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Serologic Response to Messenger RNA Coronavirus Disease 2019 Vaccines in Inflammatory Bowel Disease Patients Receiving Biologic Therapies

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Inflammatory bowel disease (IBD) patients with Crohn's disease and ulcerative colitis have been considered at increased risk of severe coronavirus disease 2019 (COVID-19) because they are often treated with immunosuppressive medications. Indeed, steroids and thiopurines in combination therapy with tumor necrosis factor (TNF) antagonists, but not TNF antagonist monotherapy, have been associated with a risk of severe COVID-19 in IBD patients.[1,2] Expert consensus advocates that IBD patients should be vaccinated against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[3] A study showing attenuated anti-nucleocapsid responses to SARS-CoV-2 infection in IBD patients on infliximab and another study reporting poor anti-spike antibody responses in organ transplant patients after the first dose of messenger RNA vaccines have raised concern regarding vaccine responses in IBD patients.[4–6] Still, the impact of medications on COVID-19 vaccine efficacy in IBD patients is unknown, because patients with immunosuppressed states and/or treated with immunosuppressants were excluded from vaccine trials. To address this, we evaluated serologic responses to COVID-19 vaccination with the SARS-CoV-2 spike (S) messenger RNA BNT162b2 (Pfizer-BioNTech) and messenger RNA-1273 (National Institutes of Health [NIH]-Moderna) vaccines in IBD patients.

Methods

All patients were enrolled in the CiTI (COVID-19 in Therapeutic Infusion) study, an ongoing SARS-CoV-2 serosurvey of IBD patients at the Icahn School of Medicine at Mount Sinai. All patients who self-reported at least 1 vaccination appointment between the first date of vaccine distribution in New York City on December 14, 2020 and February 12, 2021 were included.[7] Specimens were collected at routine infusion center and clinic appointments and were not timed to vaccination dates. Control groups included 14 completely vaccinated healthcare workers (HCWs) without IBD who underwent a single blood draw and 29 vaccinated healthy volunteers (PICR cohort) without IBD who underwent serial blood draws after vaccination. For comparison, we included antibody testing results from 21 study patients infected with SARS-CoV-2 to show the relation to naturally generated antibodies. The studies under which subjects were recruited were approved by the Icahn School of Medicine at Mount Sinai Institutional Review Board.

IBD patient and HCW sera were analyzed using the Siemens Healthineers COV2T and sCOVG assays testing for total immunoglobulins and IgG, respectively, to the receptor binding domain (RBD) of the SARS-CoV-2 S protein and the Roche assay for antibodies to nucleocapsid protein. An in-house ELISA tested for IgG against full-length S protein was performed for IBD patients and both HCWs and PICR control subjects. See Supplementary Methods for additional details.

Results

Forty-eight IBD patients were included in the analysis, including 23 Crohn's disease and 25 ulcerative colitis patients (see Supplementary Table 1). Most patients were receiving biologics of any kind at the time of vaccination (41 patients, 85.4%), including 16 (33.3%) TNF antagonist monotherapy, 17 (35.4%) vedolizumab monotherapy, 3 (6.3%) vedolizumab combination therapy with thiopurine, and 4 (8.3%) ustekinumab; 1 patient (2.1%) was receiving guselkumab for psoriasis. Three patients (6.3%) were on oral steroids at the time of vaccination. Five patients (10.4%) were on no medications. Control subjects, including 14 vaccinated HCWs (mean age, 35.2; 50% women) and 29 vaccinated subjects in the PICR cohort (mean age, 31.5; 37.9% women), were younger than the IBD cohort (mean age, 49; 52% women; $P = .016$ and $P < .0001$, respectively).

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***Abbreviations used in this paper:* COVID-19, coronavirus disease 2019; HCW, healthcare worker; IBD, inflammatory bowel disease; NIH, National Institutes of Health; PICR, ■■■; RBD, receptor binding domain; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF, tumor necrosis factor.**

