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ORIGINAL ARTICLE

Serological response to vaccines against SARS-CoV-2 in patients with inflammatory bowel disease

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KEYWORDS
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Abstract
Objective: To study the serological response (SR) and tolerability of COVID-19 vaccine in patients with inflammatory bowel disease (IBD) and its relation with IBD treatment and type of vaccine.
Methods: Observational, cross-sectional study in patients with IBD vaccinated against COVID-19 without known previous infection. SR was analyzed by the determination of IgG antibodies against the S1 subunit. Safety was studied using a questionnaire to identify adverse effects (AE).
Results: 280 patients with IBD were included. Type of vaccines: Comirnaty® 68.8%; Spikevax® 10.8%, Vaxzevria® 18.3%, Ad26.COV2-S® 2.2%. 51.3% had AE, being 100% mild. 65% developed IgG antibodies after vaccination. The SR was higher for vaccines with mRNA technology (100% Spikevax®, 68.5% Comirnaty®) compared to those based on adenovirus vector (38.0% Vaxzevria®, 33.3% Ad26.COV2-S®) ($P < .001$). In the multivariate analysis, SR was related to age (<60 years; OR: 3.8, 95% CI 1.9–7.0; $P < .001$). The SR in patients with aminosalicylates was 65.4%, 61.4% with immunosuppressants, 65.8% with anti-TNF, and 68.7% with non-anti-TNF biologicals ($P = .9$).
Conclusions: One third of patients with IBD did not develop antibodies with the initial vaccination against SARS-CoV-2. The SR to vaccines based on mRNA technology was higher, and it was related to age (higher in younger patients). Immunosuppressants and biologicals did not decrease SR. More than half of the patients presented AD, being mild in all cases.

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PALABRAS CLAVE
Enfermedad inflamatoria intestinal;
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Respuesta serológica a las vacunas frente a SARS-CoV-2 en pacientes con enfermedad inflamatoria intestinal

Resumen
Objetivo: Estudiar la respuesta serológica (RS) y tolerabilidad frente a la vacuna COVID-19 en pacientes con enfermedad inflamatoria intestinal (EII) y su relación con el tratamiento de la EII y tipo de vacuna.
Métodos: Estudio observacional, transversal en pacientes con EII vacunados contra COVID-19 sin infección previa conocida. La RS se analizó mediante la determinación de anticuerpos IgG frente a la subunidad S1. La seguridad se estudió mediante cuestionario para identificación de efectos adversos (EA).
Resultados: Se incluyeron 280 pacientes con EII. Tipo de vacunas: Comirnaty® 68,8%; Spikevax® 10,8%, Vaxzevria® 18,3%, Ad26.COV2-S® 2,2%. Un 51,3% tuvo EA, siendo el 100% leves. Un 65% desarrolló anticuerpos IgG tras la vacunación. La RS fue superior para vacunas con tecnología ARNm (100% Spikevax®, 68,5% Comirnaty®) frente a las basadas en vector con adenovirus (38,0% Vaxzevria®, 33,3% Ad26.COV2-S®) ($P < ,001$). En el análisis multivariante la RS se relacionó con la edad (<60 años; OR: 3,8, IC 95% 1,9–7,0; $P < ,001$). La RS en pacientes con aminosalicilatos fue del 65,4%, 61,4% con inmunosupresor, 65,8% con anti-TNF y 68,7% con biológicos no anti-TNF ($P = ,9$).
Conclusiones: Un tercio de pacientes con EII no desarrolló anticuerpos con la pauta vacunal inicial frente a SARS-CoV-2. La RS a las vacunas basadas en tecnología ARNm fue superior, y estuvo relacionada con la edad (mayor en pacientes más jóvenes). Los inmunosupresores y biológicos no disminuyeron la RS. Más de la mitad de los pacientes presentaron EA, leves en todos los casos.

Introduction

Vaccination against the SARS-CoV-2 virus is a basic prevention strategy in the current pandemic situation. Patients with inflammatory bowel disease (IBD) are often being treated with immunosuppressive or biological drugs. These patients also need frequent visits to hospital, including the Day Hospital, to have intravenous therapies administered to control their disease. Clinical trials for the approval of COVID-19 vaccines did not specifically include participants with this type of medical history.

