Postvaccination Immunogenicity of BNT162b2 SARS-CoV-2 Vaccine and Its Predictors in Pediatric Inflammatory Bowel Disease

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ABSTRACT

Objectives: We prospectively compared the postvaccination immunity to messenger ribonucleic acid BNT162b2 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine of our pediatric patients over 12 years old with inflammatory bowel disease (IBD) to that of healthy controls and looked for predictors of its robustness.

Methods: Anti-receptor binding domain, anti-spike S2, and anti-nucleocapsid immunoglobin-G (IgG) and immunoglobin-A levels were measured in 139 pediatric patients with IBD [65 fully vaccinated (2 doses), median age 16.3, interquartile range (IQR) 15.2–17.8 years, median time from vaccination (IQR) 61.0 (42.0–80.0) days] and 1744 controls (46, 37–57 years) using microblot array.

Results: All IBD and control patients developed positive anti-receptor binding domain IgG antibodies at comparable titers. The proportion of observations with positive anti-spike S2 IgG was higher in patients with IBD than in controls [63% vs 21%, odds ratio 2.99 (1.51–5.90)], as was its titer [median (IQR) 485 (92–922) vs 79 [33–180] IU/mL]. Anti-receptor binding domain and anti-spike S2 IgG levels were associated with IBD status. We found an association between anti-spike S2 IgG levels and time since vaccination (β −4.85, 95% CI −7.14 to 2.71, $P = 0.0001$), history of SARS-CoV-2 polymerase chain reaction positivity (206.76, 95% CI 39.93–374.05, $P = 0.0213$), and anti-tumor necrosis factor treatment (−239.68, 95% CI −396.44–83.55, $P = 0.0047$). Forty-three percent of patients reported vaccination side effects (mostly mild). Forty-six percent of observations with positive anti-nucleocapsid IgG had a history of SARS-CoV-2 infection.

Conclusions: Patients with IBD produced higher levels of postvaccination anti-spike S2 antibodies than controls. Previous SARS-CoV-2 infection is associated with higher production of postvaccination antibodies and anti-tumor necrosis factor treatment with lower production.

Key Words: COVID-19, nucleocapsid antigen, receptor binding domain, spike protein, tumor necrosis factor

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What Is Known

- Patients with inflammatory bowel disease (IBD) were excluded from registration trials of BNT162b2 messenger ribonucleic acid vaccine.
- There is scarce data on the efficacy and safety in patients with IBD, especially children.

What Is New

- Pediatric IBD patients produced higher levels of anti-spike S2 antibodies than controls.
- Previous severe acute respiratory syndrome coronavirus 2 infection was associated with higher production of postvaccination antibodies and anti-tumor necrosis factor treatment with lower production.

Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in patients with inflammatory bowel disease (IBD) is recommended by many professional societies (1–3). However, patients with IBD were excluded from registration trials of vaccines; thus, there is scarce data on the efficacy and safety in patients with IBD, especially children. Vaccination by messenger ribonucleic acid (mRNA) vaccine BNT162b2 (Comirnaty—Pfizer/BioNTech) of children 12 years and older was approved by the European Medicine Agency in spring 2021, and in the Czech Republic, it commenced on July 1, 2021. A clinical study in healthy individuals has shown that immune responses in the age group of 12–15 year-olds were comparable with those in the age group of 16–25 year-olds, and the side effects were mild (4). Based on the

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J.B. received lectures/congress fees/consultation fees from MSD, AbbVie, Nutricia, and Nestlé. T.L. received lectures/congress fees/consultation fees from AbbVie, Nutricia, Ferring, and Biocodex. K.M. received lectures/congress fees/consultation fees from AbbVie and Takeda. A.K. received congress fees from Takeda and shares from AbbVie, ThermoFisher Scientific, and Becton Dickinson. O.H. received lectures/congress fees/consultation fees from MSD, AbbVie, Takeda, Nutricia,

recommendation of the Czech Working Group for Pediatric Gastroenterology, children with IBD in our country were not prioritized for vaccination against SARS-CoV-2, and vaccination in this group started along with other healthy children after vaccine approval in July 2021. According to a position paper by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition Porto IBD working group, surveillance of postvaccination antibodies in patients with pediatric IBD (pIBD) are recommended (5). Based on this recommendation, we initiated a prospective follow-up of patients with pIBD.

Information about postvaccination SARS-CoV-2 immunity in patients with pIBD is scarce (6–8). This is the first prospective study focused primarily on patients with pIBD (12–18 years) vaccinated against SARS-CoV-2 using an mRNA vaccine.

SARS-CoV-2 virus contains various epitopes. Antibodies against some of them are used for testing of postinfection and/or postvaccination status. Anti-receptor binding domain of S1 subunit of spike protein (anti-RBD) antibodies and anti-spike S2 antibodies are against antigens on the viral surface and are considered markers of postvaccination or postinfection status. On the contrary, anti-nucleocapsid antibodies are formed against an antigen inside of the viral particle and are thus considered as markers of postinfection status only.

Our primary aim was to compare postvaccination immunity (production of anti-RBD immunoglobin-G [IgG], and anti-spike S2 IgG) in patients with pIBD and healthy controls (HCs). We also focused on predictors of postvaccination immunity status and the role of history of SARS-CoV-2 infection, IBD treatment used, and disease activity at the time of observation.

