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Alimentary Tract

Reduced humoral response to two doses of COVID-19 vaccine in patients with inflammatory bowel disease: Data from ESCAPE-IBD, an IG-IBD study

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ABSTRACT

Background: Patients on immunosuppressive drugs have been excluded from COVID-19 vaccines trials, creating concerns regarding their efficacy.
Aims: To explore the humoral response to COVID-19 vaccines in patients with inflammatory bowel disease (IBD)
Methods: Effectiveness and Safety of COVID-19 Vaccine in Patients with Inflammatory Bowel Disease (IBD) Treated with Immunomodulatory or Biological Drugs (ESCAPE-IBD) is a prospective, multicentre study promoted by the Italian Group for the study of Inflammatory Bowel Disease. We present data on serological response eight weeks after the second dose of COVID-19 vaccination in IBD patients and healthy controls (HCs).

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Results: 1076 patients with IBD and 1126 HCs were analyzed. Seropositivity for anti-SARS-CoV-2 IgG was reported for most IBD patients, even if with a lesser rate compared with HCs (92.1% vs. 97.9%; $p<0.001$). HCs had higher antibody concentrations (median OD 8.72 [IQR 5.2-14-2]) compared to the whole cohort of IBD patients (median OD 1.54 [IQR 0.8-3.6]; $p<0.001$) and the subgroup of IBD patients (n=280) without any treatment or on aminosalicylates only (median OD 1.72 [IQR 1.0–4.1]; $p<0.001$).
Conclusions: Although most IBD patients showed seropositivity after COVID-19 vaccines, the magnitude of the humoral response was significantly lower than in HCs. Differently from other studies, these findings seem to be mostly unrelated to the use of immune-modifying treatments (ClinicalTrials.govID:NCT04769258).

1. Introduction

Defined as a pandemic by the World Health Organization on March 11, 2020 [1], the infection due to SARS-CoV-2 and its related disease – COVID-19 – represent the global health crisis of our times. The introduction of effective COVID-19 vaccines is a cornerstone in its prevention, and patients with inflammatory bowel disease (IBD) need be vaccinated against SARS-CoV-2 [2,3]. Patients on immunosuppressive drugs have been excluded from COVID-19 vaccination trials, creating concerns regarding their efficacy among subjects on immune-modifying therapies, including those with IBD [4]. Notably, infliximab was associated with reduced humoral responses to several vaccines, including those against hepatitis B, pneumococcal, and influenza [5–7]. PREVENT-COVID and CORALE-IBD studies showed that the majority of IBD patients mount an immune response after completing mRNA COVID-19 vaccine regimens [8,9]. This reassuring finding was also confirmed by a recent meta-analysis [10]. Other reports showed that IBD patients on immune-modifying therapy had lower antibody concentrations compared with those who were on no treatment, aminosalicylates (5-ASA), or vedolizumab (VDZ) [11,12]. In particular, the lowest levels were observed in patients treated with anti-TNFs and concomitant immunomodulators [13]. Another recent study found lower anti-SARS-COV-2 spike protein levels in IBD patients receiving infliximab, infliximab plus thiopurines, and tofacitinib, compared with other immunomodulating agents [14]. Despite these emerging data, there is still a need for a better understanding of the humoral responses to COVID-19 vaccines in patients with IBD, in order to discriminate between the impact of different treatments and the potential influence of the IBD itself. Indeed, there is a need for cohort studies with an adequate sample size to compare humoral responses in IBD patients treated with immune-modifying agents, IBD patients not treated with immunosuppressive agents, and healthy controls (HCs).

This prospective, case-control study aims to assess the humoral response to two doses of COVID-19 vaccines in IBD patients on different treatment regimens and in HCs.

2. Materials and methods

2.1. Patients and study design

Effectiveness and safety of COVID-19 vaccine in patients with Inflammatory Bowel Disease treated with immunomodulatory or biological drugs (ESCAPE-IBD) is a prospective, multicentre, case-control study comparing effectiveness and safety of COVID-19 vaccines among IBD patients treated with different regimens and HCs. This study was promoted by the Italian Group for the Study of Inflammatory Bowel Diseases (IG-IBD - ClinicalTrials.gov ID: NCT04769258). Here, we present data on rates of seropositivity and anti-SARS-CoV-2 IgG levels eight weeks after the second dose of COVID-19 vaccines (or after a single dose in case of administration of the Ad26.COV2.S vaccine). Safety data will be presented in a separate paper.