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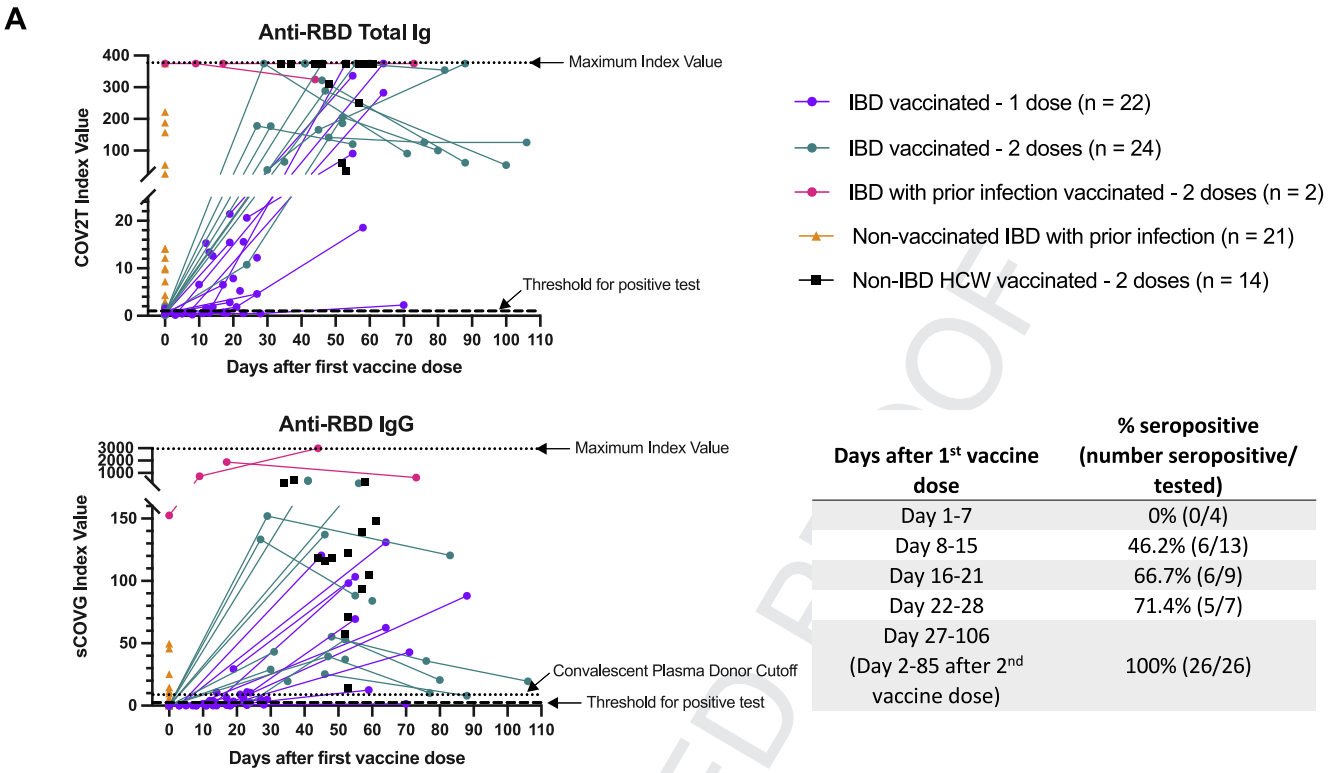

Days after 1st vaccine dose	% seropositive (number seropositive/ tested)
Day 1-7	0% (0/4)
Day 8-15	46.2% (6/13)
Day 16-21	66.7% (6/9)
Day 22-28	71.4% (5/7)
Day 27-106 (Day 2-85 after 2nd vaccine dose)	100% (26/26)

