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Patients With Inflammatory Bowel Diseases Have Impaired Antibody Production After Anti-SARS-CoV-2 Vaccination: Results From a Panhellenic Registry

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Background: Four EMA-approved vaccines against SARS-CoV-2 are currently available. Data regarding antibody responses to initial vaccination regimens in patients with inflammatory bowel diseases (IBD) are limited.

Methods: We conducted a prospective, controlled, multicenter study in tertiary Greek IBD centers. Participating patients had completed the initial vaccination regimens (1 or 2 doses, depending on the type of COVID-19 vaccine) at least 2 weeks before study enrolment. Anti-S1 IgG antibody levels were measured. Demographic and adverse events data were collected.

Results: We tested 403 patients (Crohn's disease, 58.9%; male, 53.4%; median age, 45 years) and 124 healthy controls (HCs). Following full vaccination, 98% of patients seroconverted, with mRNA vaccines inducing higher seroconversion rates than viral vector vaccines ($P = .021$). In total, IBD patients had lower anti-S1 levels than HCs ($P < .001$). In the multivariate analysis, viral vector vaccines ($P < .001$), longer time to antibody testing ($P < .001$), anti-TNFα treatment ($P = .013$), and age ($P = .016$) were independently associated with lower anti-S1 titers. Vedolizumab monotherapy was associated with higher antibody levels than anti-TNFα or anti-interleukin-12/IL-23 monotherapy ($P = .023$ and $P = .032$). All anti- SARS-CoV-2 vaccines were safe.

Conclusions: Patients with IBD have impaired antibody responses to anti-SARS-CoV-2 vaccination, particularly those receiving viral vector vaccines and those on anti-TNFα treatment. Older age also hampers antibody production after vaccination. For those low-response groups, administration of accelerated or prioritized booster vaccination may be considered.

Lay Summary

Thisis a multicenter study on IBD patients after COVID-19 vaccination and anti-S1 IgG antibody levels measurement. Patients with IBD have lower antibody responses than healthy controls, particularly those receiving viral vector vaccines and those on anti-TNFα or combination treatment.

Key Words: IBD, Crohn's disease, ulcerative colitis, COVID-19 vaccines, antibody response

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which causes Corona virus disease (COVID)-19 was first detected in December 2019 in the Wuhan region, China, and has evolved into pandemic status beginning March 2020.[1] It prompted immediate efforts for the development of anti-SARS-CoV-2-vaccines. Although vaccine production typically requires years of research and testing before reaching the clinic, 114 anti-SARS-CoV-vaccines are currently being tested in clinical trials, of which 48 have reached the final stages of testing, and 28 have already been authorized or approved for use in different countries.[1]

In the European Union (EU), 4 vaccines are currently approved by European Medicines Agency (EMA). Those include both mRNA (mRNA-1273 [Moderna/NIH], BNT162b2 [Pfizer-BioNTech]) and viral vector vaccines (Ad26.CoV2.S [J&J], ChAdOx1 [AstraZeneca]).[2–5] The characteristics of the 4 available vaccines are shown in Supplementary table 1. The initial national COVID-19 vaccination program in Greece included a 2-dose regimen for mRNA vaccines and ChAdOx1 or a 1-dose regimen for Ad26.CoV2.S. Immunocompromised patients have preferentially received vaccination with mRNA vaccines and especially BNT162b2, according to local protocols.

Inflammatory bowel diseases (IBD), which include Crohn's disease (CD) and ulcerative colitis (UC), are characterized by chronic intestinal inflammation due to altered immunological response to commensal flora in genetically predisposed patients.[6] Available treatment strategies include corticosteroids, immunomodulators (azathioprine, methotrexate), biologic agents (anti-TNF-a, anti-α4β7 integrin, anti-interleukin [IL]-12/23) and small molecules (JAK inhibitors).[7] All such treatments induce variable degrees of immunosuppression, thus raising the possibility of inadequate responses to vaccines, including those against SARs-COV-2. Indeed, suboptimal responses of patients with IBD with or without immunosuppression have been reported for influenza, pneumococcal, and hepatitis B vaccines; nevertheless, the particular type of therapy may also be of importance.[8–12]

Patients with immune-mediated inflammatory diseases (IMIDs) who received systemic immunosuppressants were excluded from initial clinical trials of SARs-COV-2 vaccines, and thus, data about efficacy and safety in this population are limited.[3,13] There is, however, accumulating evidence that following SARS-CoV-2 vaccination, immunosuppressed patients such as on-treatment patients for IMIDs or oncological patients showed lower seroconversion rates than HCs.[14,15] In addition, IBD patients treated with infliximab showed lower antibody levels after a single dose of the BNT162b2 and ChAdOx1 vaccines compared with patients treated with vedolizumab.[16] In regards to safety, there were no specific signals after mRNA vaccination in IBD patients in comparison with non-IBD recipients, and adverse events (AEs) may even be less common among biologic-treated IBD patients.[17,18]

Taken together, the impact of IBD therapies on safety and efficacy of COVID-19 vaccines remains to be elucidated. We undertook the present study with the aim to investigate the immune response to vaccination against COVID-19 in a real-world setting involving Greek IBD patients.