Patients were recruited at 16 IBD centers in Italy. They were included if they were aged 18 years or older, willing to receive the COVID-19 vaccine, if they had an established diagnosis of Crohn's disease or ulcerative colitis or unclassified colitis using standard definitions and if they were on a stable treatment for at least eight weeks at the time of the first dose of COVID-19 vaccination. Exclusion criteria were: primary immunodeficiencies or human immunodeficiency virus infection, vaccination against SARS-CoV-2 started before enrolment, known contraindications to COVID-19 vaccine or intolerance to its components, known previous occurrence of COVID-19 or asymptomatic SARS-CoV-2 infection.

At baseline, all enrolled patients underwent a detailed assessment including: demographics, type of disease (Crohn's disease or ulcerative colitis or unclassified colitis), smoking habits, disease duration, co-morbidities, location and behavior of the disease according to Montreal classification, disease activity (assessed with the Harvey-Bradshaw Index for Crohn's disease and Partial Mayo Score for ulcerative colitis), current medication for IBD. All enrolled patients were tested for the quantitative assessment of IgG against SARS-CoV-2. Participants for the HC group were recruited from the staff working at Istituto Europeo di Oncologia IRCCS, Milan (Italy), where all serological assessments were centrally performed for both IBD patients and HCs. The interval between the evaluation at baseline and the first dose of vaccine did not exceed 10 days. The vaccine was administered to patients and HCs according to the times and modalities established by the Italian National Vaccination Plan: a preferential 21-day interval between the first and second dose for the BNT162b2 vaccine, a 28-day interval for the mRNA-1273 vaccine, and a 56-84-day interval for the ChAdOx1 vaccine, while the Ad26.COV2.S vaccine was administered as a single-dose. The quantitative detection of IgG against SARS-CoV-2 was repeated eight weeks (± ten days) after the second dose (after the single dose for the Ad26.COV2.S vaccine).

2.2. Ethical statement

All participants were included after providing informed, written consent. All data were collected anonymously in a specifically arranged electronic CRF form inside the IG-IBD registry. The National Institute for Infectious Disease "Lazzaro Spallanzani IRCSS" Ethics Committee approved the study (reference 336/2020-201) in April, 2021. All authors had access to the study data and reviewed and approved the final manuscript.

2.3. Assessment of anti-SARS-CoV-2 IgG

The ELISA assay to detect IgG uses a fragment of the SARS-CoV-2 Spike glycoprotein (S protein) as antigen, based on a recently published protocol [15,16]. Briefly, after binding the RBD proteins to a Nunc MaxiSorp ELISA plate, and blocking non- specific binding with PBS-BSA 3%, patient sera were applied to the plate to

allow antibody binding at a final dilution of 1:200 revealed with secondary anti-human-IgG (BD, clone G18-145) antibodies conjugated to HRP. Samples were read on a GloMax reader at 450 nm. This ELISA test is not intended for commercial use. Positivity threshold levels were determined by ROC curves. Positivity for RBD was OD 0.29 for IgG.

2.4. Outcomes

Two outcomes were assessed at eight weeks following the second dose of COVID-19 vaccines (or the single dose for the Ad26.COV2.S vaccine): (i) seropositivity rates (positivity for anti-SARS-CoV-2 IgG as previously defined); (ii) anti-SARS-CoV-2 IgG levels**.** Both outcomes were compared in IBD patients and HCs, and in IBD patients treated with different therapeutic agents, divided into five subgroups: no treatment or monotherapy with 5-ASA, thiopurines, anti-TNFs, VDZ, and ustekinumab (UST).