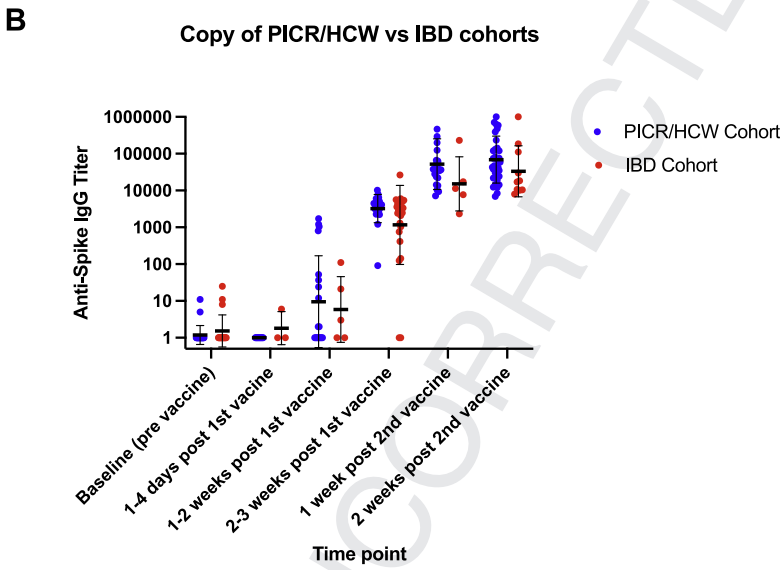

Figure 1. Antibody response to SARS-CoV-2 immunization in IBD patients compared with HCW control subjects. (*A*) Siemens COV2T and sCOVG testing for total immunoglobulin and IgG against SARS-CoV-2 RBD. Thresholds for positive tests and maximum index value for COV2T are shown by *dotted lines* as indicated. The percentage of seropositivity over time since fist vaccine dose in IBD patients is shown in the table. (B) Anti-S IgG results comparing IBD with PICR/HCW cohorts over time.

Participants received either Pfizer-BioNTech (IBD, 23 patients; HCWs, 11; PICR cohort, 20) or NIH-Moderna (IBD, 25; HCWs, 3; PICR cohort, 9) vaccines. Of IBD patients, 26 completed 2 doses and 22 completed 1 dose. All HCW control subjects and 26 (89.7%) PICR control subjects completed 2 doses.

Three IBD patients (2 with prior COVID-19 and 1 with mild COVID-19 as defined by NIH guidelines between doses 1 and 2) and 1 HCW reported laboratory-confirmed COVID-19 infection by nasopharyngeal polymerase chain recation or SARS-CoV-2 antibody testing after recovery. Prevaccine baseline sera (19 patients) showed absence of anti-RBD and anti-nucleocapsid antibodies in all but 1 patient with prior COVID-19 who had both antibody types at baseline. Because we did not have baseline sera for all patients, we screened all samples for evidence of pre-existing antibodies by anti-

nucleocapsid testing, which were only positive for the patients with known prior COVID-19. In addition, among PICR control subjects, 5 (17.2%) had baseline IgG reactivity to S protein because of prior infection.

All 26 IBD patients who completed the 2-dose vaccine schedules had positive anti-RBD tests, of whom 22 of 26 (84.6%) achieved index levels that would qualify for convalescent plasma donation (Figure 1). The percentage of seropositivity by week is shown in Figure 1. Two IBD patients with prior infection achieved high index values after a single vaccine dose, well above values achieved from natural SARS-CoV-2 infection (Figure 1*A*). Analysis of anti-S IgG levels of IBD patients compared with the PICR and HCW cohorts showed similar titers at all time points (Figure 1*B*). For patients who received 2 vaccine doses, multiple linear regression analyses revealed no association between timing of infusion and antibody response (Supplementary Table 1).

Of the 26 patients who completed both COVID-19 vaccine doses, 8 were receiving TNF antagonist monotherapy, 12 vedolizumab monotherapy, 2 ustekinumab, and 4 no medications. Analyses of the effects of anti-TNF and vedolizumab monotherapy on serologic response in these patients revealed that anti-TNFs were associated with lower anti-RBD total immunoglobulin only ($P = .0299$) and vedolizumab was associated with lower anti-RBD total immunoglobulin ($P = .0069$), anti-RBD IgG ($P = .045$), and anti-S IgG ($P = .0043$) than in HCW control subjects (Supplementary Figure 1).

Discussion

Here we report serologic responses with 100% seropositivity after 2-dose Pfizer-BioNTech and NIH-Moderna COVID-19 vaccination in IBD patients on biologic therapies. In IBD patients with previous SARS-CoV-2 seroconversion, a single dose of either vaccine induced high index values, mirroring findings from a recent HCW study.[7] Despite achieving antibody levels consistent with presumed protection, we also found an association of lower antibody levels in patients with vedolizumab for all antibodies tested and with anti-TNFs for anti-RBD total immunoglobulin only. This finding warrants further investigation, because results could have been affected by timing, vaccine, or clinical characteristics such as age.

These are the first data of serologic responses to COVID-19 vaccines in IBD patients with detailed analysis of antibodies to both nucleocapsid and RBD/S proteins. Despite study limitations such as small sample size, single-center experience, and differences in time to blood collections, this study brings a reassuring message to IBD patients and healthcare practitioners. Larger studies with more detailed measurements including cell-mediated responses, particularly between dose 1 and 2, are required to assess immune responses and the effects of medications. In the meantime, our results support the consensus recommendation for IBD patients to receive COVID-19 vaccines when available.[3]

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org and at https://doi.org/10.1053/j.gastro.2021.04.025.