Materials and Methods

Patient and Control Groups

Serum samples were collected from adult IBD patients that visited 8 tertiary IBD centers, either in outpatient or inpatient department and have completed COVID-19 vaccination with any of the available vaccine (BNT162b2 [Pfizer-BioNTech], mRNA-1273 [Moderna/NIH], ChAdOx1 [Astrazeneca] and Ad26.CoV2.S [J&J]) at least 2 weeks before. Full vaccination regimen was defined as a 2-dose regimen for BNT162b2 (Pfizer-BioNTech) 21 days apart, a 2-dose regimen for mRNA-1273 28 days apart, a 2-dose regimen for ChAdOx1 4 to 12 weeks apart and a 1-dose regimen for Ad26.CoV2.S. Inflammatory bowel disease diagnosis was confirmed by reviewing the medical files and was categorized as Crohn's disease (CD), ulcerative colitis (UC), unclassified colitis (IBDU), and UC patients with ileal-pouch anal anastomosis (IPAA). Recruitment period was from May 1 to August 31, 2021. Accuracy of type and dates of vaccination were confirmed by authentic digital certificate provided to individuals by Greek authorities. Information regarding patients' demographics, treatment, previous SARS-CoV-2 known infection, comorbidities and potential AEs after either vaccine dose (including pain at injection site, fatigue, allergy reaction, fever, lymphadenopathy, myalgia/arthralgia, newly acquired diarrhea or abdominal pain, and headache) was also collected retrospectively. In our analysis, we included antibody levels from 124 healthy controls without previous history of COVID-19 who voluntarily took part in the study. Antibody levels in HCs were measured 1 month after the second dose of the vaccine (or the single dose in case of the J&J vaccine).

Measurement of Anti-SARS-COV-2 Antibodies

Antispike protein IgG S1 domain antibodies were measured with ELISA using a commercially available assay (Euroimmun Anti-SARS-CoV-2 QuantiVac ELISA [IgG]). Seroconversion was defined by manufacturer as a threshold of 11RU/mL.

Ethical Considerations

The study was conducted under the auspices of and funded from the Hellenic Group for the study of Idiopathic Inflammatory Bowel Diseases (EOMIFNE). The study protocol was approved by the institutional review boards of participating hospitals according to national legislation. All study participants provided informed consent.

Statistical Analysis

Continuous data are reported as median with interquartile range (IQR). For univariate analyses, Kruskal-Wallis test or Pearson correlation coefficient were used to identify demographic, vaccine, treatment, and adverse event factors associated with anti-S1 concentrations depending on the type of variables. Univariate logistic regression was used to identify factors associated with adverse events. Significant variables were entered in multivariate stepwise linear regression models to identify factors independently associated with anti-S1 levels and in a multivariate stepwise logistic regression model to identify factors independently associated with adverse events. A level of $P < .05$ was considered significant. Data were analysed using both MedCalc version 20.010 and IBM SPSS Statistics version 26.0.

Results

Patient Characteristics

Between May 1 and August 31, 2021, a total of 403 IBD patients (59% CD, 38% UC, 1% IBDU, and 2% with Ileal pouch-anal anastomosis) were recruited from 8 tertiary centers in regions across the country. Patient characteristics are shown in Table 1. Median age was 45 years (IQR, 34-56), median disease duration 8 years (4-15.25), and 53.4% of patients were male. More than half of patients (58.6%) were overweight (body mass index ≥25), the majority were nonsmokers (active smokers 25.8%), and one-third of patients reported comorbidities. Seven patients (2.6%) reported history of COVID-19 infection, which was confirmed by appropriate testing.

Overall, IBD treatments included single biologic therapy (296 patients, 73.4%), single immunomodulators (azathioprine/MP/Methotrexate, 28 patients, 6.9%), and combination of biologic plus immunomodulator (49 patients, 12.2%); 70 patients did not receive any immunosuppressive agent (17.4%).

Patients With IBD Show High Seroconversion Rates But Diminished Antibody Responses After Anti-SARs-COV-2 Vaccination

Antibody testing was conducted at a median of 31 days (IQR 23-46) after completion of the vaccination protocol with any of the available vaccines. Most patients received BNT162b2 (340 patients, 84.4%), whereas the rest were vaccinated with ChAdOx1 (41 patients, 10.2%), Ad26.CoV2.S (15 patients, 3.7%), and mRNA-1273 (6 patients, 1.5%).

In total, we observed that 98.0 % of patients seroconverted following full vaccination with any of the available vaccines. Seroconversion rate in our HCs cohort was 93.5% (P = .011). Nevertheless, we observed that IBD patients had significantly lower antibody concentrations than HCs (RU/mL 108 vs 132.7 RU/mL, P = .0001). Interestingly, further analysis revealed that the group of IBD patients without immunosuppression also had lower anti-S1 IgG levels than HCs (117.1 RU/mL vs 132.7 RU/mL; P = .046; Figure 1a).