METHODS

Study Subjects

After the approval of SARS-CoV-2 vaccination for children 12 years and older in the Czech Republic in July 2021, we started to prospectively recruit patients with pIBD irrespective of treatment at our IBD center. Participation in the study was offered to all ambulatory and hospitalized patients with IBD during the period of September 8, 2021 to December 17, 2021, irrespective of the time since SARS-CoV-2 infection or vaccination. Altogether, 195 observations [median age 15.6, interquartile range (IQR) 13.6–17.1] of 139 patients were obtained. Of these, 83 observations were from 65 patients [median age 16.4, IQR 14.5–17.9, 40 patients with Crohn's disease (CD), 21 with ulcerative colitis, and 4 with IBD unclassified] fully vaccinated against SARS-CoV-2 [received 2 doses of mRNA vaccine BNT162b2 (Comirnaty—Pfizer/BioNTech); median time from vaccination (IQR) was 61.0 (42.0–80.0) days]. The basic characteristics of vaccinated patients with pIBD are listed inTables 1A and 1B.

Forty-four of the patients had previously tested positive for SARS-CoV-2 by polymerase chain reaction (PCR) (67 observations, 34 in the fully vaccinated group and 33 in the nonvaccinated group). Seventy-nine observations were neither vaccinated nor had positive SARS-CoV-2 PCR. We also included 1744 adult HCs (1460 female, median age 46, IQR 37–57 years) who were previously fully vaccinated against SARS-CoV-2 [received 2 doses of mRNA vaccine BNT162b2 (Comirnaty—Pfizer/BioNTech); the median time from vaccination was 97 (70–124) days]. HCs consisted of healthcare workers of our University Hospital who voluntarily agreed to participate in testing of postvaccination antibodies between April and June 2021.

Collection of Clinical Data and Laboratory Samples

Clinical data (patient characteristics, disease phenotype, disease activity, clinical indices, laboratory markers, IBD treatment, history of SARS-CoV-2 infection or vaccination, and potential side effects of vaccination) were prospectively recorded in the database. Information on SARS-CoV-2 infection had been collected prospectively into our database since the outbreak of the SARS-CoV-2 pandemic in the population in spring 2020. The data underlying this article will be shared upon reasonable request by the corresponding author. Two mL of blood was drawn from each patient to measure postinfection and postvaccination antibodies. Blood was allowed to clot and then centrifuged, and the separated serum was frozen at −20°C until analysis.

Laboratory Methods

Antibodies were measured in all patients using the Microblot-Array COVID-19 IgG/IgA (TestLine Clinical Diagnostics, Brno, Czech Republic) according to the manufacturer's instructions. We measured anti-RBD IgG and IgA, anti-spike S2 IgG and IgA, and anti-nucleocapsid IgG and IgA. Antibody titers were quantified in U/mL based on the intra-assay calibration curve. Titers >210 U/mL were considered positive, and titers 185–210 U/mL were considered borderline positive. The assay validity was verified using an internal assay and conjugate controls.

Definitions of Postvaccination and Postinfection Status

For the purpose of this study, we considered history of SARS-CoV-2 PCR positivity as positive postinfection status. Anti-RBD antibodies and anti-spike S2 antibodies were considered markers of postvaccination or postinfection status. Anti-nucleocapsid antibodies were considered markers of postinfection status but were analyzed independently of the history of SARS-CoV-2 PCR positivity.

Evaluation of IBD Treatment Used and Disease Activity

IBD treatments of any length received at the time of observation were evaluated in this study. Disease activity was evaluated using clinical indices [weighted Pediatric Crohn's Disease Activity Index (wPCDAI) and Pediatric Ulcerative Colitis Activity Index (PUCAI)] (9,10), C-reactive protein (CRP), and fecal calprotectin (F-CPT) levels.

Aims of the Study

The primary aim [tested in 83 observations in fully vaccinated pIBD patients (N = 65) and fully vaccinated HCs (N = 1744)] was to compare the immunogenicity of the mRNA SARS-CoV-2 BNT162b2 vaccine (defined as the production of anti-RBD IgG and anti-spike S2 IgG) in patients with pIBD and HCs.

Nestlé, Ferring, and Falk. The remaining authors report no conflicts of interest.

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TABLE 1A. Basic characteristics of the patients

No. of patients	CD (N = 40)	IBDU (N = 4)	UC (N = 21)	Overall (N = 65)
General characteristics				
Female sex	19 (47.5%)	0 (0%)	7 (33.3%)	26 (40.0%)
Age at diagnosis (median, IQR), y	10.7 (9.49–13.0)	6.73 (6.73–6.73)	11.1 (8.23–13.2)	10.8 (9.29–12.9)
Age at observation (median, IQR), y	16.4 (15.2–18)	16.1 (16–16.1)	16.3 (15.2–17)	16.3 (15.2–17.8)
Paris classification				
A1a: <10 y	16 (40.0%)	2 (50.0%)	6 (28.6%)	24 (36.9%)
A1b: 10–16 y	22 (55.0%)	2 (50.0%)	14 (66.7%)	38 (58.5%)
A2: 17–40 y	2 (5.0%)	0 (0%)	1 (4.7%)	3 (4.6%)
L1: ileal	10 (25.0%)	NA	NA	NA
L2: colonic	9 (22.5%)	NA	NA	NA
L3: ileocolonic	21 (52.5%)	NA	NA	NA
L4: upper GI	19 (47.5%)	NA	NA	NA
B1: nonstricturing, nonpenetrating	34 (85.0%)	NA	NA	NA
B2: stricturing	4 (10.0%)	NA	NA	NA
B2B3: stricturing + penetrating	1 (2.5%)	NA	NA	NA
B3: penetrating	1 (2.5%)	NA	NA	NA
Perianal disease	6 (15.0%)	NA	NA	NA
G0: no history of growth retardation	31 (77.5%)	2 (50.0%)	18 (85.7%)	51 (78.5%)
G1: history of growth retardation	9 (22.5%)	2 (50.0%)	3 (14.3%)	14 (21.5%)
E1: proctitis	NA	1 (0%)	1 (4.8%)	NA
E2: left sided	NA	1 (25.0%)	4 (19.0%)	NA
E3: extensive	NA	0 (0%)	2 (9.5%)	NA
E4: pancolitis	NA	2 (25.0%)	14 (66.7%)	NA
S0: never severe	NA	3 (50.0%)	18 (85.7%)	NA
S1: ever severe	NA	1 (0%)	3 (14.3%)	NA

CD = Crohn's disease; IBDU =inflammatory bowel disease unclassified; IQR = interquartile range; NA = not applicable; UC = ulcerative colitis.