In our IBD Unit, we previously carried out a cross-sectional observational study in which we contacted all the patients undergoing treatment (more than 800), detecting that 10.2% of the patients had had SARS-CoV-2 infection in the first wave.[1] We also recently reported on how the incidence of COVID-19 had evolved in our patients in the 2nd and 3rd waves.[2] In a joint communication with the patients' Asociaciones de Crohn y Colitis Ulcerosa (ACCU) [Crohn's and Ulcerative Colitis Associations) and the Grupo Enfermero de Trabajo en Enfermedad Inflamatoria Intestinal (GETEII) [Nursing Working Group on Inflammatory Bowel Disease]), the Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa (GETECCU) [Spanish Working Group on Crohn's Disease and Ulcerative Colitis] explains that the vaccine is safe in patients with IBD.[3] There is no evidence to suggest an increased risk in other immune-based diseases or patients on steroid, immunosuppressive or biological treatment. GETECCU, GETEII and ACCU recommend vaccinating all patients with IBD against SARS-CoV-2, regardless of their IBD treatment.

In general, most of Spain's autonomous regions did not establish any preference or priority when vaccinating patients with IBD and in many cases, Madrid Region included, they were vaccinated by age groups along with the rest of the population. As with other vaccines, such as hepatitis B,[4] immunosuppressive or biological treatment could potentially decrease the efficacy of the vaccines for COVID-19 infection. In addition, the vaccines may have less efficacy in these patients than reported in the general population in the pivotal studies already published.[5–8,10] For all the above reasons, it is appropriate to perform post-vaccination serology in the clinical scenario of a patient with IBD, as we routinely do in hepatitis B immunisation.

The efficacy of the SARS-CoV-2 vaccines may be lower in patients with IBD. Our aim was to study the serological response (SR) and the tolerability of the COVID-19 vaccine in patients with IBD and the relationship of these aspects with the IBD treatment and type of vaccine.

Methods

Observational, single-centre, cross-sectional study in patients with IBD followed up at the Hospital de Fuenlabrada Unit in Madrid, Spain. We included patients over 18 years of age with IBD, vaccinated with any type of vaccine for COVID-19 with the regimen administered and having had the second dose (except patients vaccinated

with Ad26.COV2-S® [Janssen Pharmaceutica, JANSSEN CILAG SA, Johnson & Johnson subsidiary] who had only received a single dose) of the vaccine three months ± one month prior to inclusion. Patients with known COVID-19 infection prior to vaccination (confirmed by PCR, antigen test or serology) or with diseases other than IBD causing immunosuppression (for example human immunodeficiency virus or agammaglobulinaemia) were excluded.

The SR to the vaccine was analysed by determining specific IgG antibodies against the receptor-binding domain (RBD) of the virus spike protein subunit S1. Chemiluminescence technique (DxI-Beckman Coulter analyser) for measurement of specific IgG antibodies against the RBD of the virus spike protein subunit S1 and standardised against the 1st ISNIBSC 20/136. These antibodies appear post-vaccination for SARS CoV-2 or post-COVID-19 infection. Therefore, any positive response in the absence of proven infection was considered a positive vaccine response. In this study, any value higher than 30 IU/mL was considered as a positive vaccine response (manufacturer's data: Beckman Coulter, Inc.).

IBD activity was measured by clinical (Harvey-Bradshaw for Crohn's disease and Mayo partial score for ulcerative colitis) and biological (C-reactive protein or faecal calprotectin) indices.

Tolerability was studied using specific questionnaires to determine the occurrence of any adverse effects (AE) related to the vaccine. Other clinical data were reviewed by telephone interview and review of the medical records. An AE was considered serious if it led to the hospital admission or death of the patient.

Statistical analysis

Calculations were made to determine the sample size for the study. Considering the number of patients seen in the IBD clinic (around 800) and estimating that 20% of patients would not be candidates for inclusion, mainly because they had previously had COVID-19 infection, plus allowing a 5% margin of error and a 95% confidence interval (CI), we calculated that the overall sample size should be 230 patients.

