Journal of Crohn's and Colitis, 2022, **16**, 1070–1078
https://doi.org/10.1093/ecco-jcc/jjac010
Advance access publication 17 January 2022
Original Article

Implementation and Short-term Adverse Events of Anti-SARS-CoV-2 Vaccines in Inflammatory Bowel Disease Patients: An International Web-based Survey

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Abstract

Introduction: Anti-SARS-CoV-2 vaccine clinical trials did not include patients with immune-mediated conditions such as inflammatory bowel disease [IBD]. We aimed to describe the implementation of anti-SARS-CoV-2 vaccination among IBD patients, patients' concerns, and the side effect profile of the anti-SARS-CoV-2 vaccines, using real-world data.

Methods: An anonymous web-based self-completed survey was distributed in 36 European countries between June and July 2021. The results of the patient characteristics, concerns, vaccination status, and side effect profile were analysed.

Results: In all 3272 IBD patients completed the survey, 79.6% had received at least one dose of anti-SARS-CoV-2 vaccine, and 71.7% had completed the vaccination process. Patients over 60 years old had a significantly higher rate of vaccination [$p < 0.001$]. Patients' main concerns before vaccination were the possibility of having worse vaccine-related adverse events due to their IBD [24.6%], an IBD flare after vaccination [21.1%], and reduced vaccine efficacy due to IBD or associated immunosuppression [17.6%]. After the first dose of the vaccine, 72.4% had local symptoms and 51.4% had systemic symptoms [five patients had non-specified thrombosis]. Adverse events were less frequent after the second dose of the vaccine and in older patients. Only a minority of the patients were hospitalised [0.3%], needed a consultation [3.6%], or had to change IBD therapy [13.4%] after anti-SARS-CoV-2 vaccination.

Conclusions: Although IBD patients raised concerns about the safety and efficacy of anti-SARS-CoV-2 vaccines, the implementation of vaccination in those responding to our survey was high and the adverse events were comparable to the general population, with minimal impact on their IBD.

Key Words: Inflammatory bowel disease; COVID-19; SARS-CoV-2; vaccination

Received: October 28, 2021. **Revised:** December 6, 2021. **Accepted:** January 13, 2022

1. Introduction

The severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] is a novel RNA coronavirus that is known to cause acute respiratory syndrome, pneumonia, and multi-organ failure.[1] This ensuing public health crisis has triggered the need for a massive global vaccination campaign, with effective vaccination against SARS-CoV-2 entailing not only protection against the morbidity and mortality caused by the disease, but also a reversal of its associated socioeconomic burden.

The promising clinical trials and subsequent roll-out of the BNT162b2 [Pfizer/BioNTech], ChAdOx1 nCoV-19 [Oxford/AstraZeneca], mRNA-1273 [Moderna], and JNJ-78436735 [Johnson and Johnson] vaccines have heralded a step towards the control of the pandemic..[2–4] However, some individuals with pre-existing conditions, such as inflammatory bowel disease [IBD] patients, were excluded from the original anti-SARS-CoV-2 vaccines developmental trials, and therefore uncertainties remain regarding vaccine safety and efficacy in this specific patient population. Nevertheless, international societies have published recommendations for the vaccination of these patients.[5,6]

Regarding efficacy, some studies have shown that IBD patients may have a suboptimal response to vaccination. Patients taking anti-tumour necrosis factor [anti-TNF] drugs are considered to have a decreased immune response to other vaccines, such as those administered for influenza and viral hepatitis.[7,8] Two recent studies have raised a concern that infliximab-treated patients may have lower seroprevalence of anti-SARS-CoV2 antibodies and lower seroconversion rates either after infection or after the first dose of the vaccine, when compared with vedolizumab-treated patients.[9,10]

Few studies have investigated potential causal relationship between anti-SARS-CoV-2 vaccine administration and disease flare-up in IBD patients, although some reassurance can be found in the extrapolation of data from the administration of other vaccines to IBD patients.[9] However, further studies are needed to clarify the concerns and willingness of IBD patients to get vaccinated and the impact of anti-SARS-CoV2 vaccination in IBD patients' management, as well as the impact of IBD medication on vaccination safety.

Since refusal to get vaccinated with anti-SARS-CoV-2 vaccines, due to fear of side effects or due to fear of getting vaccinated, can compromise the entire public health vaccination campaign against SARS-CoV-2, we aimed to report on: [i] the implementation of anti-SARS-CoV-2 vaccination among IBD patients; [ii] patients' concerns and fears before vaccination; and [iii] short-term adverse events [AEs] of the anti-SARS-CoV-2 vaccines in IBD patients.