TABLE 1B. Characteristics of the patients at the time of observation

	CD (N = 49)	IBDU (N = 5)	UC (N = 29)	Overall (N = 83)
Treatment				
Adalimumab	21 (42.9%)	0 (0%)	1 (3.4%)	22 (26.5%)
Infliximab	16 (32.7%)	0 (0%)	14 (48.3%)	30 (36.1%)
Ustekinumab	1 (2.0%)	0 (0%)	0 (0%)	1 (1.2%)
Vedolizumab	7 (14.3%)	2 (40.0%)	2 (6.9%)	11 (13.3%)
Immunomodulator	26 (53.1%)	3 (60.0%)	17 (58.6%)	46 (55.4%)
Combo therapy	30 (61.2%)	5 (100%)	22 (75.9%)	57 (68.7%)
5-Aminosalicylates	0 (0%)	2 (40.0%)	25 (86.2%)	27 (32.5%)
Disease activity				
wPCDAI (median, IQR)	0 (0–7.50)	NA	NA	0 (0–7.50)
PUCAI (median, IQR)	NA	0 (0–0)	0 (0–0)	0 (0–0)
CRP (median, IQR) mg/l	0.50 (0.50–2.80)	0.50 (0.50–0.50)	0.50 (0.50–1.20)	0.50 (0.50–2.30)
Fecal calprotectin (median, IQR), µg/g	79.0 (25.0–519)	224 (42.0–273)	28.0 (9.0–229)	55.0 (17.5–398)

CD = Crohn's disease; Combo therapy = combination of biological therapy and immunomodulator; CRP = C-reactive protein; IBDU = inflammatory bowel disease unclassified; IQR = interquartile range; PUCAI = Paediatric Colitis Activity Index; UC = ulcerative colitis; wPCDAI = weighted Paediatric Crohn's Disease Activity Index; NA = not applicable.

The secondary aims [tested in 83 observations in fully vaccinated pIBD patients (N = 65)] were to describe:

1. the association between postvaccination antibody titers in patients with pIBD and postinfection status, IBD treatment used, and disease activity at the time of observation;
2. the association of postinfection antibody titers in patients with pIBD and postinfection status, IBD treatment, and disease activity at the time of observation; and
3. side effects of SARS-CoV-2 vaccination in patients with pIBD.

Other aims [tested in 195 observations in all pIBD patients (N = 139)–both fully vaccinated (N = 65) and nonvaccinated (N = 74)] were to compare:

1. IgG antibody levels in vaccinated and nonvaccinated patients with pIBD; and
2. history of SARS-CoV-2 PCR positivity and anti-nucleocapsid IgG positivity in patients with pIBD.

IgA Antibodies

Data on anti-RBD, anti-spike S2, and anti-nucleocapsid IgA antibodies were analyzed separately and are presented in the Supplemental Digital Content, *http://links.lww.com/MPG/C992*.

Statistical Analysis

All data were analyzed using R statistical software version 4.0.4 (R Core Team, 2021, https://www.R-project.org/). Continuous variables are described as medians and IQR. Categorical variables are described as absolute frequencies and percentages. Missing data were not imputed. Three different data sets were established: (1) vaccinated patients with pIBD and vaccinated HCs; (2) fully vaccinated patients with pIBD; and (3) fully vaccinated and not fully vaccinated patients with pIBD. To avoid pseudoreplication, we used mixed models for all analyses; for categorical outcomes (eg, positivity for SARS-CoV-2 antibodies), we used a generalized linear mixed model; for linear outcomes (eg, level of SARS-CoV-2 antibodies), we used a linear mixed model. Only fixed effects of the predictors were presented. Due to the assumption that antibodies levels decline over time, we added the variable "time since vaccination" to all models with RBD and Spike S2 as outcomes. We also adjusted models for "history of SARS-CoV-2 PCR positivity." When appropriate, we added interaction effects to our model. We constructed a final prediction model based on the clinical selection of the predictors.

RESULTS

Primary Aim—Postvaccination Immunity in pIBD and HCs

We compared 65 fully vaccinated patients with pIBD (83 observations) with 1744 fully vaccinated HCs. All patients with pIBD and HCs developed positive anti-RBD IgG antibodies, and levels were similar in both groups [median (IQR) 971 (960–987) vs 972 (781–1030 IU/mL); Figure 1a, Supplemental Digital Content, *http://links.lww.com/MPG/C992*]. In an adjusted linear-mixed model, anti-RBD IgG levels were associated with pIBD status (Fig. 1A).

The proportion of observations with positive anti-spike S2 IgG was higher in patients with pIBD than in HCs [63% vs 21%, OR 2.99 (1.51–5.90), $P = 0.02$; Figure 1b, Supplemental Digital Content, *http://links.lww.com/MPG/C992*], as were anti-spike S2 IgG titers [median (IQR) 485 (92–922) vs 79 (33–180) IU/mL, Figure 1c, Supplemental Digital Content, *http://links.lww.com/MPG/C992*]. In adjusted linear-mixed model, anti-spike S2 IgG levels were associated with pIBD status (Fig. 1B).