For the statistical analysis, we carried out a descriptive analysis with the qualitative variables being represented by percentages and 95% CI. The Kolmogorov-Smirnov test was performed to assess the normality of continuous variables. Quantitative variables were expressed as mean and standard deviation or median and interquartile range if the variable did not follow a normal distribution. In the bivariate study, categorical variables were compared using the chi-square test (χ^2) and comparisons between quantitative and qualitative variables were made using Student's *t*-test or the Mann-Whitney *U* test if the variables did not follow a normal distribution. The percentage of efficacy of the vaccine was calculated stratifying by type of drug and by type of vaccine.

Multivariate analysis was performed to identify potential risk factors for decreased vaccine efficacy using a logistic regression model. The IBM® SPSS® Statistics program was used to carry out the analysis.

Results

Baseline characteristics of the patients included

We included 280 patients with IBD. The baseline characteristics of these 280 patients are shown in Table 1. When they were vaccinated, 24.6% had IBD activity. The IBD treatments patients were receiving at the time of inclusion were as follows: 1) anti-TNF biological agents: 26.4% (N = 74); 2) non-anti-TNF biological agents: 11.8% (N = 33); 3) immunosupressors 37.1% (N = 104); and 4) aminosalicylates 21.1% (N = 59). Only five patients (1.8%) were receiving combined biological and immunosuppressant therapy.

Serological response to vaccines for SARS-CoV-2 in patients with inflammatory bowel disease

The distribution of the different types of vaccines was as follows: Comirnaty® 68.8% (N = 192); Spikevax® 10.8% (30); Vaxzevria® 18.3% (51); and Ad26.COV2-S® 2.1%.6 Overall, 51.3% had AE with the vaccine (N = 135), all of which were mild, the most common being pain at the vaccination site (45.9%), asthenia (25.9%), fever (25.9%), headache (16.3%), myalgia (14.1%) and general malaise (15.6%). After being vaccinated, 65% (N = 174) developed IgG antibodies. Table 2 shows the efficacy and AE according to the specific type of vaccine. Vaccines with mRNA technology had a higher SR than vector-based vaccines with adenovirus (Comirnaty® [Pfizer-BioNTech]/Spikevax® [Moderna] 72.8% vs Vaxzevria®/Ad26.COV2-S® [Ad26.COV2-S: Janssen-Cilag International] 37.5%, $P < .0001$). The AE rate was higher with vaccines based on mRNA technology (55.0% vs 37.0%; $P = .018$).

The SR to the vaccine was related to age, such that the patients who generated antibodies after the vaccine were younger than those who had no response (50 ± 12 vs 56 ± 13 years; $P < .001$). The efficacy of the vaccine was not related to the type of IBD treatment. The percentage efficacy of the vaccine was as follows: patients on no treatment or only on aminosalicylates, 65.4%; patients on immunosuppressive treatment, 61.4%; patients on anti-TNF treatment, 65.8%; and patients on treatment with non-anti-TNF biological drugs, 68.7% ($P = .9$). Efficacy was also not related to IBD activity (percentage efficacy in patients in remission, 65.8% vs patients with IBD activity at the time of vaccination, 65.6%; $P = .72$), gender (64.0% efficacy in females vs 66.2% in males; $P = .2$), type of IBD (efficacy in patients with Crohn's disease 63.7% vs patients with ulcerative colitis, 67.7%; $P = .967$); or previous comorbidities (percentage efficacy in patients with comorbidities, 63.0%, vs 89.2% in patients without comorbidities; $P = .08$).

In the multivariate analysis, only age was considered a factor related to SR; patients under the age of 60 had a higher SR than patients over 60 (OR: 3.8, 95% CI, 1.9–7.0; $p < .001$).

Discussion

Published studies on the efficacy of the initial vaccination schedule for SARS-CoV-2 in the general population place it

Table 1 Baseline characteristics of the patients included in the study.