2. Methods

2.1. Study design and population

We performed a multicentre European cross-sectional survey study, with the collaboration of the European Federation of Crohn's & Ulcerative Colitis Associations [EFCCA], IBD physicians, and National Patient Associations where IBD patients were invited to participate. No exclusion criteria were defined. An anonymous structured web-based self-completed questionnaire was developed using Research Electronic Data Capture [REDCap] and made available in nine different languages [English, Italian, German, Spanish, Portuguese, Danish, Czech, French, Greek]. The survey was distributed by IBD physicians in outpatient clinics, and online with the collaboration of different national and international patients' association groups, including EFCCA to known IBD patients. Completion of the entire questionnaire was not compulsory.

2.2. Data collection

Demographic data including patients' baseline characteristics, country of origin [stratified according to the geographical sub-regions of Europe, as defined by the EuroVoc[10]], smoking status, type of IBD (Crohn's disease [CD], ulcerative colitis [UC], or undefined IBD], disease activity [inactive vs active], current treatment, and previous IBD-related surgery were collected. Vaccination status against SARS-CoV-2 was assessed, including the number of doses and the type of vaccine received. Vaccination against the influenza virus was also evaluated so as to understand the overall willingness of patients to get vaccinated. Data regarding patients' fears and concerns related to vaccination were collected, alongside local and systemic adverse events [AE] after each dose of the vaccine and its impact on professional absenteeism. The impact of the vaccine on IBD, namely exacerbation of symptoms, need for consultation, hospitalization, therapy escalation, or need for treatment readjustment [including infusion re-scheduling] was also evaluated.

2.3. Statistical analysis

Descriptive analysis for baseline characteristics was performed. Continuous variables were described as mean and standard deviation or median and interquartile range, as appropriate. Categorical variables were expressed as frequencies with 95% confidence intervals [CI] and proportions. Univariable and multivariable logistic regression analysis was performed. A p-value <0.1 in univariate analysis was used to select variables to include in multivariable models. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using Stata package version 16.

3. Results

3.1. Patients baseline characteristics

Between June 2021 and July 2021, 3272 patients from 36 European countries answered the survey. Most patients had CD [58.1%], with a median patient age of 43 years [IQR 33-54]. There was a female predominance [60.4%], and most patients [69.4%] were from southern European countries. A description of patient participation by country of origin can be found in Supplementary Table 1, available as Supplementary data at *ECCO-JCC* online. From the cohort of patients who were recruited, 7.8% were on no medications and 19.1% were on 5-aminosalicylic acid [5-ASA] medications only. The remaining 2392 patients [73.1%] were on immunosuppressive treatment of whom 231 patients [7.1%] were receiving corticosteroids, in monotherapy or in combination with other medications [Table 1].

3.2. Patients' concerns regarding anti-SARS-CoV-2 vaccine

More than half of the patients [66.5%, 1721/2589] were not afraid, reluctant, or hesitant of being vaccinated and more than one-third [35.2%, 1151/3272] had no concerns regarding vaccination. Of those who reported concerns about SARS-

Table 1. Baseline characteristics.

Age [years; IQR]	**43 [33-54]**
Gender [%, *N*]	
Female	60.4% [1969/3258]
Male	39.4% [1283/3258]
Other	0.2% [6/3258]
Country	
Southern Europe	69.3% [2103/3031]
Northern Europe	3.7% [111/3031]
Western Europe	11.1% [335/3031]
Central and Eastern Europe	15.9% [482/3031]
Smoking [%, *N*]	18.4% [597/3251]
Disease type [%, *N*]	
Crohn's disease	58.0 [1887/3250]
Ulcerative colitis	40.4% [1312/3250]
Unclassified IBD	1.6% [51/3250]
No medical treatment or did not provide information on medical treatment [%, *N*]	7.8% [371/3272]
5-ASA monotherapy	19.1% [625/3272]
Corticosteroids use	7.1% [231/3272]
Immunomodulators	
Methotrexate	2.5% [82/3272]
Azathioprine/6-Mercaptopurine	20.7% [676/3272]
Calcineurin inhibitors	0.2% [6/3272]
Biologics	
Anti-TNF	31.6% [1034/3272]
Vedolizumab	7.5% [245/3272]
Ustekinumab	7.5% [246/3272]
Immunomodulators alone without biologics	13.7% [449/3272]
Biologics without immunomodulators	36.8% [1205/3272]
Combined immunomodulators and biologics	9.5% [311/3272]
Tofacitinib use	0.5% [18/3272]
Other therapy non specified on the survey	4.8% [158/3272]
Disease activity [%, *N*]	
Active	58.9% [1927/3272]
Clinical remission	41.1% [1345/3272]
Previous IBD surgery [%, *N*]	31.4% [1023/3257]
Vaccine received [%, *N*]	
BNT162b2 [Pfizer/BioNTech]	55.9% [1829/3272]
mRNA-1273 [Moderna]	10.5% [343/3272]
ChAdOx1 nCoV-19 [Oxford/AstraZeneca]	10.4% [339/3272]
JNJ-78436735 [Johnson and Johnson]	1.5% [51/3272]
Sputnik V	0.2% [6/3272]
Other	0.6% [20/3272]
Do not know or did not answer	20.9% [684/3272]