2.5. Statistics

Continuous variables were expressed as median with interquartile ranges (IQR) and categorical variables were summarized as frequency and percentage. The Chi-square, or Fisher's exact test when appropriate, and the independent samples T-test were applied for categorical and continuous variables, respectively. The comparison of seropositivity rates between IBD patients and HCs was performed with the Chi-square or Fisher's exact test, while the T-test was used for the comparison of anti-SARS-CoV-2 IgG levels. One way ANOVA test with post hoc multiple comparison (LSD method) was performed to compare the two outcomes among the subgroups of IBD patients treated with different regimens. The influence of the variables at baseline was assessed using a binary logistic regression multivariate with Backward Wald method analysis for seropositivity rates, and using a linear regression multivariate analysis with Backward method for anti-SARS-CoV-2 IgG levels. The following candidate risk factors were selected: age, gender, smoking habits, type of disease (Crohn's disease or ulcerative colitis), disease duration, number of co-morbidities, disease activity, systemic steroids at baseline, type of vaccine, anti-SARS-CoV-2 IgG positivity at baseline. All statistical analyses were performed using SPSS version 25. A p-value $\leq$ 0.05 was considered statistically significant.

3. Results

3.1. Patients

The baseline characteristics of both IBD patients and HCs are shown in Table 1. One thousand and seventy-six IBD patients (Crohn's disease: 56.2%; ulcerative colitis: 43.8%) and 1126 HCs were included. The groups differed for age (median 47.0 years [IQR 32.0-59.0] vs 43.7 years [IQR 33.0-52.0] in IBD patients and HCs, respectively; P<0.001) and gender (males: 57.2% vs. 32.8% in IBD patients and HCs, respectively; P<0.001). The rate of positivity for anti-SARS-CoV-2 IgG at baseline was comparable between patients and HCs (8.9% vs. 10.7%; p=0.17). Almost all patients and all HCs underwent homologous double-dose vaccination, and the great majority received mRNA vaccines: 99.0% of IBD patients received BNT162b2 or mRNA-1273, 92.7% of HCs received BNT162b2 (p<0.001). Only three IBD patients received the single-dose Ad26.COV2.S vaccine.

At least one comorbidity was reported in more than half of patients (52.1%). Regarding IBD activity at baseline, 658 (61.2%) patients were in clinical remission, 269 (25.0%) had mild activity, 122 (11.3%) moderate activity, and 27 (2.5%) patients had severe activity. The majority of patients were on anti-TNF monotherapy (40.6%), while only a small percentage (0.9%) were treated with an anti-TNF plus a thiopurine. Monotherapy with 5-ASA was reported in 23.0% of patients, thiopurines in 9.3%, VDZ in 17.0%, and UST in 6.1% of cases. No therapy was reported for 33 patients (3.1%).

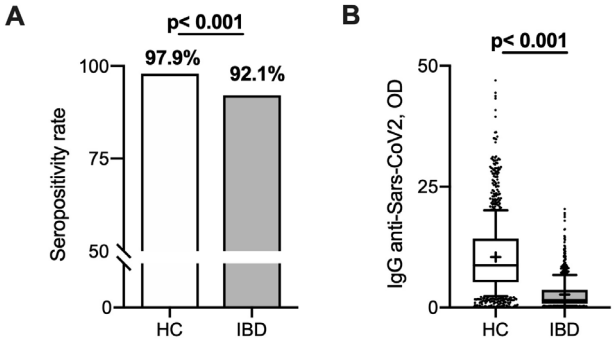

Fig. 1. Seropositivity rates (A) and anti-SARS-CoV-2 IgG levels (B) among healthy controls (HCs) and IBD patients (IBD).

3.2. Seropositivity rates and anti-SARS-CoV-2 IgG levels among IBD patients and HCs

Eight weeks after completing the COVID-19 vaccine cycle, most IBD patients mounted an antibody response, with a slightly lower rate compared with HCs: the IgG seropositivity rate in IBD patients and HCs was 92.1% and 97.9%, respectively (p<0.001– Fig. 1A). This difference remained significant in the subgroup of patients aged ≥ 65 years (83.8% vs. 100.0% in IBD patients and HCs, respectively; p=0.017), and when the analysis excluded subjects with IgG positivity at baseline (91.9% vs. 97.8% in IBD patients and HCs, respectively; p<0.001). HCs had significantly higher anti-SARS-CoV-2 IgG concentrations (median OD 8.72 [IQR 5.2-14-2]) compared with IBD patients (median OD 1.54 [IQR 0.8-3.6]; p<0.001 - Fig. 1B). Patients with IBD receiving immune-modifying drugs (defined as treated with thiopurines, anti-TNFs, VDZ, or UST; n=796) had similar rates of seropositivity for IgG and anti-SARS-CoV-2 IgG concentrations compared with IBD patients (n=280) who were on no treatment or on monotherapy with 5-ASA (seropositivity rates: 91.6% and 93.7%, respectively, p=0.37; anti-SARS-CoV-2 IgG levels: median OD 1.46 [IQR 0.7-3.4] vs. 1.72 [IQR 1.0–4.1]; p=0.15). Conversely, when comparing HCs with IBD patients receiving immune-modifying drugs, and HCs with IBD patients receiving no treatment or 5-ASA monotherapy, there was a statistically significant difference in seropositivity rates (p<0.001 and p=0.003, respectively – Fig. 2A) and anti-SARS-CoV-2 IgG concentrations (p<0.001 and p<0.001, respectively – Fig. 2B) in favor of HCs . Finally, when comparing HCs with IBD patients after exclusion of those treated with anti-TNFs (n=629) the difference in seropositivity rates (97.9% vs. 92.5%) and antibody concentrations (median OD 8.72 [IQR 5.2-14-2] vs. median OD 1.65 [IQR 1.0-3.8]) remained significant (p<0.001 for both comparisons).