Secondary Aims

In this part of the study, 65 fully vaccinated patients with pIBD (83 observations) were included.

Predictors of Postvaccination Immunity in Patients with pIBD

In the linear-mixed model adjusted for time from vaccination, no association was found between numerical values of anti-RBD IgG levels and history of SARS-CoV-2 PCR positivity (Figure 2, Supplemental Digital Content, *http://links.lww.com/MPG/C992*). We found no association between the history of SARS-CoV-2 PCR positivity and the presence of anti-spike S2 IgG as a categorical variable, however in linear-mixed model adjusted for time from vaccination, numerical values of anti-spike S2 IgG were positively associated with a history of SARS-CoV-2 PCR positivity (Fig. 2).

The association between IBD treatment and postvaccination IgG antibody levels is shown in Table 2. In linear regression mixed model adjusted for time interval from vaccination and history of SARS-CoV-2 PCR positivity, anti-spike S2 IgG levels were lower in observations treated with anti-TNF (tumor necrosis factor) (β −215, 95% CI −379 to −53, $P = 0.01$, Figure 3, Supplemental Digital Content, *http://links.lww.com/MPG/C992*).

As most of our patients were in clinical remission (Table 1B), we did not test the association between clinical indices of disease activity (wPCDAI and PUCAI) and postvaccination antibodies. In linear mixed models adjusted for time since vaccination and history of SARS-CoV-2 positivity, CRP, but not F-CPT, was associated with postvaccination production of anti-RBD and anti-spike S2 antibodies. Thus, CRP was added to the final mixed model to predict the anti-RBD IgG and anti-spike S2 IgG status.

We made final mixed models containing time interval from vaccination (β −6.57, 95% CI −12.92 to −0.28, $P = 0.0496$), history of SARS-CoV-2 PCR positivity (β 9.41, 95% CI −43.98 to 63.34, $P = 0.7372$), anti-TNF (β −9.53, 95% CI −59.71 to 40.59, $P = 0.72$), immunomodulatory treatment (β −1.56, −34.34 to 30.63, $P = 0.93$), and CRP (β −6.57, −12.92 to −0.28, $P = 0.0496$). We found an association between CRP levels and anti-RBD IgG levels (Table 1a, Supplemental Digital Content, *http://links.lww.com/MPG/C992*). We also found association between anti-spike S2 IgG levels and time since vaccination (β −4.85, 95% CI −7.14 to 2.71, $P = 0.0001$), history of SARS-CoV-2 PCR positivity (β −4.85, 95% CI −7.14 to 2.71, $P = 0.0001$), and anti-TNF treatment (β −239.68, 95% CI −396.44 to −83.55, $P = 0.0047$), but not with immunomodulatory treatment (β −105.48, −242.93 to 33.70, $P = 0.15$) or CRP (β −3.71, 95% CI −25.25 to 17.82, $P = 0.74$; Table 1b, Supplemental Digital Content, *http://links.lww.com/MPG/C992*). The levels of anti-RBD and anti-spike S2 IgG stratified according to various types of biological therapy are shown in Figures 4a and b, Supplemental Digital Content, *http://links.lww.com/MPG/C992*.

Predictors of Postinfection Immunity in Vaccinated Patients with pIBD

In linear regression mixed model adjusted for time interval from vaccination and history of SARS-CoV-2 PCR positivity, anti-nucleocapsid IgG levels were lower in observations treated with anti-TNF (β −220, 95% CI −345 to −96, $P < 0.001$) and with immunomodulators (IMM) (β −119, 95% CI −229 to 9.49, $P = 0.04$; Table 2). In categorical model, lower proportion of observations

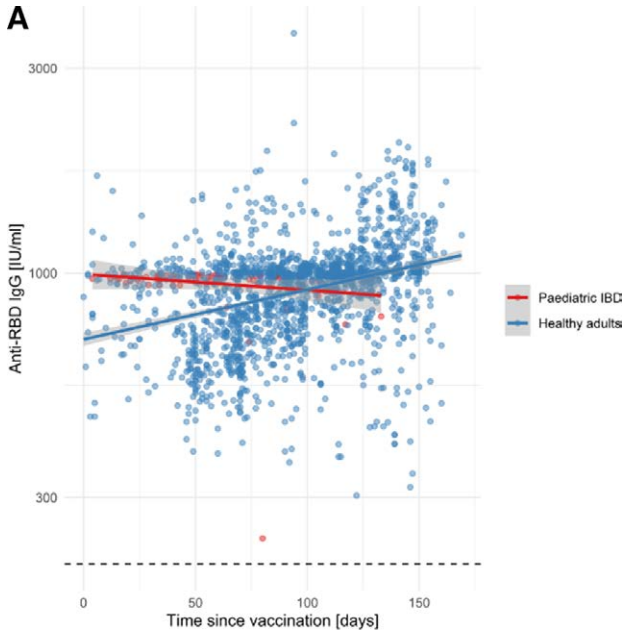

FIGURE 1a. Association of anti-RBD IgG antibodies and time since vaccination in pIBD patients and healthy adults. Linear mixed model adjusted for time from vaccination, age, and interaction between time from vaccination and case/control variable; IgG=immunoglobulin G; pIBD=paediatric inflammatory bowel disease; CI95 = 95% confidence interval.