IBD, inflammatory bowel disease; TNF, tumour necrosis factor; ASA, aminosalicylates; IQR, interquartile range.

COV2 vaccination, the most common were the possibility of having worse side effects because of their primary disease [24.6%], having a flare of IBD after vaccination [21.1%], and reduced efficacy of the vaccine due to IBD-associated immunosuppression [17.6%] [Figure 1]. The patients' most common sources of information were the attending gastroenterologist [40.5%], social media [26%], and the personal general practitioner [18.2%] [Figure 2]. Of those who got vaccinated, 97.1% would recommend vaccination to other IBD patients.

Hesitancy and fear regarding vaccination seem to be associated with being female, aged over 60 years old, living in a central European country, and being treated with corticosteroids, in a univariate analysis [Table 2]. When adjusting these variables into a multivariable logistic regression model, all predictors remained significant except treatment with corticosteroids [Table 3].

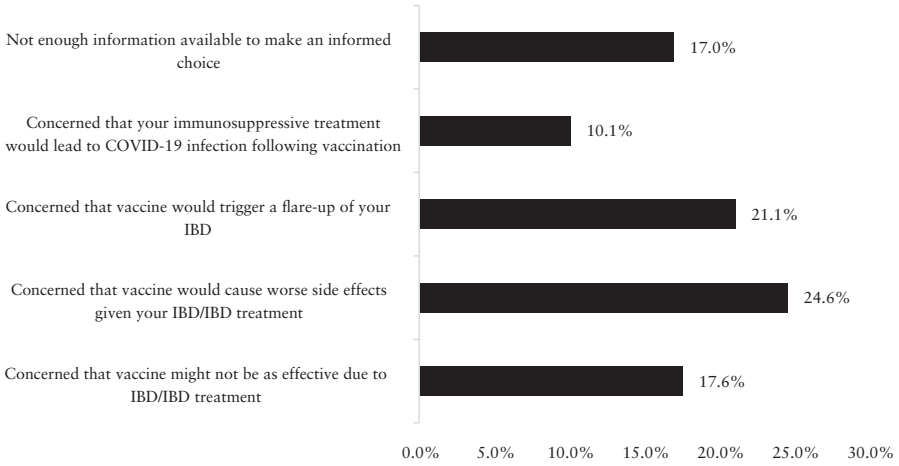

Figure 1. Patients' major concerns regarding anti-SARS-CoV-2 vaccination.

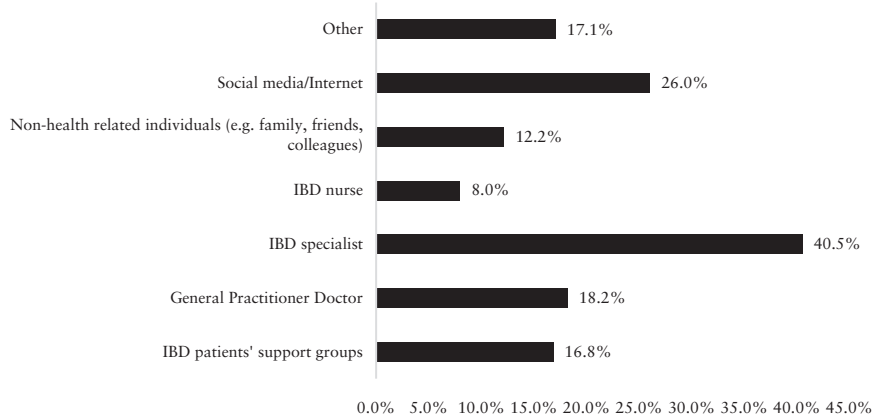

Figure 2. Most common sources of information regarding vaccination.

