Lack of seroconversion following COVID-19 vaccination is an independent risk factors for SARS-CoV-2 infection in patients with inflammatory bowel disease: data from ESCAPE-IBD, an IG-IBD study

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ABSTRACT

Background: Patients with immune conditions were excluded from COVID-19 vaccine clinical trials. Real-world data are needed to identify those patients who are likely to benefit from repeated doses.

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, observational study assessing effectiveness and safety of COVID-19 vaccines in patients with IBD (ClinicalTrials.gov ID: NCT04769258). Here we present data on the rate of SARS-CoV-2 infections in the timeframe between 14 days after the second dose and the third dose of COVID-19 vaccine (or a maximum of 9 months after the second dose). We assessed the role as risk factors for SARS-CoV-2 infection of several variables, including lack of seroconversion, IgG anti-SARS-CoV-2 levels after 8 weeks from the second dose, and types of IBD treatment.

Results: Out of 1076 patients enrolled in the ESCAPE-IBD study, data on breakthrough SARS-CoV-2 infection were available in 953 cases. Seroconversion was reported in 92.7% of cases, with median IgG anti-SARS-CoV-2 levels of 1.60 OD [IQR 0.8-3.6]), while SARS-CoV-2 infection was documented in 95 patients (10.0%), of whom 9 died. At multivariable regression analyses, age (OR 0.97, 95% CI 0.96-0.99; p<0.001), former smoker status (OR 2.23, 95% CI 1.26-3.88; p=0.005) and lack of seroconversion (OR=2.37, 95% CI 1.01-5.09; p=0.034) were independent predictors of SARS-CoV-2 infection.

Conclusions: Lack of seroconversion following COVID-19 vaccination, but not type of IBD treatment, is an independent risk factor for SARS-CoV-2 infection in patients with IBD.

Key words: Biologics; SARS-CoV-2; Vaccines.

INTRODUCTION

The introduction of vaccines against Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) represented the main strategy to manage effectively the consequences of Coronavirus disease 2019 (COVID-19). COVID-19 vaccines are generally recommended in patients with immune conditions and/or treated with immunosuppressive drugs, such as those with inflammatory bowel disease (IBD) [1]. The clinical effectiveness of a complete cycle of COVID-19 vaccination was extensively demonstrated in patients with IBD, both in terms of prevention and/or mitigation of COVID-19 and of humoral and T cell response [2,3]. These data were strengthened by studies showing high efficacy of a booster dose in restoring protection against SARS-CoV-2 infection and reducing negative clinical outcomes of COVID-19 [4-7]. In this evolving scenario, the interplay between antibody levels (or seroconversion) following COVID-19 vaccination and the clinical effectiveness of these vaccines is not fully understood: it is unclear whether low antibody titers are predictive *per se* of increased risk of breakthrough SARS-CoV-2 infections and/or severe COVID-19, as evidenced in some cohorts [8]. Another interesting topic in IBD patients is whether immunosuppressive drugs increase the risk of SARS-CoV-2 infections and/or severe COVID-19, as shown by other reports [4,5,7].

This study aimed to assess the rate of SARS-CoV-2 infections in the timeframe between 14 days after the second and the third dose of COVID-19 vaccine (or a maximum of 9 months from the second dose), and the risk factors for SARS-CoV-2 infection, with a particular focus on the humoral response to vaccination and the different treatments for IBD.

MATERIALS AND METHODS

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, study assessing effectiveness and safety of COVID-19 vaccines among IBD

patients treated with different drugs. This study was promoted by the Italian Group for the Study of Inflammatory Bowel Diseases (IG-IBD - ClinicalTrials.gov ID: NCT04769258). 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.