3.3. Seropositivity rates and anti-SARS-CoV-2 IgG levels among subgroups of IBD patients and factors associated with the development of serological response

Seropositivity rates among IBD patients were similar across different treatment groups: 93.6% for no treatment or 5-ASA, 89.0% for thiopurines, 91.5% for anti-TNFs, 92.9% for VDZ, 92.4% for UST (p=n.s. for all comparisons – Fig. 3A). Among patients treated with anti-TNFs, no relevant difference was found between the single anti-TNF drugs: 91.4%, 91.4% and 93.1% for infliximab, adalimumab and golimumab, respectively (p=n.s. for all comparisons). Finally, 9 out of 10 (90.0%) patients treated with

Table 1
Baseline characteristics of patients with IBD and healthy controls.

Variable	IBD patients (n=1076)	Healthy controls (n=1126)	p value
Gender, n (%)			
- Male	616 (57.2)	369 (32.8)	**<0.001**
- Female	460 (42.8)	757 (67.2)	
Age (years), median (IQR)	47.0 (32.0-59.0)	43.7 (33.0-52.0)	**<0.001**
Vaccine type, n (%)			
- BNT162b2	960 (89.2)	1044 (92.7)	**<0.001**
- mRNA-1273	105 (9.8)	0	
- ChAdOx1	8 (0.7)	82 (7.3)	
- Ad26.COV2.S	3 (0.3)	0	
Anti-SARS-CoV-2 IgG positivity at baseline	96 (8.9)	120 (10.7)	0.17
Type of disease, n (%)			
- Crohn's disease	605 (56.2)		
- Ulcerative colitis	471 (43.8)		
Active smokers, n (%)	164 (15.2)		
Disease duration (years), median (IQR)	10.0 (5.0-18.0)		
No. of comorbidities, n (%)			
- 0	515 (47.9)		
- 1	328 (30.5)		
- 2	122 (11.3)		
- 3	73 (6.8)		
- $\geq$ 4	38 (3.5)		
Disease location, n (%)			
Crohn's disease			
- L1 (ileal)	234 (38.7)		
- L2 (colonic)	60 (9.9)		
- L3 (ileocolonic)	306 (50.6)		
- L4 (isolated upper GI)	5 (0.8)		
- Perianal disease	124 (20.5)		
- E1 (proctitis)	81 (17.2)		
- E2 (left-sided)	187 (39.7)		
- E3 (extensive)	203 (43.1)		
Disease behavior (Crohn's disease), n (%)			
- B1 (Non-stricturing, non-penetrating)	285 (47.1)		
- B2 (Stricturing)	240 (39.7)		
- B3 (penetrating)	80 (13.2)		
Disease activity, n (%)			
- Remission	658 (61.2)		
- Mild	269 (25.0)		
- Moderate	122 (11.3)		
- Severe	27 (2.5)		
IBD Treatment, n (%)			
- None	33 (3.1)		
- 5-ASA monotherapy	247 (23.0)		
- Thiopurine	100 (9.3)		
- Anti-TNF	447 (41.6)		
- Infliximab	198 (18.4)		
- Adalimumab	220 (20.4)		
- Golimumab	29 (2.7)		
- Anti-TNF Monotherapy	437 (40.6)		
- Anti-TNF + Thiopurine	10 (0.9)		
- Vedolizumab	183 (17.0)		
- Ustekinumab	66 (6.1)		
Systemic steroids at baseline, n (%)	15 (1.4%)		