3.3. Vaccination status

At least one dose of any vaccine against SARS-CoV-2 was reported from 79.6% of the patients [2594/3261] and 71.7% [1861/2594] of them had completed the vaccination process with either a dual- or a single-dosing vaccine. Eleven patients did not provide any information on vaccination status. Of those patients who did not get vaccinated, 52.9% [347/656] said that anti-SARS-CoV-2 vaccination was not offered to them. The vaccine most frequently received was BNT162b2 [Pfizer/BioNTech] [Table 1]. More than half of the patients [53.3%, 1727/3241] had also received the influenza virus vaccine in 2020.

The prevalence of vaccination stratified by baseline characteristics, disease activity, and medications used is shown in Table 4. Older patients were almost three times more likely to be vaccinated (odds ratio [OR] 2.98, 95% CI 2.20-4.03, $p < 0.001$) as opposed to younger patients. An increased implementation of vaccination was observed in patients from western Europe [89,0%] compared with those from central and eastern Europe [71.9%]. There was no association between the country of origin and the chance of being vaccinated [$p = 0.08$].

Furthermore, there was no significant difference in the vaccination rate between patients with active disease and patients in clinical remission [80.2% vs 78.6%, $p = 0.26$]. Patients taking 5-ASA medications alone, one immunomodulator, corticosteroids, or tofacitinib had lower rates of vaccination when compared with those who were not taking these medications [Table 2].

Table 2. Univariate logistic regression of the factors predicting fear of being vaccinated.

Variable	OR [95% CI]	*p*-value
Female	1.96 [1.64-2.33]	$p < 0.001$
Age ≥ 60 years	0.69 [0.55-0.85]	$p < 0.001$
Living in a Central European country	1.52 [1.20-1.91]	$p < 0.001$
Active disease	1.15 [0.97-1.36]	0.11
Biologic alone	0.95 [0.80-1.12]	0.54
Immunomodulator alone	0.97 [0.76-1.24]	0.81
Biologic combined with immunomodulator	1.10 [0.84-1.45]	0.49
Corticosteroids use	1.41 [1.03-1.94]	0.03

OR, odds ratio; CI, confidence interval.

Table 3. Multivariate logistic regression of the factors predicting fear of being vaccinated.

Variable	OR [95% CI]	*p*-value
Female	1.94 [1.62-2.33]	$p < 0.001$
Age ≥ 60 years	0.76 [0.60-0.96]	$p = 0.02$
Living in a Central European country	1.34 [1.06-1.71]	$p = 0.02$
Corticosteroids use	1.35 [0.97-1.87]	$p = 0.08$

OR, odds ratio; CI, confidence interval.

Table 4. Vaccination rate stratified by baseline characteristics.

Variable	Vaccination rate [%, N]	*p*-value
Age		<0.001
<60 years	77.2% [2090/2707]	
≥60 years	91.0% [504/554]	
Gender		0.38
Female	78.9% [1550/1965]	
Male	80.6% [1028/1276]	
Other	66.7% [4/6]	
Country		0.08
Southern Europe	79.8% [1675/2100]	
Northern Europe	84.7% [94/111]	
Western Europe	89,0% [298/335]	
Central Europe	71.9% [346/481]	
Smoking		0.32
Yes	78.1% [466/597]	
No	79.9% [2118/2652]	
Disease type		0.46
Crohn's disease	79.5% [1497/1884]	
Ulcerative colitis	79.8% [1045/1310]	
Unclassified IBD	72.6% [37/51]	
Disease activity		0.26
Active	80.2% [1537/1916]	
Clinical remission	78.6% [1057/1345]	
Previous IBD surgery		0.18
Yes	81.0% [829/1023]	
No	79.0% [1763/2232]	
Immunosuppressive IBD treatment		
5-ASA alone		0.43
Yes	78.4% [490/625]	
No	79.8% [2104/2636]	
Biologics alone		<0.001
Yes	83.0% [999/1203]	
No	77.5% [1595/2058]	
Immunomodulators alone		0.3
Yes	77.7% [349/449]	
No	79.8% [2245/2812]	
Combined therapy with biologics and immunomodulators		0.72
Yes	80.3% [249/310]	
No	79.5% [2345/2951]	
Corticosteroids		0.13
Yes	75.7% [174/230]	
No	79.8% [2420/3031]	
Tofacitinib		0.85
Yes	77.8% [14/18]	
No	79.6% [2580/3243]	