Study design, eligibility criteria, methods, and timing of assessment of anti-SARS-CoV-2 IgG levels were extensively described in two recently published papers analyzing humoral responses and safety of COVID-19 vaccines [9,10]. The study protocol included a proactive surveillance after 3, 6, and 9 months from the second dose (first dose in case of the single-dose Ad26.COV2.S vaccine) – with pre-scheduled outpatient visits or via remote contacts - to report the occurrence of SARS-CoV-2 infection. Here we present data on the rate of breakthrough SARS-CoV-2 infections in the timeframe between 14 days after the second dose and the third dose of COVID-19 vaccine (or a maximum of 9 months after the second dose). All diagnoses of infection were based on polymerase chain reaction or antigen testing on a nasopharyngeal swab performed in case of symptoms compatible with COVID-19, or in the context of contact tracing. We performed univariable and multivariable regression analyses of factors associated with breakthrough SARS-CoV-2 infection using a stepwise model selection. As candidate risk factors, we selected the following variables: 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 before the first dose of COVID-19 vaccine, lack of seroconversion (cut-off for IgG anti-SARS-CoV-2: OD 0.28), IgG anti-SARS-CoV-2 levels 8 weeks after the second dose, and medications for IBD. All statistical analyses were performed using R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria). A p-value ≤ 0.05 was considered statistically significant.

RESULTS

Data on breakthrough SARS-CoV-2 infections were available in 953 patients (Crohn's disease: 56.5%; ulcerative colitis: 43.5%), out of the 1076 IBD patients originally enrolled in the ESCAPE-IBD study. Their baseline characteristics are shown in table 1. Most patients received homologous, double-dose, mRNA-based vaccines (BNT162b2 or mRNA-1273: 99.2%), 5 patients received ChAdOx, and 3 patients the single-dose Ad26.COV2.S vaccine. No comorbidity was reported in approximately half of the population. The rate of positivity for anti-SARS-CoV-2 IgG before the first dose of vaccine was 8.9%. The majority of patients were on anti-TNF monotherapy (39.0%), while mesalamine monotherapy was reported in 23.6% of patients, thiopurines in 10.3%, vedolizumab in 15.8%, and ustekinumab in 6.5% of cases. No therapy was reported for 36 patients (3.8%).

Eight weeks after completing the COVID-19 vaccine cycle, seroconversion was documented in 92.7% of cases, while the median anti-SARS-CoV-2 IgG concentration was 1.60 OD (IQR 0.8-3.6). SARS-CoV-2 infection was reported in 95 patients (10.0%). The most frequently recorded COVID-19 symptoms were fever (60.0%), arthromyalgia (44.2%), and cough (40.0%). Diarrhea was reported by 21.1% of patients. The infection was fully asymptomatic in 17 cases (17.9%). Nine patients died (case fatality rate: 9.5%). All 9 patients who died had seroconversion after the second dose. At multivariable regression analysis, younger age (OR 0.97, 95% CI 0.96-0.99; $p<0.001$), former smoker status (OR 2.23, 95% CI 1.26-3.88; $p=0.005$), and lack of seroconversion (OR 0.42, 95% CI 0.20-0.99; $p=0.034$) were independent predictors of SARS-CoV-2 infection (table 2). None of the various IBD treatments were associated with an increased rate of breakthrough SARS-CoV-2 infection (figure 1 - p = not significant).

DISCUSSION

Conflicting data exist on the interplay between humoral immunity following COVID-19 vaccination and protection against SARS-CoV-2 infection in IBD patients treated with different drugs. It is unclear whether antibody titers are predictive *per se* of the risk of SARS-CoV-2 infection and/or severe COVID-19, and whether immunosuppressive drugs are critical risk factors. Our prospective, multicentre study reported two main findings: (i) lack of seroconversion following two doses of COVID-19 vaccines was an independent predictor of SARS-CoV-2 infection; (ii) none of the treatments for IBD was associated with an increased risk of SARS-CoV-2 infection.

The present study is the second part of an overall assessment of the effectiveness of COVID-19 vaccines in patients with IBD. In the first part, we highlighted that seropositivity rates and anti-SARS-CoV-2 IgG levels were significantly lower among IBD patients compared with healthy controls, and that these percentages were significantly lower also amongst IBD patients who were not treated with immunomodulatory drugs. These findings suggested that the overall impact of immune-modifying therapies on the serological response to COVID-19 vaccines was limited. In the present analysis, we found that lack of seroconversion was an independent predictor for an increased rate of breakthrough SARS-COV- 2 infections, while there were no significant differences between IBD patients receiving various therapies. This finding, coupled with the evidence of the effectiveness of the booster dose in patients with IBD [4-7], suggests that booster/additional doses may be useful in case of lack of seroconversion. Younger age and former smoker status were found to be independent predictor of SARS-CoV-2 infection. We can hypothesize that the tendency to have a more active social life may play a role in the higher risk of infection reported amongst young people. We do not have an explanation for the association between former smoker status and infection rates, and the study design is not adequate to clarify the reasons underlying this finding and/or any potential immunological explanation. All nine COVID-19

related deaths occurred in patients who had seroconverted following two doses of COVID-19 vaccine. The low number of events prevents any statistical analysis or firm conclusion. However, it is well known that the humoral response may not always be adequate alone in describing the actual protection against severe COVID-19, since many other factors - mostly related to cell-mediated immunity - are certainly involved [11].