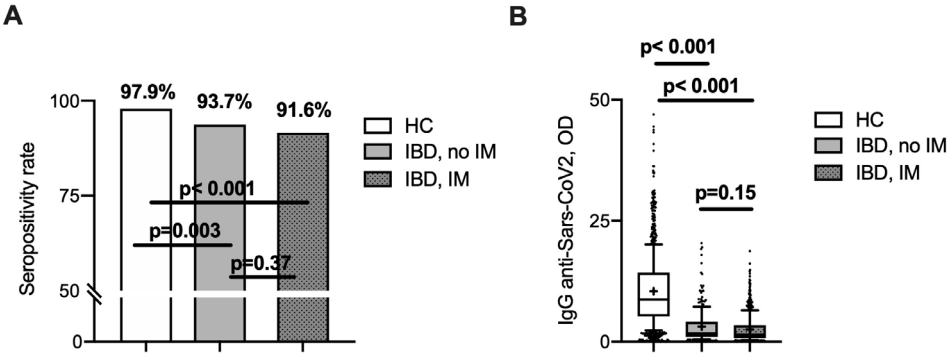

Fig. 2. Seropositivity rates (A) and anti-SARS-CoV-2 IgG levels (B) among healthy controls (HCs), IBD patients who were on no treatment or on monotherapy with 5-ASA (IBD NO IM) and IBD patients receiving immune-modifying drugs (IBD IM).

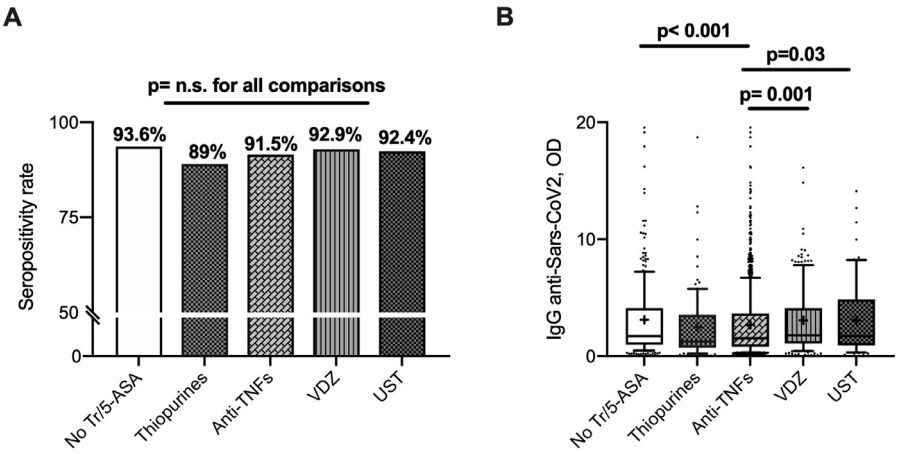

Fig. 3. Seropositivity rates (A) and anti-SARS-CoV-2 IgG levels (B) among IBD patients who were on no treatment or monotherapy with 5-ASA (No TR/5-ASA), thiopurines, anti-TNFs, Vedolizumab (VDZ), and Ustekinumab (UST).

Table 2
Multivariable logistic regression analysis of factors associated with seropositivity following two doses of COVID-19 vaccination (only the last step of the backward elimination method is shown).

Variable	Odds Ratios (CI 95%)	p value
Age, years	0.9561 (0.947-0.976)	**<0.001**
Crohn's disease *(vs. ulcerative colitis)*	0.251 (0.140-0.450)	**<0.001**
Disease remission *(vs. disease activity)*	1.892 (1.184-3.023)	**0.008**

Table 3
Multivariable linear regression analysis of factors associated with anti-SARS-CoV-2 IgG levels following two doses of COVID-19 vaccination (only the last step of the backward elimination method is shown).