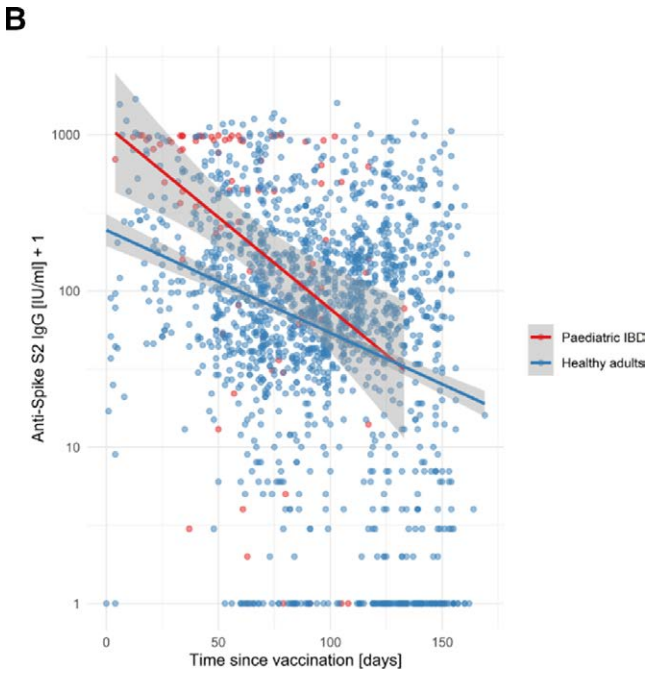

FIGURE 1b. Association of anti-spike S2 IgG antibodies and time since vaccination in pIBD patients and healthy adults. Linear mixed model adjusted to time from vaccination, age and interaction between time from vaccination and case/control variable; IgG=immunoglobulin G; pIBD=paediatric inflammatory bowel disease; CI95 = 95% confidence interval

with anti-TNF developed positive anti-nucleocapsid IgG (OR 0.137, 95% CI 0.025–0.762, $P = 0.023$). Levels of anti-nucleocapsid IgG stratified according to various types of biological therapy are shown in Figure 4c, Supplemental Digital Content, *http://links.lww.com/MPG/C992*. As most of our patients were in clinical remission (Table 1B), we did not test the association between clinical indices of disease activity (wPCDAI and PUCAI) and postinfection antibodies. We did not find an association between anti-nucleocapsid IgG levels and CRP or F-CPT levels.

Side Effects of Vaccination in Patients with pIBD

Out of 65 vaccinated patients with pIBD, 28 (43%) reported side effects following the first dose of vaccination (2 with fever, 26 with mild complaints—pain, edema, or erythema in the injection site, fatigue, headache, or slightly elevated body temperature). Twenty-eight patients (43%) reported side effects after the second dose (3 with fever, 1 with vomiting with subsequent proven SARS CoV-2 PCR positivity, 1 with worsening of pustulous skin lesions, and 23 with mild complaints). In all patients, the side effects were short-lasting and self-limiting.

Other Aims

In this part of the study, 139 patients with pIBD (195 observations) were included, of which 65 were fully vaccinated (83 observations) and 67 observations (34 observations from the vaccinated group and 33 observations from the nonvaccinated group) in 44 patients had a history of SARS-CoV-2 PCR positivity.

Comparison of Vaccinated and Nonvaccinated Patients with pIBD

Observations in fully vaccinated pIBD had higher levels of all investigated IgG antibodies than nonvaccinated patients with pIBD (anti-RBD: β 630, 95% CI 537–722, $P < 0.0001$; anti-spike S2: 258, 95% CI 157–359, $P < 0.0001$; anti-nucleocapsid: 133, 95% CI 64–202, $P = 0.0002$), even after adjustment for history of SARS-CoV-2 PCR positivity. Both anti-spike S2 IgG and anti-nucleocapsid IgG were also associated with a history of SARS-CoV-2 PCR positivity in linear regression mixed model adjusted to postvaccination status (β 292, 95% CI 182–402, $P < 0.0001$ and 119, 95% CI 41–197, $P = 0.0033$, respectively; Table 2 and Figure 5, Supplemental Digital Content, *http://links.lww.com/MPG/C992*).

Comparison of History of SARS-CoV-2 PCR Positivity and Anti-Nucleocapsid IgG Positivity in Patients with pIBD

Among observations with positive anti-nucleocapsid IgG antibodies (N = 46), 25 had a history of SARS-CoV-2 PCR positivity (54%). Among observations with insufficient anti-nucleocapsid IgG antibodies (N = 149), 42 had a history of SARS-CoV-2 PCR positivity (28%; Table 3, Supplemental Digital Content, *http://links.lww.com/MPG/C992*).

Postvaccination and Postinfection IgA Antibodies

In linear mixed model, anti-RBD IgA antibodies were associated with time from vaccination and age but not with pIBD status. Anti-spike S2 IgA antibodies were associated with pIBD status, time from vaccination, and the interaction between these 2 variables (Figure 6a and b, Supplemental Digital Content, *http://links.lww.com/MPG/C992*).