	N = 280
Gender	
Male	150 (53.6%)
Age	
Mean ± standard deviation	52 ± 13 years
Smoking	
Yes	55 (22.1%)
Tipo de enfermedad inflamatoria intestinal	
Crohn's disease	166 (59.3%)
Ulcerative colitis	106 (37.9%)
Unclassified/indeterminate colitis	8 (2.9%)
Age at diagnosis (Crohn's disease)	
A1 (age ≤ 16)	10 (6.2%)
A2 (aged 17–40)	99 (61.5%)
A3 (age > 40)	52 (32.3%)
Location (Crohn's disease)	
L1 terminal ileum	56 (36.4%)
L2 colon	25 (16.2%)
L3 ileocolic	72 (46.0%)
L1 + L4 (upper gastrointestinal tract)	–
L2 + L4	1 (0.6%)
Disease behaviour, n (%)	
B1 inflammatory	74 (57.8%)
B2 stenosing	22 (17.2%)
B3 fistulising	32 (25.0%)
Location (ulcerative colitis)	
Extended	42 (39.6%)
Left-sided colitis	55 (51.9%)
Proctitis	10 (9.4%)
Type of treatment for the inflammatory bowel disease	
Mesalazine	59 (21.1%)
Azathioprine/mercaptopurine	89 (31.8%)
Tofacitinib	6 (2.1%)
Methotrexate	9 (3.2%)
Infliximab	33 (11.8%)
Adalimumab	36 (12.9%)
Golimumab	5 (1.8%)
Ustekinumab	24 (8.6%)
Vedolizumab	9 (3.2%)
Corticosteroids	3 (1.1%)
Open-label clinical trial (mirikizumab, etrolizumab, filgotinib)	14 (5.0%)
Comorbidities	
Yes	162 (62.5%)
Type of comorbidity	
Chronic kidney disease	10 (3.7%)
Chronic obstructive pulmonary disease	37 (14.6%)
Congestive heart failure	2 (0.8%)
Coronary heart disease	5 (2.0%)
Diabetes mellitus	33 (12.9%)
Hypertension	74 (29.1%)
Dyslipidaemia	87 (34.0%)
Cancer	23 (9.1%)
Liver disease	37 (14.3%)

at around 90% in terms of infection prevention.[5,7,10,11] The available vaccines are not sterilising, but they do reduce the severity and mortality rates of the different variants of SARS-CoV-2.[7,9] Our approach was to find out the SR to the available vaccines in patients with IBD and the possible influence of the base treatments on this response. The SR in our study was 65% and was higher for mRNA-based vaccines; Comirnaty®/Spikevax® 72.8% vs Vaxzevria®/Ad26.COV2-S® 37.5%. The phase I-II trial of the Janssen Ad26.COV2-S® vaccine obtained 97%–100% seroconversion with the different doses used in the trial in patients aged 18–65, while the seroconversion rate was lower in patients over 65 (75%–77%).[5] The SR in our study was also related to the age of the patients; the patients who generated antibodies after the vaccine were younger than those who did not. Other studies carried out with the vaccines for the hepatitis B virus and flu had similar findings.[4,12] Intrinsic changes in B cells with age could contribute to reduced antibody response, such as that seen with the influenza vaccine.[12]

Also, simply having IBD, IBD activity at the time of vaccination or the treatments used to control the disease could affect the development of antibodies after vaccination. Studies conducted in patients with liver or kidney transplants found that these patients develop a substantially lower immune response to the mRNA-based vaccine (Comirnaty®) than controls. All the control patients generated antibodies against the vaccine compared to 47.5% of liver transplant patients and 37.5% of kidney transplant patients. Age was also among the predictors of worse SR to the vaccine.[13,14]

As in previous studies, we found that disease activity did not seem to be related to a better or worse response to the vaccine.[15] Although around a quarter of the patients had IBD activity at the time of vaccination, they did not have a lower SR than the rest.

With regard to the treatments used, it was reported that patients treated with infliximab may have attenuated immunogenicity with a single dose of the BNT162b2 (Comirnaty®) and ChAdOx1 nCoV-19 (Vaxzevria®) vaccines and vaccination was urged after SARS-CoV-2 infection, or not delaying a second dose, in these patients.[16] In our case, seroconversion after vaccination was not related to the type of IBD treatment, with very similar percentages of positive IgG antibodies in all treatment groups, in line with other recently published data.[17,18] Vaccination therefore continues to be an effective option in all IBD patients regardless of the treatment they are receiving, including immunosuppressive or biological drugs.

In their article published in *Lancet Rheumatology*, Mahil et al. found that methotrexate may have decreased the SR to the Pfizer vaccine (Comirnaty®) in a group of 17 patients with rheumatic diseases, but immunosuppressive and biological treatments did not (27 patients with anti-TNF therapies and 25 patients with anti-IL-23), although they concluded that verification is needed from more pharmacovigilance studies with real-life data.[19]

Other studies also reporting data from patients with rheumatological and musculoskeletal diseases on biological therapy with anti-TNF found, like us, that these therapies did not affect the generation of antibodies after vaccination. However, they did find that treatment with cor-

Table 2 Serological response to vaccination (generation of specific IgG antibodies against the receptor-binding domain of the S protein S1 subunit) and associated adverse effects according to the type of vaccine used.