Variable	*β*	S.E.	*p* value
Age, years	- 0.024	0.006	**<0.001**
Current smoking	- 0.200	0.114	0.079
Crohn's disease	- 0.336	0.180	0.062
Anti-SARS-CoV-2 IgG positivity at baseline	1.120	0.305	**<0.001**
Type of vaccine *(BNT162b2 vs. mRNA-1273)*	- 2.056	0.281	**<0.001**
IBD treatment	0.222	0.061	**<0-001**

anti-TNF plus a thiopurine showed seropositivity. At multivariable logistic regression analysis (Table 2), age ($p<0.001$) and Crohn's disease ($p<0.001$) were found to be independent predictors of reduced seropositivity rates (notably, seroconversion rates in Crohn's disease and ulcerative colitis were 89.1% and 96.0%, respectively; OR 1.428, CI 1.257-1.622, $p<0.001$), while disease remission was found to be predictor of higher seroconversion rates ($p=0.008$).

With regards to anti-SARS-CoV-2 IgG levels, IBD patients treated with anti-TNFs showed significantly lower median concentrations compared with those on no treatment or treated with 5-ASA (median OD 1.30 [IQR 0.7-3.0] vs.1.72 [IQR 1.0–4.1]; $p<0.001$), with those treated with VDZ (median OD 1.30 [IQR 0.7-3.0] vs.1.78 [IQR 1.1–4.1]; $p=0.001$), and with those treated with UST (median OD 1.30 [IQR 0.7-3.0] vs.1.71 [IQR 0.9–4.9]; $p=0.03$), while the difference with the thiopurine group was not significant (median OD 1.30 [IQR 0.7-3.0] vs.1.26 [IQR 0.7–3.5]; $p=0.45$). All other comparisons between groups were not significant (Fig. 3B). Among patients treated with anti-TNFs, significantly lower median anti-SARS-CoV-2 IgG levels were reported in patients treated with golimumab compared with those treated with adalimumab (median OD 1.10 [IQR 0.5-1.5] vs.1.45 [IQR 0.7–3.2]; $p=0.03$), while the difference between golimumab and infliximab groups was not significant (median OD 1.10 [IQR 0.5-1.5] vs.1.26 [IQR 0.7–3.0]; $p=0.20$), as well as the difference between adalimumab and infliximab groups ($p=0.07$). Among the 10 patients treated with anti-TNFs and thiopurines, median OD anti-SARS-CoV-2 IgG levels were 0.97 (IQR 0.4-2.5). At multivariable linear regression analysis, IBD treatment was confirmed as independent predictor of anti-SARS-CoV-2 IgG levels ($p<0.001$) together with anti-SARS-CoV-2 IgG positivity at baseline ($p<0.001$), while age ($p<0.001$) and use of BNT162b2 vaccine (compared with mRNA-1273; $p<0.001$) were inversely associated (Table 3). Of note, median OD anti-SARS-CoV-2 IgG levels were 1.44 (IQR 0.7–3.9) for patients with Crohn's disease and 1.68 (IQR 0.9–4.1) for patients with ulcerative colitis.

4. Discussion

This work aims to contribute to the discussion on the humoral immunity developed following COVID-19 vaccination in patients with IBD with two strong points: (i) a large sample size; (ii) the comparison of IBD patients on immune-modifying treatments with HCs, as well as IBD patients not treated with immunosuppressive agents. We believe that these two factors are fundamental to correctly discriminate between the impact of different treatments and the potential influence of the chronic inflammatory disease on the immune response to COVID-19 vaccination. Our prospective, multicentre study reported four main findings: (i) the great majority of IBD patients showed seropositivity after two doses of COVID-19 vaccines; (ii) seropositivity rates and anti-SARS-CoV-2 IgG levels among IBD patients were significantly lower compared with HCs (iii); compared with HCs, seropositivity rates and anti-SARS-CoV-2 IgG levels were significantly lower also among IBD patients who were not treated with immunomodulatory drugs; (iiii) IBD patients treated with anti-TNFs showed the lowest median concentrations of anti-SARS-CoV-2 IgG levels compared to the other subgroups of IBD patients. Taken together, these findings suggest that the magnitude of the serological response is lower in IBD patients than in the general population and that this effect is mostly independent of immune-modifying therapy use.