Observations in fully vaccinated patients with pIBD had higher levels of anti-RBD IgA antibodies than nonvaccinated

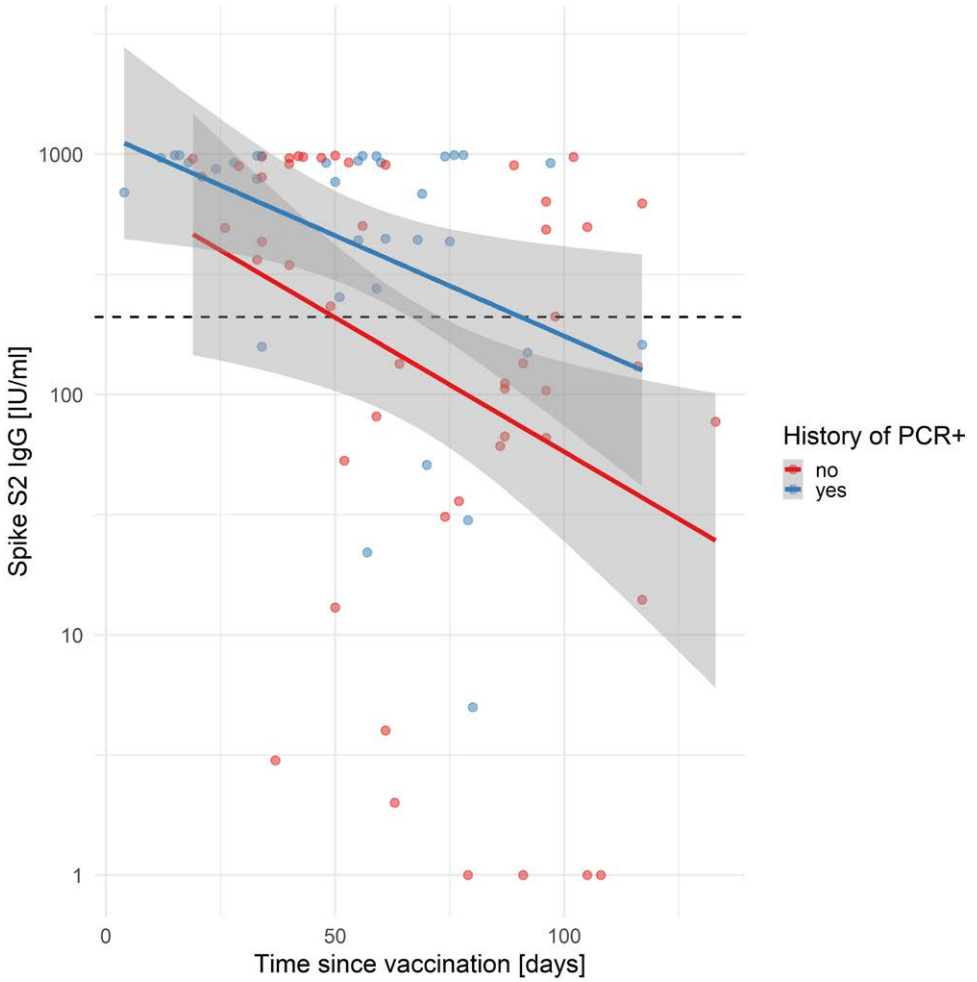

FIGURE 2. Association of anti-spike S2 IgG antibodies and history of SARS-CoV-2 PCR positivity in pIBD patients. IgG = immunoglobin-G; PCR = polymerase chain reaction; pIBD = pediatric inflammatory bowel disease; SARS-CoV-2 = severe acute respiratory syndrome-associated coronavirus 2.

patients with pIBD (β 169, 95% CI 82–255, $P = 0.0001$), even after adjustment for history of SARS-CoV-2 PCR positivity (Figure 7a, Supplemental Digital Content, *http://links.lww.com/MPG/C992*). No association was found between anti-spike S2 IgA or anti-nucleocapsid IgA levels and vaccination status or history of SARS-CoV-2 positivity (Figure 7b and c, Supplemental Digital Content, *http://links.lww.com/MPG/C992*).

Based on visual evaluation of the data in vaccinated patients with pIBD, anti-spike S2, but not anti-RBD IgA antibodies, was higher in patients with a history of SARS-CoV-2 PCR positivity, and both antibody types decreased over time after vaccination (Figures 8a and b, Supplemental Digital Content, *http://links.lww.com/MPG/C992*).

Based on visual evaluation of the data in vaccinated patients with pIBD, anti-RBD, but not anti-spike S2 and anti-nucleocapsid IgA was lower in those with anti-TNF and combination treatments (Figure 9, Supplemental Digital Content, *http://links.lww.com/MPG/C992*).

DISCUSSION

We have shown the excellent postvaccination status of patients with pIBD when evaluated using anti-RBD IgG antibodies. These were positive in both patients with pIBD and HCs, which is in line with data published so far in adult patients with IBD (11–14). However, higher anti-RBD and anti-spike S2 IgG levels were independently associated with pIBD status, suggesting a better response to vaccination in our pIBD population than in adult HCs. In contrast, most studies show lower seroconversion rates in adult patients with IBD than that in HCs (11,15–17); however, the difference is small, and the rates are still better than in patients with other immune-mediated disorders (12). The pooled relative risk of breakthrough infections in vaccinated patients with IBD is similar to that of vaccinated controls (11,13). Our data suggest that pediatric patients with IBD may have a better response to the SARS-CoV 2 mRNA vaccine than adult patients with IBD; however, studies comparing these 2 cohorts are lacking. There were differences in the production of postvaccination antibodies, especially anti-spike S2 IgG. Unlike anti-RBD, anti-spike S2 has also been associated with anti-TNF treatment. This suggests that anti-spike S2 may be a more sensitive marker of postvaccination status than anti-RBD.