Seroconversion Rates and Magnitude of Antibody Response According to Type of Vaccine

Patients who received mRNA vaccines showed higher seroconversion rates than those who received viral vector vaccines (98.6% vs 93.6%, P = .021). The BNT162b2 vaccination demonstrated the highest seroconversion rate (98.8%), followed by ChAdOx1 (97.6%), mRNA-1273 (93.3%), and Ad26.CoV2.S (66.7%).

Overall, the median anti-SARS-CoV-2 IgG S1 antibody concentration in IBD patients was 108 RU/mL. Median antibody concentrations were higher following mRNA vaccines (BNT162b2 or mRNA-1273) than viral vector vaccines (ChAdOx1 or Ad26.CoV2.S; 111.2 RU/mL vs 76 RU/mL, P < .001; Figure 1b). No statistical differences were observed in antibody concentrations between the 2 mRNA vaccines (medians: BNT162b2, 111.2 RU/mL; mRNA-1273, 117.4 RU/mL) or between the 2 viral vector vaccines (medians: ChAdOx1, 80.4 RU/mL; Ad26.CoV2.S, 18 RU/mL, respectively; Figure 2).

Factors Associated With Antibody Response in IBD Patients

We initially compared postvaccination serum anti-S1 antibodies between IBD patients who did or did not receive immunosuppressive therapy, including biologics, immunomodulators (IMMs) or systemic corticosteroids. We found that patients without immunosuppression had higher antibody titers (median, 117.1 RU/mL vs 106.2 RU/mL in patients on immunosuppression; P = .012; Figure 1a).

In the univariate analysis (Table 2), Crohn's disease, viral vector vaccines, older age, and longer time between vaccination and antibody measurement were associated with lower anti-S1 titers. As far as type of IBD treatment is concerned, we observed significantly lower antibodies in patients treated with systemic corticosteroids (P = .017), IMMs (P = .015), anti-TNFα (P = .016), combination of biologic plus IMMs (P = .009), or any 2 immunosuppressive agents (P = .006). In contrast, vedolizumab (VDZ)-treated patients demonstrated higher antibody concentrations compared with all other treatments (median 119.2 vs 106, P = .027). Interestingly, patients receiving methotrexate (MTX) but not thiopurines showed lower antibody levels compared with all other treatments (P = .020). In regards to type of IBD, patients with UC showed higher antibody levels than patients with CD (113.8 RU/mL vs 103.8RU/mL, P = .030).

In our multivariate model, we confirmed that mRNA vaccines are associated with higher antibody levels (P < .001). In addition, older age (P = .016), longer timing of antibody measurement after vaccination, (P < .001) and treatment with anti-TNF (P = .013) were negatively associated with anti-S1 concentrations (Table 3).

Comparative Analysis of the Effect of Different Biologics on Antibody Response to Vaccination

To specifically dissect the effect of biological therapy on vaccination response, we compared antibody concentrations between patients who were on monotherapy with any of the currently available biologics at the time of vaccination. Our analysis showed that IBD patients treated with VDZ had higher serum concentrations of anti-SARS-CoV-2 IgG antibodies (median concentration, 121 RU/mL) than those treated with anti-TNFα (106.8 RU/mL, P = .023) or ustekinumab (UST) monotherapy (95.9 RU/mL, P = .032; Supplementary Figure 1). No difference was seen between anti-TNFα- and UST-treated patients or between intravenous (infliximab) and subcutaneous (adalimumab) anti-TNFα therapies.

There was no observed correlation between antibody titers and distance from previous or next biologic treatment in days.

In our cohort, there were 7 patients with IBD and confirmed previous COVID-19 disease who all received BNT162b2 mRNA vaccine. There was no statistically significant difference regarding the levels of anti-SARS-CoV-2 IgG S1 antibodies postvaccination between those patients and patients without a history of infection (median, 124.7RU/mL vs 109.1RU/mL, respectively, P = .232).

Further analysis on anti-S1 levels in IBD patients was conducted regarding the timing of serum collection following vaccination (Supplementary Figure 2). We observed that anti-S1 levels were significantly lower when measured more than 56 days after vaccination, when all vaccine types were analyzed (P = .011). When only mRNA-vaccinated patients were analyzed, we detected that the antibody response wanes significantly after 53 days postvaccination (P = .049; Supplementary Figure 3). Such analysis did not achieve significant results in viral vector-vaccinated patients, possibly due to the smaller number of this cohort.

Table 1. Demographic and Clinical Characteristics of Participants.