IBD, inflammatory bowel disease; ASA, aminosalicylates

3.4. Short-term adverse events of anti-SARS-CoV-2 vaccine and its impact on IBD management

After the first dose of the vaccine, 72.4% [1879/2594] of the patients self-reported local symptoms at the injection site and 51.4% [1334/2594] systemic symptoms. Following the second dose of the vaccine where necessary, both local and systemic AE were less prevalent [46.1%, 1195/2594 and 41.9%, 1087/2594, respectively]. Younger patients [aged below 60 years old] reported more AE than older patients, although this difference was only statistically significant for local symptoms after the first dose and systemic symptoms after the second dose [Table 5].

Table 5. Adverse events from anti-SARS-CoV-2 vaccine stratified by age.

Variable	Age < 60 years	Age ≥ 60 years	*p*-value
Local AE after 1st dose	59.0% [1603/2718]	49.8% [276/554]	<0.001
Systemic AE after 1st dose	41.4% [1124/2718]	37.9% [210/554]	0.13
Local AE after 2nd dose	37.2% [1010/2718]	33.4% [185/554]	0.09
Systemic AE after 2nd dose	34.3% [931/2718]	28.2% [156/554]	0.01

AE, adverse events.

Table 6. Local and systemic adverse events of anti-SARS-CoV-2 vaccine [*N* = 2594].

Local adverse events	1st dose of the vaccine	2nd dose of the vaccine
Pain	65.5% [1698]	40.9% [1060]
Erythema	6.5% [169]	5.6% [144]
Warmth	8.7% [225]	5.4% [139]
Swelling	10.0% [258]	6.6% [172]
Other	5.6% [144]	2.9% [74]
Systemic adverse events	**1st dose of the vaccine**	**2nd dose of the vaccine**
Fever [> 37.5°C]	9.3% [242]	12.1% [315]
Tiredness	36.5% [947]	31.6% [820]
Shivering	6.6% [172]	7.0% [181]
Muscle pain	18.2% [473]	17.3% [448]
Joint pain	11.1% [289]	12.8% [332]
Headache	20.3% [526]	17.7% [459]
Irritability	3.1% [79]	2.5% [64]
Nausea	5.5% [143]	5.5% [143]
Swollen glands	2.2% [57]	2.1% [55]
Thrombosis	0.08% [2]	0.12% [3]
Other	5.3% [138]	4.1% [105]

The most frequent AE at the injection site was pain [65.5% and 40.9% after the first and second dose, respectively] and the most frequent systemic symptoms were tiredness [36.5% and 31.6%, respectively], headache [20.3% and 17.7%, respectively], and muscle pain [18.2% and 17.3%, respectively] [Table 6 and Table 7]. A total of five patients [0.2%] self-reported an episode of thrombosis after vaccination, two of them following the first dose [both received the Oxford/AstraZeneca vaccine] and the other three following the second dose [one vaccinated with the Pfizer-BioNTech vaccine and the other two with the Moderna vaccine]. No further details about the type or severity of these self-reported thrombotic events were collected in the questionnaire. On logistic regression analysis, being on immunosuppressive treatment [either corticosteroids, biologic alone, immunomodulator alone, combination therapy, or small

Table 7. Comparison of anti-SARS-CoV-2 vaccine adverse events between IBD patients in the study cohort and previous studies from the general population.

	Study cohort		BNT162b2 [Pfizer][3]		mRNA-1273 [Moderna][2]		ChAdOx1 nCoV-19 [Oxford/AstraZeneca][16]	
Adverse effects	1st dose [%]	2nd dose [%]	1st dose 18-55years/ >55 years [%]	2nd dose 18-55years/ >55 years [%]	1st dose 18-64 years/ ≥ 65 years [%]	2nd dose 18-64 years/ ≥ 65 years [%]	1st dose 18-55 years/ 56-69 years [%]	2nd dose 18-55 years/ 56-69 years [%]
Pain	65.5	40.9	83.1/71.1	77.8/66.1	86.9/74	89.9/83.2	61.2/43.3	49/34.5
Erythema	6.5	5.6	4.5/4.7	5.9/7.2	3/2.3	8.9/7.5	0/0	2/0
Warmth	8.7	5.4	N/A	N/A	N/A	N/A	14.3/6.7	12.2/13.8
Swelling	10.0	6.6	5.8/6.5	6.3/7.5	6.7/4.4	12.6/10.8	0/0	0/0
Fever	9.3	12.1	3.7/1.4	15.8/10.9	0.9/0.3	17.4/10	24.5/0	0/0
Tiredness	36.5	31.6	47.4/34.4	59.4/50.1	38.5/38.5	67.6/58.3	32.7/16.7	6.1/17.2
Shivering	6.6	7.0	14/6.3	35.1/22.7	9.2/5.4	48.6/30.9	34.7/10	14.3/10.3
Muscle pain	18.2	17.3	21.3/13.9	37.3/28.7	23.7/19.8	61.5/47.1	53.1/36.7	34.7/24.1
Joint pain	11.1	12.8	11/8.6	21.9/18.9	16.6/16.4	45.5/35	32.7/16.7	6.1/17.2
Headache	20.3	17.7	41.9/25.2	51.7/39	35.4/33.3	62.8/46.2	65.3/50	30.6/34.5
Nausea	5.5	5.5	N/A	N/A	9.3/5.2[a]	21.4/11.8[a]	26.5/13.3	8.2/20.7