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CRediT Authorship Contributions

Serre-Yu Wong, MD, PhD (Conceptualization: Lead; Data curation: Equal; Formal analysis: Equal; Funding acquisition: Lead; Investigation: Equal; Methodology: Equal; Project administration: Equal; Supervision: Lead; Visualization: Lead; Writing – original draft: Lead; Writing – review & editing: Equal).

Rebekah Dixon, BS (Conceptualization: Equal; Investigation: Equal; Methodology: Equal; Project administration: Equal; Writing – review & editing: Equal).

Vicky Martinez Pazos, BS (Investigation: Equal; Methodology: Equal; Writing – review & editing: Supporting).

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Jean-Frederic Colombel, MD (Conceptualization: Equal; Formal analysis: Equal; Funding acquisition: Equal; Methodology: Supporting; Writing – review & editing: Equal).

Ken Cadwell, PhD (Conceptualization: Equal; Formal analysis: Equal; Funding acquisition: Equal; Methodology: Equal; Writing – review & editing: Equal).

Conflicts of interest
These authors disclose the following: Sacha Gnjatic receives research grants from Bristol-Myers Squibb, Genentech, Immune Design, Agenus, Janssen R&D, Pfizer, Takeda, and Regeneron and has advisory roles with Merck, Neon Therapeutics, and OncoMed. Jean-Frederic Colombel receives research grants from AbbVie, Janssen Pharmaceuticals, and Takeda; receives payment for lectures from AbbVie, Amgen, Allergan, Inc, Ferring Pharmaceuticals, Shire, and Takeda; receives consulting fees from AbbVie, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, BMS, Celgene Corporation, Eli Lilly, Ferring Pharmaceuticals, Galmed Research, Genentech, Galxo Smith Kline, Janssen Pharmaceuticals, Kaleido Biosciences, Imedex, Immunic, Iterative Scopes, Merck, Microba, Novartis, PBM Capital, Pfizer, Sanofi, Takeda, TiGenix, and Vifor; and holds stock options in Intestinal Biotech Development. Ken Cadwell receives research funding from Pfizer, Takeda, and Abbvie; has consulted for or received honorarium from Puretech Health, Genentech, and Abbvie; and holds US patent 10,722,600 and provisional patent 62/935,035. The remaining authors disclose no conflicts.

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Supplementary Methods

Patients

Research personnel corresponded beginning January 29, 2021 with all CiTI study patients, including new study participants and those previously enrolled returning for follow-up appointments, to invite them to self-report COVID-19 vaccination. All patients who responded and provided vaccine dates and type were included. Patients enrolled in the study reported COVID-19 vaccination status and reported dates and types of vaccination, vaccine reactions by self-reporting, current medications, COVID-19 testing, and illness history by an online survey, email responses, and follow-up phone calls. Age, sex, race, type of IBD, and medications were confirmed by medical record.

Sample Processing

Blood specimens were collected in SST tubes, allowed to clot, and centrifuged at 1100–1300*g* for 20 minutes at room temperature. The specimens were aliquoted into sterile cryovials and stored immediately at −80°C until testing.

Serology Testing

The emergency use authorization (EUA) Siemens COV2T chemiluminescence-based assay measures total antibodies to the SARS-CoV-2 RBD of the S protein, and the EUA sCOVG is a semiquantitative assay for anti-RBD IgG. Although both the COV2T and sCOVG are semiquantitative assays, at the time of this writing only the sCOVG assay has EUA for semiquantitative index value results. An index value of 1 equals a positive test. These tests are expected to detect seroconversion both to SARS-CoV-2 infection and vaccines designed to deliver S protein antigen. To distinguish serologic response secondary to vaccine vs natural infection, all sera were additionally tested by the EUA Roche assay for antibodies (IgG) to nucleocapsid protein, which is not targeted by currently approved vaccines in the United States and would therefore be expected only to be positive in sera from individuals with SARS-CoV-2 infection.

For the in-house ELISA to S protein, sera were serially diluted from 1:100 to 1:6400, and results were expressed as reciprocal titers based on the predicted dilution at which a linear extrapolation of the titration curve meets a cutoff determined from a healthy donor serum pool. A titer ≥ 100 was considered positive and 4× titer increase from baseline as significant. The cutoff of 100 is empirical and based on the fact that ELISA titrations start from 1:100 onward, in 4-fold dilutions.[1]

Statistical Methods

Statistical analysis was performed using R v3.5.3 and GraphPad Prism v9. For categorical covariates, *P* values were calculated using the χ^2 test with Yates continuity correction. For continuous covariates, *P* values were calculated using Student's *t* test, Mann-Whitney test, or Wilcoxon test.