		IBD Patients N = 403	Healthy Controls N = 124	*P*
Age (years; median [IQR])		45 (34-56)	51 (48-54)	0.001
Gender	Male	215 (53.4%)	52 (42%)	0.026
	Female	188 (46.7%)	72 (58%)	
Diagnosis	Crohn's disease	237 (58.8%)		
	Ulcerative colitis	153 (38%)		
	IBD unclassified	4 (1%)		
	Ileal pouch	7 (1.7%)		
Disease duration (years; median [IQR])		8 (4-15.25)		
Age at IBD diagnosis (years; median [IQR])		34 (24-46)		
BMI [kg/m^2;median (IQR)]		25.8 (22.8-29.3)		
Current Smokers (N, %)		104/363 (25.8%)		
Comorbidities (N, %)	Any	153 (38%)		
	Cardiovascular disease	38 (9.4%)		
	Diabetes mellitus	27 (6.7%)		
	Rheumatic disease	43 (10.7%)		
	Kidney failure	0		
	Liver disease	6(1.5%)		
	Respiratory disease	18 (4.5%)		
	Cancer- hematologic disease	6 (1.5%)		
	Hypertension	30 (7.4%)		
	Hyperlipidemia	25 (6.2%)		
	Other	67 (16.6%)		
Treatment (N, %)	5-ASA	135 (33.5%)		
	Systemic corticosteroids	15 (3.7%)		
	Thiopurines	53(13.2%)		
	Methotrexate	24 (6%)		
	Infliximab	134 (33.3%)		
	Adalimumab	51 (12.7%)		
	Golimumab	3 (0.7%)		
	Vedolizumab	71 (17.6%)		
	Ustekinumab	33 (8.2%)		
	Tofacitinib	3 (0.7%)		
	IMM monotherapy	28 (6.9%)		
	Anti-TNFα monotherapy	153 (38%)		
	Anti-TNFα + IMM	39 (9.7%)		
	Biologic monotherapy	247 (61.3%)		
	Biologic + IMM	49 (12.2%)		
	Two immunosuppressive agents	55 (13.6%)		
	Three immunosuppressive agents	2 (0.5%)		
	No immunosuppression	70 (17.4%)		
Vaccine name (N, %)	BNT162b2 (Pfizer	340 (84.4%)		
	mRNA-1273 (Moderna)	15 (3.7%)		
	ChAdOx1 (AstraZeneca)	41 (10.2%)		
	Ad26.CoV2.S (Johnson&Johnson)	6 (1.5%)		
Vaccine type (N, %)	mRNA (BNT162b2 & mRNA-1273)	355 (88.1%)		
	Viral vector (Ad26.CoV2.S & ChAdOx1)	47 (11.7%)		
Prior positive test for COVID-19 (N, %)		7 (1.73%)		
Days from last vaccine (median [IQR])		31 (23-46.75)		

Abbreviations: BMI, body mass index; COVID-19, corona virus disease 2019; IQR, interquartile range; IMM, immunomodulator (methotrexate, thiopurines); N, number.

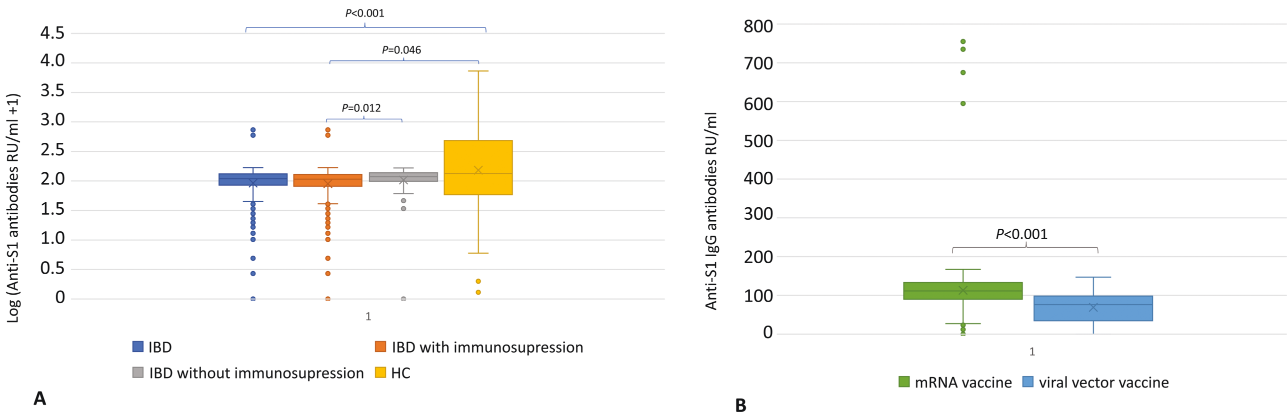

Figure 1. A, Comparison of anti-S1 IgG levels among inflammatory bowel disease (IBD) patients, IBD patients with immunosuppressive therapy, IBD patients without immunosuppressive therapy and healthy controls (HC). Error bars represent the 95% CI of the median values. Y axis represent log (Anti-S1 antibodies RU/mL + 1). B, Comparison of anti-S1 IgG levels between mRNA- vaccine and viral vector vaccine recipients. Error bars represent the 95% CI of the median values.

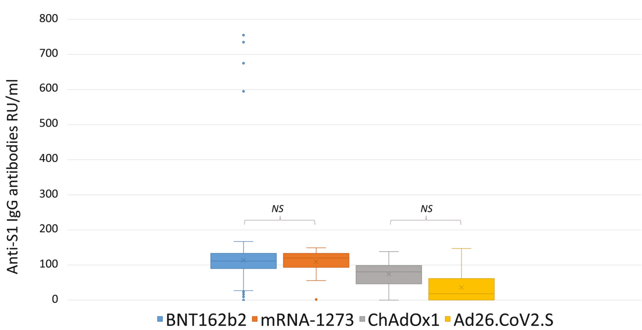

Figure 2. Comparison of anti-S1 IgG levels among BNT162b2, mRNA-1273, ChAdOx1, and Ad26.CoV2.S recipients. Error bars represent the 95% CI of the median values.