IBD, inflammatory bowel disease; N/A, not available.
[a]Includes vomiting.

molecules] seemed to be a predictor of the development of adverse effects of the vaccine [local AE: OR 1.39, 95% CI 1.20-1.61, $p < 0.001$ and systemic AE: OR 1.24, 95% CI 1.07-1.43, $p = 0.003$]. However, when analysing each of these therapies individually, only the use of biologics in monotherapy remained a predictor [local AE: OR 1.25, 95% CI 1.08-1.45, $p = 0.03$ and systemic AE: OR 1.28, 95% CI 1.11-1.48, $p = 0.001$]. Further analysis of different type of biologics demonstrated a significant association for vedolizumab [local AE: OR 1.81, 95% CI 1.35-2.42, $p < 0.001$ and systemic AE: OR 1.58, 95% CI 1.21-2.06, $p = 0.001$] and ustekinumab [local AE: OR 1.38, 95% CI 1.05-1.83, $p = 0.02$ and systemic AE: OR 1.56, 95% CI 1.19-2.04, $p = 0.001$] but not with anti-tumour necrosis factor [TNF] [local AE OR 1.00, 95% CI 0.86-1.16, $p = 0.99$ and systemic AE OR 1.03, 95% CI 0.89--1.19, $p = 0.73$].

Almost one-fifth [19.2%, 499/2594] of the patients had to miss work at least once due to vaccination-related AE.

3.5. Impact of vaccination on IBD management

A total of 94 patients [3.6%] had a consultation with their IBD physician following the first dose of the vaccine. In 73.4% of the cases, these consultations were requested by the patients in view of new onset of symptoms or concerns regarding interaction between IBD medication and the vaccine. The rest [26.6%] were previously planned and scheduled appointments. Following the second dose, the number of consultations was lower [2.95%, 53/1799], but more than a half were due to relapse of IBD [62.3%, 33/53]. The most frequent symptoms were increased stool frequency [12.6%, 328/2594], feeling unwell [11.3%, 294/2594], and abdominal pain [10.0%, 260/2594]. In more than half of the patients [67.5%, 872/1291] symptoms subsided on their own without needing any change in medication. Eight patients were hospitalized, three of them [37.5%] due to IBD flare needing medical therapy. These 3
three patients had already moderately active disease at baseline and there seemed to be an association between the severity of disease activity and hospitalization due to IBD flare [OR 4.23, 95% CI 1.09-16.41, $p = 0.04$].

Concerning medication, in most of the patients [86.6%, 2247/2594] the routine treatment did not require any modifications. However, 8.6% [223/2594] had to re-schedule biologic infusion due to COVID-19 vaccination and 1.3% [33/2594] had to temporarily stop oral treatment. After anti-SARS-CoV-2 vaccination, 5.7% [130/2302] of the patients reported escalation of IBD therapy. Of those, the most frequent change was the introduction of corticosteroids [30.8%, 40/130].