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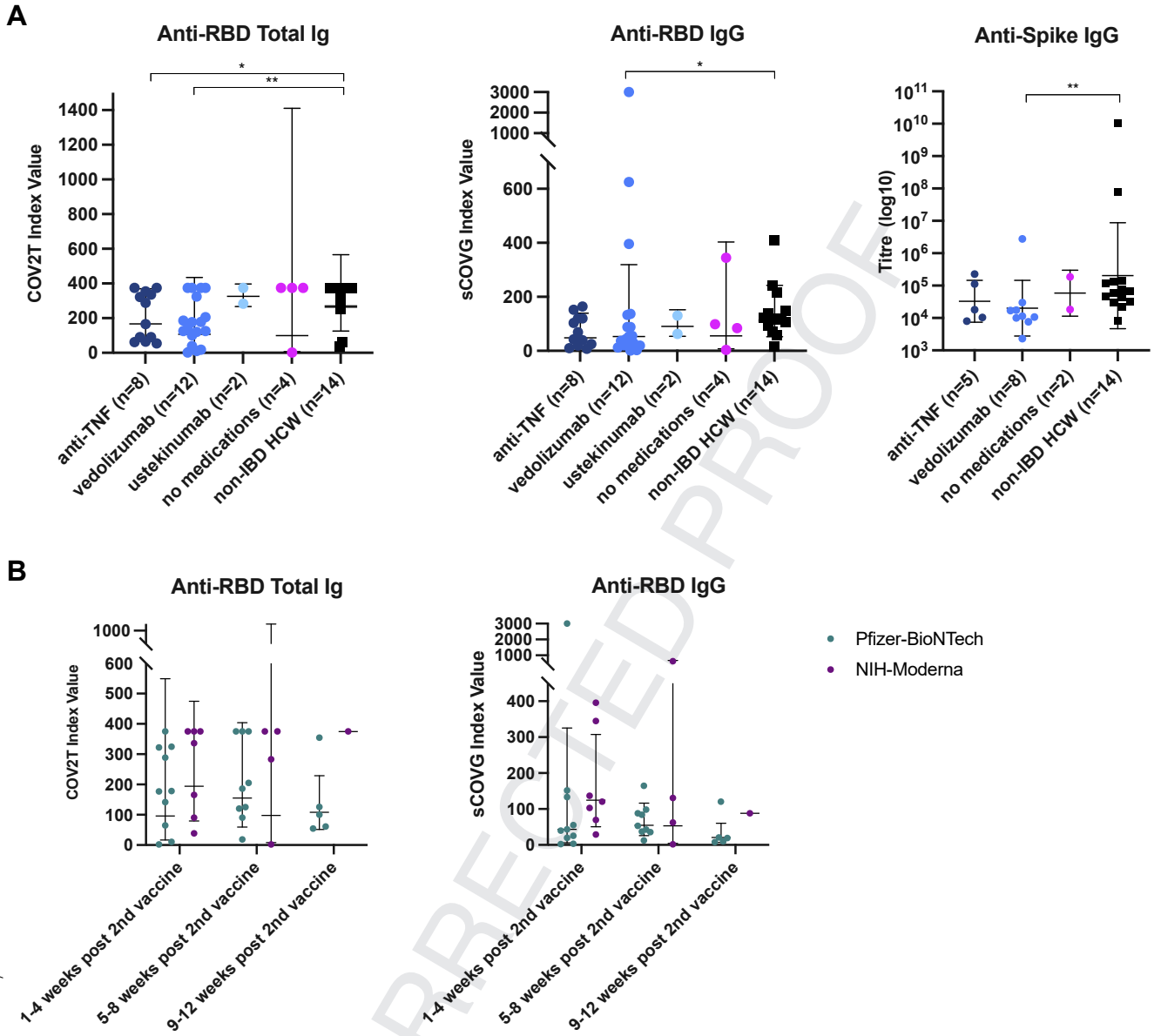

Supplementary Figure 1. Comparison of SARS-CoV-2 antibody measurements in IBD patients after completing 2 doses of Pfizer-BioNTech or NIH-Moderna vaccination by (*A*) medications and (*B*) vaccine make. Differences between groups were nonsignificant ($P > .05$) unless otherwise noted. *$P \leq .05$, **$P \leq .01$.