Factors Affecting Antibody Responses to Different Types of Vaccination

We also conducted a separate subanalysis on antibody responses in patients who received either mRNA or viral vector vaccines, exclusively (Supplementary Table 2). In the mRNA-vaccinated cohort, treatment with anti-TNFα (P = .008) and combination treatment with biologics plus IMMs (P = .021) was independently associated with lower antibody titers when all significant factors were analyzed. In addition, we confirmed that older age was also correlated with attenuated vaccine response (P = .014). With respect to viral vector vaccines, none of the factors was significantly correlated to lower anti-S1 levels in the univariate analysis. We hypothesize that the small number of patients who received viral vector vaccines may preclude identification of additional associations.

Safety and Adverse Events

We collected data on immediate and short-term adverse events using a questionnaire at the time of serum collection (available data on 362 patients). No serious AEs observed during the observation period and only minor AEs were reported, as shown in Supplementary Table 4. After the first vaccine dose, 79.4% of respondents reported an AE (47.3% excluding pain at the injection site). The most common reported AEs after the first dose were pain at the site of injection (73%), fatigue (38%), and myalgia/arthralgia (19%). Following the second vaccine dose (available data on 350 patients), 72% of patients reported an AE (49% excluding pain at the injection site). The most common reported AEs after the second dose were pain at the site of injection (63.1%), fatigue (40%), myalgia/arthralgia (23.7%), fever (18%), and headache (16%). We analyzed the correlation between presence of AEs after the second vaccine dose and patient characteristics (Supplementary Table 3). In the multivariate analysis younger age, female gender and mRNA vaccines were significantly correlated to AEs following the second vaccine dose (P = .003, P < .001, and P = .001, respectively), although a tendency was observed for BMI without reaching statistical significance threshold (P = .052; Table 4).

Discussion

Herein, we report high seroconversion rates in Greek patients with IBD following complete vaccination with any of the available anti-SARS-CoV-2 vaccines (2 doses of BNT162b2, mRNA-1273 or ChAdOx1 or 1 dose of Ad26.CoV2.S, respectively). In fact, our analysis showed that seroconversion rates for individual vaccines were similar or even higher to those reported in the general population.[19] Recently, Hadi et al reported that mRNA vaccination is as efficacious in IBD patients, even in biologic-treated ones, as in general population.[17] In our cohort, the highest seroconversion rates were obtained with 2 doses of BNT162b2 mRNA vaccine compared with other vaccine types. This result is in line with a recent study from the Israeli IBD group that reported 100% seropositivity in 185 IBD patients 2 weeks after the second dose of BNT162b2 mRNA vaccine.[20] On the other hand, the single-dose Ad26.CoV2.S vaccination regimen demonstrated the lowest seroconversion rate, which has been reported in previous literature.[21–23] However, the fact that our cohort included only 6 patients receiving Ad26.CoV2.S vaccine may influence our result. Finally, we observed that in our IBD cohort, 2 doses of ChAdOx1 vaccination resulted in higher seroconversion rates than previously reported in HCs (70.4% efficacy).[5] Indeed, there is accumulating evidence that IBD patients on biologic treatments demonstrate high seroconversion rates after ChAdOx1 vaccination.[24]

Table 2. Univariate Associations With Anti-SARS-CoV-2 S1 Antibodies.