4. Discussion

The significant public health, social, and economic impacts caused by the COVID-19 pandemic have led to the rapid development of several vaccines against SARS-CoV-2 that are deemed to help control the burden caused by the disease. However, there have been some concerns regarding the use of anti-SARS-CoV-2 vaccines in IBD patients, related not only to their efficacy as highlighted by the CLARITY group, but also to their safety.[11,12] Despite these fears, two recent studies have demonstrated that the majority of IBD patients were willing to get vaccinated, with vaccination intent being as high as 81%.[13,14] Furthermore, current guidance suggests that patients on immunosuppressants who received a two-dose mRNA vaccine series should receive a third dose [if possible, of the same vaccine formulation] as part of their primary vaccine series. This highlights the important role of adequate vaccination in this cohort of patients.[15]

In our study, we confirmed the achievement of this vaccination intent, with almost 80% of our study population having received at least one dose of the vaccine. The adherence to the anti-SARS-CoV-2 vaccine was even higher than the adherence to the influenza vaccine in 2020 [53.3%]. This may be explained by patients' awareness of the severity of COVID-19 and the significant burden already caused by this pandemic, with the vaccine being considered a global solution to control the disease. Of those patients who did

not get vaccinated, more than half [52.9%] said that SARS-CoV-2 vaccination was not offered to them and therefore does not directly reflect an unwillingness to be vaccinated. Rules for access to vaccination were different across countries, and in most areas, vaccination was prioritised for older people and those working in medical facilities, bearing serious comorbidities, or receiving immunosuppressive therapies.

In a multivariate logistic regression model, female gender, older age, and being from a central European country were independent predictors of fear of being vaccinated. Older age is also consistent with the fact that at the time of the survey most countries were prioritising the older population. Despite this, global vaccination rates across all these groups were above 70%, and 97% of the patients who received the vaccine would recommend vaccination to other IBD patients. A campaign led by the different stakeholders may be required to increase the uptake of the vaccine in the patient cohorts who are at higher risk of severe disease and ensure the uptake of the third dose of the vaccine in those who received the two-dose mRNA vaccine series.

In our population of IBD patients, local and systemic AE were very similar, though slightly lower than those reported in the general population, with pain at the injection site being the most common local side effect and fatigue the most common systemic effect[2,3,16] [Table 7]. Similarly to previous studies on the AE of anti-SARS-CoV-2 vaccines in the general population, we also demonstrated that younger patients experienced more AE with the vaccine when compared with older patients, although this difference was only statistically significant for local AE after the first dose of the vaccine and for systemic AE after the second dose of the vaccine.[2,3,16] This may be explained by the higher immunological response that is probably mounted in younger patients, and that may lead to an increased frequency of AE. However, this does not seem to have compromised vaccination adherence. There was a total of five cases of thrombosis, which occurred with three different types of vaccines. As a limitation of our study, the clinical details of the thrombosis episodes and their consequences were not characterised. Interestingly, all five patients were considered to have active disease, three of them with mild activity and the other two with moderate activity. Furthermore, we were unable to ascertain if these cases fulfilled the diagnostic criteria of vaccine-induced immune thrombotic thrombocytopenia [VITT].[17]

Though on logistic regression analysis, immunosuppressive treatment seemed to be a predictor of the development of AE of the vaccine, individual assessment of these therapies demonstrated that biologic monotherapy was a predictor for the development of AE. Further subanalysis showed that this remained significant only for vedolizumab and ustekinumab. The presence of bias due to small sample size of patients on these medications cannot be excluded.

Regarding the impact of the anti-SARS-CoV-2 vaccine on IBD management, only a minority [3.6%] of the patients needed to consult their gastroenterologist after vaccination, and in less than a half of those this was due to an IBD flare. Only three patients were hospitalized due to an IBD relapse after vaccination, and there was a significant association between hospitalization and disease severity at the baseline [OR 4.23, 95% CI 1.09-16.41, $p = 0.04$]. Data from vaccine side effects in the general population demonstrate that diarrhoea occurs in approximately 10% of the people who receive the vaccine and therefore may be confused with exacerbation of the disease.[2,3,16]

Most of the patients did not have to change IBD medication after vaccination and only a minority [5.7%] had to escalate therapy. Nevertheless, almost 9% of the patients re-scheduled their infusion. The reason for this was not clarified. A possible explanation could be that this was done as a preventive measure to be able to determine whether any symptoms were due to vaccination or were secondary to infusion reactions.

Our study has strengths and limitations. This is the largest study presenting data on anti-SARS-CoV-2 vaccination in IBD patients from different geographical locations, treated with different drug regimens. Our results are reassuring, with local and systemic AEs being very similar to those reported in the general population. Moreover, through this study we were able to evaluate patients' concerns and vaccination adherence. Our major limitation is the fact that, being designed to be answered by patients, disease related features and disease activity were self-reported, which may have introduced some reporting bias.