We acknowledge that there are some limitations in our study. First, we did not provide data on the cell-mediated response elicited by COVID-19 vaccines. Secondly, our study focused on the effectiveness given by a second dose of COVID-19 vaccines, and the temporal interval of our study covered the pre-variant era of SARS-CoV-2 infection. As a consequence, we cannot exclude that our findings may not be perfectly relevant today, when highly transmittable omicron variants (and sub-variants) of SARS-COV-2 are circulating, and several patients have already undergone additional/booster doses of vaccine. However, despite these limitations, we believe that the association between the absence of seroconversion and the risk of SARS-CoV-2 infection may be an assumption that is overall valid even today in relation to the new variants of the virus. We feel comfortable in suggesting additional doses in patients with IBD who do not obtain seroconversion after a full cycle or even additional COVID-19 vaccine doses.

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Table 1. Baseline characteristics

Variable	IBD patients (n=953)
Gender, n (%)	
- Male	549 (57.6)
- Female	404 (42.4)
Age (years), median (min-max)	47.0 (18-89)
Vaccine type, n (%)	
- BNT162b2	839 (88.1)
- mRNA-1273	106 (11.1)
- ChAdOx1	5 (0.5)
- Ad26.COV2.S	3 (0.3)
Anti-SARS-CoV-2 IgG positivity at baseline, n (%)	85 (8.9)
Type of disease, n (%)	
- Crohn's disease	538 (56.5)
- Ulcerative colitis	415 (43.5)
Smokers, n (%)	
- Active	152 (15.9)
- Former	172 (18.1)
- Never	629 (66.0)
Disease duration (years), median (min-max)	10.0 (0.5-51.0)
No. of comorbidities, n (%)	
- 0	458 (48.1)
- 1	285 (29.9)
- 2	105 (11.0)
- 3	57 (6.0)
- ≥ 4	38 (4.0)
Disease localization, n (%)	
Crohn's disease	
- L1 (ileal)	218 (40.5)
- L2 (colonic)	51 (9.5)
- L3 (ileocolonic)	265 (49.3)
- L4 (isolated upper GI)	4 (0.7)
- Perianal disease	111 (20.6)
Ulcerative colitis	
- E1 (proctitis)	73 (17.6)
- E2 (left-sided)	166 (40.0)
- E3 (extensive)	176 (42.4)
Disease behaviour (Crohn's disease), n (%)	
- B1 (Non-stricturing, non-penetrating)	256 (47.6)
- B2 (Stricturing)	212 (29.4)
- B3 (penetrating)	70 (13.0)
Disease activity, n (%)	
- Remission	570 (59.8)
- Mild	243 (25.5)
- Moderate	113 (11.9)
- Severe	27 (2.8)
IBD Treatment, n (%)	
- None	36 (3.8)
- Mesalamine monotherapy	225 (23.6)
- Thiopurine	98 (10.3)
- Anti-TNF	381 (40.0)
- Infliximab	149 (15.6)
- Adalimumab	206 (21.6)
- Golimumab	26 (2.7)
- Anti-TNF Monotherapy	372 (39.0)
- Anti-TNF + Thiopurine	9 (0.9)
- Vedolizumab	151 (15.8)
- Ustekinumab	62 (6.5)

Systemic steroids at baseline, n (%)	14 (1.5%)

Table 2. Multivariable regression analysis of factors associated with breakthrough SARS-CoV-2 infection (stepwise model selection)

Variable	**OR**	**CI**	***p* value**
Age, years	0.97	0.96-0.99	**<0.001**
Smoking *[ref.Never smoker]*			
Current smoker	1.45	0.78-2.60	0.228
Former smoker	2.23	1.26-3.88	**0.005**
Lack of seroconversion	2.37	1.01-5.09	**0.034**

FIGURE LEGEND

Figure 1. COVID-19 breakthrough rates according to the different treatments for IBD