History of SARS-CoV-2 PCR positivity is strongly associated with higher levels of anti-spike S2 IgG antibodies. This suggests that previous infection may increase the production of antibodies after vaccination, even in patients with pIBD. This phenomenon is independent of treatment with immune-mediating drugs and points

TABLE 2. Association of postvaccination antibodies and IBD treatment—summary of regression models adjusted to time from vaccination and history of SARS-CoV-2 PCR positivity

Postvaccination antibody	Treatment modality	Yes (IQR or %)	No (IQR or %)	Beta (95% CI)	*P* value
Anti-RBD IgG	aTNF	978 (960.75–990)	966 (959.5–984)	−15.32 (−65.99 to 35.22)	0.56
Anti-spike S2 IgG	**aTNF**	**253.5 (58–829)**	**892 (354–974)**	**−214.86 (−378.65 to 52.77)**	**0.01**
Anti-nucleocapsid IgG	**aTNF**	**90 (12–247)**	**379 (109–619)**	**−220.18 (−345.37 to 95.8)**	**<0.001**
Anti-spike S2 IgG categorical	aTNF	27 (0.52)	25 (0.48)	0.171 (0.029 to 1.011)	0.051
Anti-nucleocapsid IgG categorical	**aTNF**	**14 (0.27)**	**38 (0.73)**	**0.082 (0.008 to 0.848)**	**0.036**
Anti-RBD IgG	IFX	976.5 (946.5–990)	971 (960–985)	2.51 (−43.32 to 48.34)	0.92
Anti-spike S2 IgG	IFX	253.5 (58–889.75)	502 (105–962)	−44.47 (−218.2 to 130.42)	0.62
Anti-nucleocapsid IgG	IFX	78 (14.25–243.5)	195 (58–437)	−93.11 (−228.91 to 43.38)	0.19
Anti-spike S2 IgG categorical	IFX	16 (0.53)	14 (0.47)	0.557 (0.156 to 1.986)	0.367
Anti-nucleocapsid IgG categorical	IFX	8 (0.27)	22 (0.73)	0.313 (0.082 to 1.205)	0.091
Anti-RBD IgG	combo	969 (960–986)	979 (961.5–989.25)	1.91 (−32.72 to 37.22)	0.92
Anti-spike S2 IgG	combo	493 (80–962)	464.5 (103.5–914)	−28.22 (−191.48 to 135)	0.73
Anti-nucleocapsid IgG	combo	160 (45–435)	121.5 (16–312.5)	−1.49 (−127.33 to 125.26)	0.98
Anti-spike S2 IgG categorical	combo	37 (0.65)	20 (0.35)	1.047 (0.292 to 3.759)	0.943
Anti-nucleocapsid IgG categorical	combo	24 (0.42)	33 (0.58)	1.193 (0.317 to 4.488)	0.794
Anti-RBD IgG	IMM	969 (959.25–985.75)	978 (960–988)	−4.39 (−37.4 to 28.82)	0.8
Anti-spike S2 IgG	IMM	435 (77–895)	622 (105–938)	−131.14 (−277.79 to 15.63)	0.08
Anti-nucleocapsid IgG	**IMM**	**120.5 (29.5–356.5)**	**170 (45–477)**	**−119.37 (−229.08 to 9.49)**	**0.04**
Anti-spike S2 IgG categorical	IMM	28 (0.61)	18 (0.39)	0.673 (0.176 to 2.572)	0.563
Anti-nucleocapsid IgG categorical	IMM	16 (0.35)	30 (0.65)	0.452 (0.116 to 1.762)	0.253
Anti-RBD IgG	5-ASA	976 (960.5–986.5)	970.5 (958.75–986.25)	19.33 (−27.41 to 65.72)	0.42
Anti-spike S2 IgG	5-ASA	439 (105–918.5)	497.5 (96.25–922)	−28.01 (−204.85 to 144.6)	0.75
Anti-nucleocapsid IgG	5-ASA	139 (50.5–380)	149 (13.5–394.25)	−13.61 (−172.78 to 129.4)	0.85
Anti-spike S2 IgG categorical	5-ASA	17 (0.63)	10 (0.37)	0.908 (0.265 to 3.115)	0.878
Anti-nucleocapsid IgG categorical	5-ASA	11 (0.41)	16 (0.59)	1.323 (0.316 to 5.545)	0.701

Significant results are highlighted in bold. 5-ASA = 5-aminosalicylic acid; aTNF = anti-tumor necrosis factor alpha therapy; "categorical" = IgG levels of antibodies above the cut-off of the assay; combo = combination therapy (aTNF + immunomodulator); IBD = inflammatory bowel diseases; IFX = infliximab; IMM = immunomodulator; "No" = median levels (IU/mL)/no. of postvaccination antibodies in subjects not receiving the treatment modality; PCR = polymerase chain reaction; RBD = receptor binding domain of S1 subunit of spike protein; SARS-CoV-2 = severe acute respiratory syndrome-associated coronavirus 2; "Yes" = median levels (IU/mL)/no. of postvaccination antibodies in subjects receiving the treatment modality.

to the potentiation of postinfection and postvaccination status of the immune system in healthy individuals. Importantly, this mechanism was not disrupted in individuals with immune-suppressed pIBD.

Anti-TNF treatment was independently and strongly associated with lower anti-spike S2 IgG levels. The negative effect of anti-TNF treatment (especially infliximab, IFX) on postvaccination status has been observed in many studies in adult patients with IBD and thoroughly discussed by the scientific community (11,12,15,16,18–30). However, other studies failed to find any association (31,32) and even large systematic reviews and meta-analyses have shown conflicting results, especially when combination therapy with IMM is considered (11–13). In our study, neither IFX alone nor combination therapy was associated with postvaccination IgG antibody levels. The use of IMM had a slight association with lower anti-spike S2 levels; however, the difference was not statistically significant ($P = 0.08$). Although anti-TNF might attenuate postvaccination serological response, it seems that the rate of SARS-CoV-2 infection does not increase in vaccinated patients with IBD on anti-TNF therapy (32,33). Given the lack of evidence that anti-TNF increases the risk of severe COVID-19, it is unclear whether subjects treated with anti-TNF require either an accelerated booster vaccine or postvaccination serological monitoring (34). Based on our data (Figure 3, Supplemental Digital Content, *http://links.lww.com/MPG/C992*), anti-TNF treatment was associated with a faster decrease in anti-spike S2 titers.