Supplementary Table 1. Baseline Characteristics of Vaccinated Individuals

Characteristic	Subcategory	Vaccinated IBD Patients (n = 48)	Vaccinated Non- IBD HCWs (Control Subjects) (n = 14)	Vaccinated PICR Cohort (Control Subjects) (n = 29)	*P*
Age, y, mean (SD)		49.1 (20.2)	35.2 (9.4)	31.5 (10.3)	.016 <.0001
Gender, female		25 (52)	7 (50)	11 (37.9)	1.000 .34
Race	White	42 (87.5)	10 (71.4)	18 (62.1)	.21
	Nonwhite	6 (12.5)	4 (28.6)	11 (37.9)	.02
Type of IBD	Crohn's disease	23 (47.9)	—	—	—
	Ulcerative colitis	25 (52.1)	—	—	—
IBD medications	Infliximab monotherapy	14 (29.2)	—	—	—
	Adalimumab monotherapy	2 (4.2)	—	—	—
	Vedolizumab monotherapy	17 (35.4)	—	—	—
	Vedolizumab + immunomodulator	3 (6.3)			
	Ustekinumab	5 (10.4)	—	—	—
	Tofacitinib	1 (2.1)	—	—	—
	Biologic, any[a]	41 (85.4)	—	—	—
	Steroids, oral[b]	3 (6.3)	—	—	—
	Immunomodulator[b]	3 (6.3)	—	—	—
	Mesalamine[b]	11 (22.9)	—	—	—
	No IBD medications	5 (10.4)	14 (100)	—	—
Known prior COVID-19 infection		3 (6.3)	1 (7.1)	—	1.000
Vaccine type	Pfizer-BioNTech	23 (47.9)	11 (78.6)	20 (69)	.066
	NIH-Moderna	25 (52.1)	3 (21.4)	9 (31)	.12
Doses completed	1 dose	22 (45.8)	—	3 (10.3)	.0011
	2 doses	26 (54.2)	14 (100)	26 (89.7)	.0012
Median time from prior infusion to first dose (range)[c]		25.5 (0–58)	—	—	—
Median time from first dose to next infusion (range)[c]		16 (2–28)	—	—	—
Median time from prior infusion to second dose (range)[d]		10 (0–28)			
Median time from second dose to next infusion (range)[d]		18 (2–45)			
Median time to blood collection after first dose (range)		14 (3–28)	30 (7–37)	9 (1–40)	<.0001
Median time to blood collection after second dose (range)		18 (2–36)		8 (6–18)	.0001 <.0001
Vaccine reaction, yes		29/36 (80.6)	13/14 (92.9)	—	.024
	Severe reaction	0 (0)	0 (0)	—	
	Local arm pain/swelling/rash	19 (65.5)	9 (69.2)	—	.68
	Myalgia	12 (41.3)	8 (61.5)	—	.22
	Arthralgia	1 (3.4)	3 (23.1)	—	.11

Supplementary Table 1. Continued

Characteristic	Subcategory	Vaccinated IBD Patients (n = 48)	Vaccinated Non- IBD HCWs (Control Subjects) (n = 14)	Vaccinated PICR Cohort (Control Subjects) (n = 29)	*P*
	Fatigue	14 (48.3)	7 (53.8)	—	.69
	Headache	9 (31.0)	6 (46.2)	—	.37
	Fever/subjective fever	12 (41.4)	2 (15.4)	—	.32
	Chills	8 (27.6)	2 (15.4)	—	.81
	GI symptoms[e]	4 (13.8)	0 (0)	—	.47
	Other rash[f]	1 (3.4)	0 (0)	—	.53
	Other localized pain[h]	3 (10.3)	0 (0)	—	.65

Values are n or n/N (%) unless otherwise defined. —, .
[g]Pain localized to breast, knee, and leg.
[a]One patient received guselkumab (anti-IL-23) for psoriasis but takes no medications for ulcerative colitis.
[b]Steroids, immunomodulators, and mesalamine were taken in combination with 1 of the above treatments.
[c]Calculated for 37 patients who received at least 1 vaccine dose while treated with infusion biologics (infliximab, vedolizumab, ustekinumab).
[d]Calculated for 22 patients who completed 2 vaccine doses while treated with infusion biologics (infliximab, vedolizumab, ustekinumab).
[e]Gastrointestinal symptoms included nausea, diarrhea, and self-described Crohn's flare.
[f]Stomach rash.