In line with other studies, our findings confirm that almost all patients with IBD are able to mount a humoral response following two doses of COVID-19 vaccination in terms of seropositivity rate (92.1%). However, this rate is significantly lower than in HCs, and also slightly lower compared with 95%-100% of patients in PREVENT-IBD, CORALE-IBD, and HERCULES study [8–11]. In addition, this reduction in the immune response does not seem to be related to therapy, as no differences were noted between IBD patients without any treatment or with 5-ASA only and those

with different immunosuppressive therapies. This finding is probably the most interesting point of our study. This possible impact of the deregulation of the immune system in IBD patients on the ability to mount a humoral response following COVID-19 vaccination is indirectly supported by the fact that Crohn's disease *per se* was found to be an independent predictor of reduced seroconversion, while disease remission was correlated with higher rates of seroconversion. The design of this study is not adequate to clarify the reasons underlying these findings, and it does not analyze the cell-mediated response elicited by COVID-19 vaccines. However, we believe that our data are sufficient to define IBD patients as "frail" - about the humoral response to COVID-19 vaccines - hence requiring booster/additional doses of COVID-19 vaccines. Data on the effects of the third dose of COVID-19 vaccines in our cohort are ongoing.

Relevant findings were also obtained analyzing the differences in anti-SARS-CoV-2 IgG levels among subgroups of IBD patients. In line with other studies [11–14], treatment with anti-TNFs was associated with lower median antibody concentrations compared with other treatments. This is probably due to a higher level of immunosuppression induced by anti-TNFs compared to all other treatments, with a consequent interference with the mechanisms necessary to mount an effective immune response towards antigens. Therefore, particular attention to the immunization of IBD patients treated with anti-TNFs should be warranted, and priority of additional doses should be reserved to them. Furthermore, compared with HCs, anti-SARS-CoV-2 IgG concentrations were significantly lower not only in patients with IBD receiving immune-modifying drugs, but also in patients with IBD receiving no treatment or 5-ASA only. These data reinforce the aforementioned perception of a reduction in the immune response which could be a consequence of the chronic inflammatory disease itself and not related to the use of specific therapeutic agents. It could be argued that HCs and patients are not perfectly balanced, as HCs are slightly younger than IBD patients and there were differences in the type of vaccine they received, but the magnitude of the effect (median IgG levels more than five times higher in HCs) still seems too large to be due to such slight differences.

In conclusion, our prospective, case-control, multicenter study showed a reduced humoral response elicited by two doses of COVID-19 vaccines in patients with IBD. Differently from other studies, these findings seem to be mostly unrelated to the use of immune-modifying treatments. Waiting for ongoing data on additional/booster doses, our results suggest that IBD patients should be considered as "frail" - regarding the response to COVID-19 vaccines - emphasizing the need for studies investigating repeated doses of COVID-19 vaccines in this population.

Conflict of interest

FSM served as an advisory board member and/or received lecture grants from AbbVie, Biogen, Galapagos, Janssen, MSD, Pfizer, Samsung Bioepis, Takeda Pharmaceuticals. MP served as an advisory board member and/or received lecture grants from MSD, Takeda, Janssen, Pfizer, Abbvie. SS received lecture fees from or served as a consultant and advisory board member for AbbVie, Arena, Gilead, Janssen Pharmaceuticals and Takeda. CB received lecture fees from Takeda, MSD, AbbVie and Janssen. FC received lecture fees from or served as a consultant or advisory board member for Abbvie, Janssen, Pfizer, Takeda Pharmaceuticals. OMN received lecture fees from Ferring, Fresenius Kabi, and Janssen. MCF received consultancy fees from Roche, Takeda, Jannsen-Cilag, Pfizer, Sandoz, Biogen, Galapagos and research economic support from Abbvie. GF served as a consultant and advisory board member for Janssen, Takeda, Pfizer, Amgen, Celltrion, Sandoz, Samsung Bioepis, Ferring, Vifor, Galapagos. FC served as consultant to Abbvie, MSD, Takeda, Janssen, Roche, Celgene, Bristol Myers Squibb, Galapagos, Gilead, Pfizer, Mundipharma, Galapagos, Biogen, received lecture fees from Abbvie, Ferring, Takeda, Allergy Therapeutics, Janssen, Pfizer, Biogen, and unrestricted research grants from Giuliani, Sofar, MSD, Takeda, Abbvie .AO served as an advisory board member for AbbVie, Galapagos, MSD, Janssen, Pfizer, Takeda Pharmaceuticals, and received lecture grants from AbbVie, MSD, Sofar, Chiesi, Janssen, Pfizer, and Takeda Pharmaceuticals. All other authors: nothing to disclose.

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