Variable		IBD patients			HC	
		n/N	Correlation Coefficient rho	*P*	Correlation Coefficient rho	*P*
Age		403/403	-0.136	0.007	-0,073	0.497
BMI		374/403	0.045	0.385		
Timing of serum analysis from last vaccine dose		403/403	-0.208	<0.001		
Timing of 1st vaccine dose from last biologic administration		168/403	-0.006	0.940		
Timing of 1st vaccine dose from next biologic administration		183/403	-0.056	0.452		
Timing of 2nd vaccine dose from last biologic administration		171/403	-0.047	0.539		
Timing of 2nd vaccine dose from next biologic administration		172/403	0.021	0.787		
Variable	Categories	n/N	Median RU/mL (IQR)	*P*	Median RU/mL (IQR)	*P*
Gender	male	215/403	107 (82 -128.4)	0.134	139.2 (88.4-909.5)	0.091
	female	188/403	109.7 (88.2-132.9)		122.0 (43.0-406.8)	
Disease	CD	237/403	103.8 (76.9-130.6)	0.030 (UC vs CD)		
	UC	153/403	113.8 (92.2-133)			
	IBDU	4/403	102.8 (93.7-118.8)			
	IPAA	7/403	109.8(91.7-133.8)			
Smoking		104/363	107.8 (80.5-128.3)	0.114		
Treatment	5-ASA	135/403	115.4 (93.7-130)	0.040		
	Budesonide	15/403	113.8 (95.3-133.8)	0.357		
	Systemic CS	15/403	90.9 (52.5-105.8)	0.017		
	Thiopurines	53/403	106.2 (86.9-122.8)	0.283		
	Methotrexate	24/403	84.9 (60.2-117.4)	0.020		
	IMMs monotherapy	28/403	104.2 (88.7-126.2)	0.720		
	IMMs	78/403	97.3 (77-121.7)	0.015		
	Biologic therapy	296/403	107 (79.5-130.3)	0.139		
	Biologics monotherapy	247/403	107.7 (84.4-132.7)	0.530		
	Biologic in combination with IMMs	49/403	91 (60.8-121.5)	0.009		
	Infliximab	134/403	102.6 (68-125.9)	0.007		
	Adalimumab	51/403	103.8 (64-131.8)	0.485		
	Golimumab	3/403	143.1 (121.9-143.9)	0.104		
	Anti-TNFα	191/403	104.2 (68.5-128.7)	0.016		
	Anti-TNFα monotherapy	153/403	106.8 (74.3-132)	0.393		
	Anti-TNFα + IMMs	39/403	90 (58.5-123)	0.014		
	Vedolizumab	71/403	119.2 (95.9-138.4)	0.027		
	Vedolizumab monotherapy	66/403	98.5 (121-139.9)	0.009		
	Vedolizumab + IMMs	5/403	31.7 (103.1-115.6)	0.264		
	Ustekinumab	33/403	99.2 (86.4-117.4)	0.371		
	Ustekinumab monotherapy	28/403	95.9 (85.8-119.8)	0.329		
	Ustekinumab + IMMs	5/403	111.9 (100.8-115.3)	0.980		
	JAK inhibitors	3/0403	90.9 (71.4-105.8)	0.337		
	Two immunosuppressive agents	55/403	91(62.2-121.6)	0.006		
	Three immunosuppressive agents	2/403	59.7 (45.4-73.9)	0.085		
	No immunosupression	70/403	117.1 (98.4-136.8)	0.012		
Commorbidities	Any	154/403	105.9 (79.9-127)	0.214		
	Cardiovascular	38/403	94.2 (69.9-108)	0.004		
	Diabetes mellitus	27/403	98.2 (64.7-109.4)	0.061		
	Reumatological	43/403	94.3 (63.9-130.6)	0.252		
	Liver disease	6/403	119.2 (113.3-133.4)	0.369		
	Hyperlipidemia	25/403	94 (71.3-118.3)	0.043		
	Hypertension	30/403	109 (93.6-127)	0.615		
	Respiratory disease	18/403	104 (90.6-138.2)	0.780		
	Cancer-hematological diasease	18/403	120.6 (101.2-133.4)	0.538		

Table 2. Continued

Variable		IBD patients			HC	
		n/N	Correlation Coefficient rho	*P*	Correlation Coefficient rho	*P*
AEs after 1st vaccine dose		286/362	92.9 (112.3-133.4)	0.024		
AEs after 2nd vaccine dose	Any	256/356	114 (94-135.2)	0.003		
	Arm pain	221/356	112.6 (91.8-136.2)	0.043		
	Allergy	5/356	136.6 (95.9-147.7)	0.024		
	Fatigue	140/356	117.3 (92.2-136.8)	0.075		
	Fever	63/356	106.2 (126.4-144.8)	<0.001		
	Lymph nodes	16/356	105.5 (125.1-146.3)	0.095		
	Headache	56/356	106.7 (126.3-135.6)	0.005		
	Myalgia arthralgia	83/356	121.7 (103.1 -133.4)	0.01		
	Abdominal pain	19/356	87.7 (96.3-139)	0.348		
	Diarrhea	25/356	90.4 (87.4-128.8)	0.124		
COVID-19		7/403	124.7 (96.6-142.7)	0.232		
Vaccine type	mRNA	356/403	111.6 (90.2-133.1)	< 0.001		
	Viral vector	47/403	76(36.3-97.8)			

5-ASA, 5-aminocylate acid; AEs, adverse events; Anti-IL12/23, Interleukins 12/23 antagonist; Anti-TNFα, tumor necrosis factor α antagonist; CD, Crohn's disease; COVID-19, coronavirus disease 2019; CS, corticosteroids; IBDU, inflammatory bowel disease unclassified; IMMs, immunomodulators; IPAA, ileal pouch-anal anastomosis; JAK, janus kinase; mRNA, messenger rivonucleic acid; UC, ulcerative colitis;.

Table 3. Multivariate Linear Regression of Factors Associated With Anti-S1 IgG Antibodies (RU/mL).