	Efficacy (% IgG)[a]	Adverse effects[a]
Spikevax®-Moderna	100% (29/29)	53.6% (15/28)
Comirnaty®-Pfizer-BioNTech	68.5% (124/181)	55.2% (100/181)
Vaxzevria®-AztraZeneca	38.0% (19/50)	33.3% (16/48)
Ad26.COV2-S®-Janssen	33.3% (2/6)	66.6% (4/6)

[a] Significant differences ($P < .05$) were observed in the overall analysis of the serology response and in the development of adverse effects.

ticosteroids, rituximab or abatacept were associated with lower immunity after receiving the vaccine. In our study, only three patients were receiving corticosteroid therapy at the time of vaccination, so we cannot confirm these findings.[20–22]

Regarding the safety of the vaccine, previous studies in the IBD population with vaccines using mRNA technology, such as the study by Botwin et al., reported that 62% of the patients suffered AE after the second dose of the vaccine, with the most common being pain at the administration site (56%), asthenia (45%), headache (34%) and fever (29%).[23,24] These data are in line with ours; in our study, 51.3% of the patients overall had AE associated with the vaccine, with a higher rate of AE in patients who received mRNA vaccines than in those given adenovirus vector-based vaccines. In our case, the most common AE were pain at the vaccination site (45.9%), asthenia (25.9%), fever (25.9%), headache (16.3%), myalgia (14.1%) and malaise (15.6%).

In our study all of the AE were mild. However, in the previously mentioned study, 24 out of 246 patients had 53 serious AE after the second dose. This may be due to the definition of severity, as these authors considered severe AE to be those which limited daily activities, although only three of the 24 patients who actually suffered AE required hospital admission for that reason. In our case, the criteria were stricter, as we only considered as severe AE those which led to the hospitalisation or death of the patient, neither of which occurred with any of our patients. Therefore, although development of AE was common, they were manageable and outweighed the possible complications associated with a SARS-CoV-2 infection.

Lastly, regarding the limitations of the study, we cannot rule out with complete certainty that some of the positive IgG results were due to post-vaccination infection, as serology for envelope or nucleocapsid and protease was not performed in these patients. We can confirm, however, that none of the patients had or had had symptoms compatible with the infection or previous positive diagnostic tests (antigen test, PCR or serology) at the time of the measurement.

Additionally, it has to be taken into account that this series was carried out before the appearance of the Omicron variant, at a time when the incidence of infection in the reference population was low.

Conclusions

One third of patients with IBD failed to develop antibodies with the initial vaccination regimen for SARS-CoV-2. The response to mRNA-based vaccines was greater and was related to age, being better in younger patients. The type of treatment used for IBD did not affect the SR. Immunosuppressive and biological drugs did not decrease SR. Although more than half of the patients developed AE with the vaccine, they were mild in all cases.

This work was carried out in accordance with the World Medical Association's Code of Ethics (Declaration of Helsinki) for experiments with humans. All the patients included in the study had signed the specific Informed Consent Form for telematic contact for reasons of their IBD. They were also informed verbally and in writing in comprehensible language of the objectives and requirements of the study. The explanations the participants received included full information about the nature, purpose and possible risks and benefits of the study. They were able to ask any questions they had and informed that they were completely free to withdraw from the study at any time.

This study was approved by the Hospital Universitario de Fuenlabrada Ethics Committee.

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Conflicts of interest

A. Algaba has been a speaker and has received a research grant or consultancy fees from MSD, Lilly, Roche, Takeda and Janssen.

F. Bermejo has been a speaker, consultant and advisory member or has received research funding from MSD, Abbvie, Takeda, Janssen, Pfizer, Biogen, Amgen, Ferring, Faes Farma, Tillotts Pharma, Chiesi and Gebro Pharma.

I. Guerra has served as a speaker or consultant for Takeda, Kern Pharma, Abbvie and Janssen.

None of the declared conflicts of interest is directly related to this manuscript.

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