Adverse side effects in our study were described in 43% of patients both after the first and second doses of the mRNA vaccine. The vast majority of cases were mild and self-limiting. This is in line with data showing consistently good tolerance in adult patients with IBD and the safety of SARS-CoV-2 vaccines (35–39).

Postinfection immunity (represented by positive anti-nucleocapsid IgG levels) was augmented by BNT162b2 vaccination, as expected. This is in accordance with the above-mentioned potentiation of postinfection and postvaccination immunity, even in immune-suppressed pIBD individuals. Moreover, lower anti-nucleocapsid IgG levels were independently associated with anti-TNF and IMM treatment. These results correspond to previously published large-scale therapeutic drug monitoring studies in adult patients with IBD, showing impaired SARS-CoV-2 antibody responses in patients treated with IFX or adalimumab (ADA) (40,41). Only 54% of anti-nucleocapsid IgG positive patients with pIBD had a history of positive SARS-CoV-2 PCR, even though we had collected this information prospectively since the outbreak of the COVID-19 pandemic. Thus, in approximately half of the

patients with pIBD, the infection went undetected as it had a fully asymptomatic course or no epidemiological history.

None of the above-mentioned studies specifically reported patients with pIBD, and data on this population are scarce. In a prospective longitudinal study of patients with pIBD treated with IFX or vedolizumab (VEDO) [N = 436, mean age 17 years (2–26)], 44 patients (10%) were positive for postinfection SARS-CoV-2 anti-RBD IgG antibodies (6). The titers of these antibodies were significantly lower than those of adults (N = 23) and pediatric (N = 11) non-IBD controls and, until 6 months postinfection, were undetectable in most patients. There was no difference in the seropositivity between patients treated with IFX and VEDO (P = 0.164). None of the patients were treated with azathioprine. In contrast, postvaccination antibodies tested in a subgroup of 33 patients (age not specified in the paper) reached titers up to 15 times higher. The authors concluded that postvaccination immunity is substantially higher than postinfection immunity in patients with pIBD treated with biologic medication (6).

The above-mentioned CLARITY IBD study focused on postvaccination immunity in patients with IBD (eligibility criteria over 5 years of age) treated with biologic medication; however, most of the patients were adults [mean age 43.8 years (IQR 32.8–57.6)], and the number of pediatric patients was not listed. The authors suggested significantly lower production of postvaccination antibodies in patients treated with IFX (especially in combination with IMM) than in patients treated with VEDO (24). Another large population-based Israeli study included 20 patients with pIBD (0.4%), but no sub-analysis was presented (33). A recent large-scale prospective observational cohort study (PREVENT-COVID) measured anti-RBD IgG levels in 1909 patients with IBD (1815 of whom received mRNA vaccines) (7). A subgroup of 45 children 12–18 years old was included. Forty-four patients developed detectable postvaccination antibodies. No further sub-analyses are presented. The study has shown that older age, anti-TNF, and IMM therapy reduced the postvaccination response (7).

In a retrospective study of patients with IBD aged <21 years (N = 340), SARS-CoV-2 anti-spike IgG antibodies were measured. Fifty-eight patients (17%) had previously experienced confirmed, probable, or suspected COVID-19 infection. Fifty-four patients (16%) had a history of close contact with SARS-CoV-2 but no clinical symptoms. Two hundred and eight patients (61%) had no history of contact or symptoms. Only 20 patients [6%; mean age, 18 years (IQR 17–20)] were vaccinated against SARS-CoV-2. Nineteen of these patients (95%) received biological therapy (IFX = 7, ADA = 2, ustekinumab = 10), and 2 received tofacitinib. Seroconversion was detected in all the vaccinated patients. All patients who received the mRNA vaccine had high postvaccination titers. No association was found between postvaccination titers and the type of biological therapy. Patients vaccinated with mRNA-1273 (NIH-Moderna) vaccine had significantly higher titers than those vaccinated with BNT162b2 (Pfizer/BioNTech) and JNJ-78436735 (Johnson and Johnson) vaccines (P = 0.005) (8).

CONCLUSIONS

In conclusion, patients with pIBD in our study showed an excellent postvaccination response that might be attenuated by anti-TNF therapy. The main strengths of this study are the prospective collection of data both on vaccination status and previous SARS-CoV-2 PCR positivity (with a primary focus on the pediatric population with IBD), use of a unified vaccination strategy (full vaccination scheme only by BNT162b2 mRNA vaccine), the inclusion of a robust control group with a comparable time frame from the second dose, and a reliable microblot array assay to detect large-scale antibodies. A potential limitation for the interpretation of antibody titers is the inclusion of non-age-matched adults as a control cohort, which we attempted to manage mathematically in our models. Also, we did not collect information on comorbidities in the HCs group. Moreover, with respect to the course of pandemic, adult patients had slightly lower rate of history of SARS-CoV-2 infection when compared to the pIBD patients (28% vs 41%), but adding anti-nucleocapsid IgG levels to the mixed models neither affected the results of anti-RBD nor anti-spike S2 analysis. Despite the negative association between anti-TNF and postvaccination antibodies, it is questionable whether anti-TNF-treated patients should be prioritized for booster vaccines. They are probably not at risk of a severe course of COVID-19, however recently more frequent breakthrough infections were described in vaccinated patients treated with IFX compared to VEDO (42). Moreover, serology is a poor marker of vaccination-induced T-cell response, which might play a crucial role but has rarely been studied in patients with IBD so far (43–45).

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