	Standardized Coefficients Beta	95% CI for Beta	
Age (in years)	-0.5	-1.0	-0.1
Days elapsed since vaccination	-0.7	-1.0	-0.4
mRNA vs Vector	46.2	25.7	66.6
anti-TNF	-16.5	-29.6	-3.4

The variables disease type, adverse events after the second dose, two immunosuppressive agents, biologic in combination with IMMs, anti-TNF + immunomodulator, infliximab, vedolizumab, vedolizumab monotherapy, methotrexate, systemic corticosteroids, immunomodulators, no immunosupression, cardiovascular disease, hyperlipidaemia were also added to the multivariate model, but they were excluded during the stepwise procedure. Abbreviations: Anti-TNFα, anti-tumor necrosis α; CI, confidence interval; IMM, immunomodulator.

Table 4. Multivariable Associations of Adverse Events After 2nd Dose.

Variables		OR	95% CI
Age		0.97	0.96-0.99
Gender	Male vs Female	0.33	0.20-0.55
Vaccine type	mRNA vs Viral Vector	3.48	1.64-7.39
BMI		0.96	0.91-1.00

The variables cardiovascular disease, diabetes melitus and hyperlipidaemia were also added to the multivariate model, but they were excluded during the stepwise procedure. Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

Serocoversion rate of our HCs cohort was similar to previously reported according their median age.[25] In comparison, our IBD patients had higher seroconversion rates in total, which may be explained by their younger age.

Despite high seroconversion rates, the magnitude of response to anti-SARS-CoV-2 vaccination was lower in IBD patients than in HCs, irrespective of the type of treatment. Interestingly, we also confirmed that IBD patients without immunosuppression had lower anti-S1 IgG levels than HCs, suggesting that IBD per se leads to impaired immune responses. There are scarce data on inherent alterations regarding vaccine responses in IBD patients irrespective of immunosuppressive treatment.[26] Further research is needed to elucidate the magnitude, characteristics, and mechanisms of such immunogenicity impairment in patients with IBD.

A major finding that we report herein is that patients who were on treatment with anti-TNFα monoclonal antibodies, either as monotherapy or in combination with IMMs, had significantly lower antibody levels compared with all other treatments. Our results also align with the recent report from the REsponses to COVid-19 vaccinE IsRaeli IBD group (RECOVERI) who assessed 185 IBD patients and found that anti-S levels were significantly lower in patients treated with anti-TNFα compared with patients not treated with anti-TNFα or HCs.[20]We conducted further comparison between IFX- and ADA-treated IBD patients, and we report, for the first time, that there was no significant difference in anti-S1 IgG levels between the 2 groups. This finding extends previous evidence that patients treated with IFX or ADA show similar levels of antinucleocapsidic antibodies after SARS-CoV-2 infection.[27] Taken together, those data indicate that intravenous and subcutaneous anti-TNFα therapy affect the immune response in a similar way.

An important and novel parameter of our current work is the comparative analysis of the effect of individual biologics on antibody responses after anti-SARS-CoV-2 vaccination. Our analysis showed that patients on VDZ had significantly higher anti-S1 IgG antibody titers in comparison with patients treated with either anti-TNFα or UST, whereas no difference was seen between the 2 latter groups. Such differences most probably reflect the diverse immunological effects of specific biologics, being gut-selective for VDZ and systemic in the case of anti-TNFα or anti-IL12/23 blockade. In that sense, our findings align with previous work by Kennedy et al who compared antispike antibodies between IBD patients treated with either IFX or VDZ 2 to 10 weeks after vaccination with a single dose of mRNA vaccines; they found that IFX treatment was associated with lower antibody titers than VDZ.

With regards to IMMs, it has been reported that their use was independently associated with lower immunogenicity rates to mRNA vaccines.[16] However in our analysis, we did not reach any such conclusion.

Wong et al analyzed sera from 48 IBD patients, mostly on biologic therapy, who received 1 or 2 doses of mRNA vaccines; their study showed that following a 2-dose regimen, there was no association between anti-IgG levels and timing of biologic therapy.[28] We verified these results, as we found no significant correlation between anti-S IgG titers and distance from previous or next biologic treatment.

We also confirmed older age as a factor that is associated with attenuated vaccine response in IBD patients, as previously reported in published literature.[16]

Our study reported excellent safety profiles of all COVID-19 vaccines in patients with IBD, irrespective of treatment. In our cohort, we observed AE rates similar to those previously reported[20] and recorded no serious AEs. We did not see any myocarditis cases among 11 males younger than 21 years old and no thromboembolic events among 41 females older than 60 years old. Moreover, there was no significant increase of symptoms suggestive of IBD exacerbation, like diarrhea or abdominal pain in the period after vaccination. In the multivariate analysis of mRNA vaccines, younger age and female gender were significantly correlated to AEs following the second vaccine dose. These factors are known to positively correlate with post-COVID vaccination AEs.[29] On the contrary, biologic therapy has been associated with less common AEs.[18] Conflicting data exist in the literature regarding the effect of treatment with biologics, with some studies reporting fewer AEs in IBD patients treated with anti-TNFα, and other showing no correlation.[17,20,30,31] We did not find similar associations in our study. The role of immunosuppressive treatment in AE rate following anti-SARS-Cov-2 vaccination is yet to be elucidated.

