sponsored by AbbVie. E.B. has consulted for AbbVie, Pfizer, and Bristol Myers Squibb. F.A.F. is a consultant for Arena, BMS, Braintree Labs, Gilead, GI Reviewers, Innovation Pharmaceuticals, Iterative Scopes, Janssen, Pfizer, and Sebela; and sits on a Data Safety Monitoring Board for Lilly and Theravance. 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, Celltrion, and Arena Pharmaceuticals. M.D.L. has received research/grants from Pfizer and has consulted for AbbVie, Bristol Myers Squibb, Calibr, Eli Lilly and Company, Genentech, Gilead Sciences, Janssen Pharmaceuticals, Pfizer, Roche, Takeda Pharmaceuticals, TARGET PharmaSolutions, and Theravance Biopharma.

References

1. Polack FP, Thomas SJ, Kitchin N, et al; C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med.* 2020;383:2603-2615.
2. Baden LR, El Sahly HM, Essink B, et al; COVE Study Group. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med.* 2021;384:403-416.
3. Sadoff J, Gray G, Vandebosch A, et al; ENSEMBLE Study Group. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. *N Engl J Med.* 2021;384:2187-2201.
4. Dalal RS, McClure E, Marcus J, et al. COVID-19 vaccination intent and perceptions among patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2021;19:1730-1732.e2.
5. Fiorino G, Peyrin-Biroulet L, Naccarato P, et al. Effects of immunosuppression on immune response to pneumococcal vaccine in inflammatory bowel disease: a prospective study. *Inflamm Bowel Dis.* 2012;18:1042-1047.
6. Cullen G, Bader C, Korzenik JR, Sands BE. Serological response to the 2009 H1N1 influenza vaccination in patients with inflammatory bowel disease. *Gut.* 2012;61:385-391.
7. Launay O, Abitbol V, Krivine A, et al; MICIVAX Study Group. Immunogenicity and safety of influenza vaccine in inflammatory bowel disease patients treated or not with immunomodulators and/or biologics: a two-year prospective study. *J Crohns Colitis.* 2015;9:1096-1107.
8. Rahier JF, Papay P, Salleron J, et al; European Crohn's and Colitis Organisation (ECCO). H1N1 vaccines in a large observational cohort of patients with inflammatory bowel disease treated with immunomodulators and biological therapy. *Gut.* 2011;60:456-462.
9. Satyam VR, Li PH, Reich J, et al. Safety of recombinant zoster vaccine in patients with inflammatory bowel disease. *Dig Dis Sci.* 2020;65:2986-2991.
10. Botwin GJ, Li D, Figueiredo J, et al. Adverse events After SARS-CoV-2 mRNA vaccination among patients with inflammatory bowel disease. *Am J Gastroenterol.* 2021;116:1746-1751.
11. Kappelman MD, Weaver KN, Boccieri M, et al; PREVENT-COVID Study Group. Humoral immune response to messenger RNA COVID-19 vaccines among patients with inflammatory bowel disease. *Gastroenterology.* 2021;161:1340-1343.e2.
12. Clara I, Lix LM, Walker JR, et al. The Manitoba IBD Index: evidence for a new and simple indicator of IBD activity. *Am J Gastroenterol.* 2009;104:1754-1763.
13. Wise J. Covid-19: people who have had infection might only need one dose of mRNA vaccine. *BMJ.* 2021;372:n308.
14. Krammer F, Srivastava K, Alshammary H, et al. Antibody responses in seropositive persons after a single dose of SARS-CoV-2 mRNA vaccine. *N Engl J Med.* 2021;384:1372-1374.
15. Hadi YB, Thakkar S, Shah-Khan SM, et al. COVID-19 vaccination is safe and effective in patients with inflammatory bowel disease: analysis of a large multi-institutional research network in the United States. *Gastroenterology.* 2021;161:1336-1339.e3.
16. Curtis JR, Johnson SR, Anthony DD, et al. American college of rheumatology guidance for COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases: version 3. *Arthritis Rheumatol.* 2021;73:e60-e75.
17. Siegel CA, Melmed GY, McGovern DP, et al. SARS-CoV-2 vaccination for patients with inflammatory bowel diseases: recommendations from an international consensus meeting. *Gut.* 2021;70:635-640.