Irrespective of treatment, we demonstrated that antibody levels wane as time goes by. This goes in line with a recent observation that immune humoral response to BNT162b2 COVID-19 vaccine declines after 6 months, more importantly in male, elderly, and immunocompromised patients.[32] This observation is significant in order to produce vaccination protocols, especially for immunosupressed patients. In addition, we did not manage to correlate prior COVID-19 infection with the presence of AEs possibly because of the low rate of prior infection in our cohort (7 patients).

There are several strengths in our study. First, this is the largest adult IBD cohort assessed prospectively for both antibody production and AEs after full vaccination protocol with all 4 EMA-approved vaccines (BNT162b2 [Pfizer-BioNTech], mRNA-1273 [Moderna/NIH], ChAdOx1 [Astra Zeneca] and Ad26.CoV2.S [J&J]). It is also the only cohort that collected data about comorbidities along with other demographic details. In addition, statistical analysis included patients with all types of medications and even an important cohort of IBD patients without immunosuppression. Thus, we managed to extract results for all available drugs, including systemic corticosteroids and newer biologics. We focused on not only intravenous therapies but also subcutaneous treatments, allowing for further statistical analysis. Furthermore, we included a large number of HCs, allowing for further comparisons. Another strength is that we obtained data on the timing of vaccination along with the timing of biologic infusion or injection, providing evidence that that there is no significant correlation between these time points and anti-S1 IgG production.

However, our study is also limited by certain factors. First, the fact that recruited patients were from tertiary IBD centers suggests that disproportionally more patients on treatment with biologics and/or high disease burden were included. Second, we did not check for prior COVID-19 infection by testing collected sera for antinucleocapsidic antibodies but relied on appropriate nasopharyngeal or nasal test reporting. However due to government protocols, most of the patients conducted these tests very often in order to work or enter the hospital. Third, we did not obtain data on vaccine type for HCs, and there is a difference in gender ratio and age distribution between IBD and HC groups. However, this difference may not hamper our results, as we did not correlate the antibody concentrations with male or female gender, and HCs demonstrated higher antibody levels irrespective of the fact that they had older median age. Fourth, we obtained small sample size for some specific subgroup analysis. Finally, as far as vaccine efficacy is concerned, we assessed only anti-S1 antibodies, and we did not address neutralization of SARS-CoV-2 with other methods. Nonetheless, the ELISA we used shows very good agreement compared with available neutralization tests, according to manufacturer details.

Conclusion

Our study provides prospective controlled data on the antibody production after COVID-19 vaccination with all 4 EMA approved vaccines, suggesting that mRNA vaccines are more efficacious in IBD patients than viral vector ones and that all vaccines are safe in this population. We demonstrated that patients treated with anti-TNFα and UST have lower antibody levels than patients treated with VDZ. More importantly, the fact that IBD patients without immunosuppression have lower antibody concentrations than HCs confirms the observation that patients with IMIDs have altered immune response. However, the actual deficit in vaccine efficacy is not known, and further long-term research is needed to address this question. Until then, attention should be paid to promote vaccination in IBD patients, even those that do not currently receive immunosuppressive drugs. Vaccination protocols should be updated taking into account the waning of antibody levels as time goes by.

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Conflicts of Interest

E.Z.: Lecturer for Amgen, Takeda

M.T.: Advisor/lecturer for Janssen, Pfizer, Takeda, Abbvie, MSD, Mylan, Genesis Pharma, Amgen, Research/Clinical Trials: AbbVie, Gilead, Takeda

N.V.: Advisor/lecturer for Janssen, Pfizer, Aenorasis, Takeda, Abbvie, MSD, Mylan, Amgen, Genesis Pharma, Cooper.

G.J.M.: Advisor/lecturer for AbbVie, Celgene, Celtrion, Ferrirng, Genesis, Hospira, Janssen, Millennium Pharmaceuticals, MSD, Mylan, Pharmacosmos, Pfizer, Takeda, VIANEX, Angelini, Falk Pharma, Galenica, Omega Pharma; Consultancies for MSD and Takeda; Research support from AbbVie, Galenica, Genesis, Menarini Group, MSD, Pharmathen.

K.K.: Advisor/lecturer for Abbvie, Aenorasis, Janssen, MSD, Pfizer and Takeda, Amgen, Ferring, Galenica, Genesis Pharma.

E.Z.: Advisor/lecturer for Pfizer, Takeda, Abbvie, Amgen, Genesis Pharma, Aenorasis, Janssen

S.M.: Advisory/Lecturer for Pfizer, Takeda, Abbvie, Ferring, MSD, Janssen

G.M.: Lecturer for Janssen, Takeda, MSD, Abbvie, Pfizer

P.K.: Lecturer for Takeda, Janssen, Amgen, Ferring

C.L.: Advisor/lecturer for MSD, BOSTON SCI, Research/Clinical Trials: Epsilon Health Co

I.E.K.: Advisor for Abbvie, Astelas, Genesis, Janssen, MSD, Pharmacosmos, Pfizer, Shire, Vianex and Takeda; Lecturer for AbbVie, Astelas, Genesis, Janssen, MSD, Vianex Takeda and Viatris; research support Abbvie, Vianex, Unipharma, Viatris, Takeda and Ferring

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