Despite some concerns shared by patients and physicians on the safety and efficacy of anti-SARS-CoV-2 vaccines in IBD patients, adherence to vaccination was still high, with a rate of AEs similar to that of the general population and with a low impact on IBD control and management. This data should reassure patients who are still unvaccinated and encourage their caring physicians to develop a stronger shared decision making towards vaccination against SARS-CoV2.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

Funding

This work was funded by the Portuguese Society of Gastroenterology, through support of its online platform for multicentric studies, CEREGA.

Conflict of Interest

MC: has served as a speaker, or has received research or education funding from MSD, Abbvie, Hospira, Pfizer, Takeda, Janssen, Ferring, Shire Pharmaceuticals, Dr Falk Pharma, Tillotts Pharma. JPG has served as speaker, consultant, and advisory member for or has received research funding from MSD, Abbvie, Pfizer, Kern Pharma, Biogen, Mylan, Takeda, Janssen, Roche, Sandoz, Celgene, Gilead/Galapagos, Ferring, Faes Farma, Shire Pharmaceuticals, Dr Falk Pharma, Tillotts Pharma, Chiesi, Casen Fleet, Gebro Pharma, Otsuka Pharmaceutical, Norgine, and Vifor Pharma. MA: as per COI submitted to *JCC* by ECCO. GF: as per COI submitted to *JCC* by ECCO. GM: speaker fees for Takeda, MSD, Jannsen, Abbvie. GJM: received fees as adviser/lecturer for AbbVie, Celgene, Celtrion, Ferrirng, Genesis, Hospira, Janssen, MSD, Mylan, Pfizer, Takeda, Vianex, Falk Pharma; consultation fees from AbbVie, MSD, and Takeda; research support from AbbVie, Genesis, Vianex, MSD. IK: advisory board member for Abbvie, Astelas, Genesis, Janssen, MSD, Pharmacosmos, Pfizer, Vianex, Shire, and Takeda; speaker for AbbVie, Astelas, Genesis, Janssen, MSD, Takeda, Vianex, and Mylan; re-

search support from Abbvie, Vianex, and Ferring. KK: COI submitted to *JCC* by ECCO. KHK: COI submitted to *JCC* by ECCO. DD: lecture fees from Janssen, Takeda, Pfizer. JB reports personal fees from AbbVie, personal fees from Janssen-Cilag, personal fees from Celgene, grants and personal fees from MSD, personal fees from Pfizer, grants and personal fees from Takeda, grants and personal fees from Tillots Pharma, personal fees from Samsung Bioepis, grants from Bristol Myers Squibb, grants from Novo Nordisk, personal fees from Pharmacosmos, personal fees from Ferring, outside the submitted work. CM: as per COI submitted to *JCC* by ECCO. NA: as per COI submitted to *JCC* by ECCO. AB: consulting fees for Abbvie, Amgen, Arena, Biogen, CTMA, Galapagos, Janssen, MSD, Nexbiome, Pfizer, Roche, Takeda, and Tillots; lecture fees from Abbvie, Amgen, Biogen, Janssen, Mayoly-Spindler, MSD, Norgine Pfizer, Roche, Takeda, and Tillots. LA: related to EFCCA's activities/projects as well as my participation in symposia, conference, advisory groups for Abbvie, Amgen, Atlantic Health Care, Celgene, Celltrion, Ferring Pharmaceutical, Janssen, Merck-MSD, Mundipharma, Otsuka, Pfizer, Shields, Shire, Tigenix, Takeda, Galapagos,Arena, Norgine, Vifor Pharma. JT: as per COI submitted to *JCC* by ECCO.

Acknowledgements

We would like to thank EFFCA and all National Patient Associations that distributed the survey online.

Author Contributions

PE: study design, formulation of questionnaire, writing of manuscript. JR: statistical analysis; writing of manuscript. BA: translating questionnaire to native language, promotion of study and local data collection, review of manuscript. MA: reviewing and formulation of questionnaire, translating questionnaire to native language, promotion of study and local data collection, review of manuscript. JPG: reviewing and formulation of questionnaire, translating questionnaire to native language, promotion of study and local data collection, review of manuscript. MA: translating questionnaire to native language, promotion of study and local data collection, review of manuscript. GF: review and formulation of questionnaire, promotion of study and local data collection, review of manuscript. BB: translating questionnaire to native language, promotion of study and local data collection, review of manuscript. FZ: promotion of study and local data collection, review of manuscript. AP: promotion of study and local data collection, review of manuscript. DC: initial formulation of questionnaire, promotion of study and local data collection. GM: promotion of study and local data collection, review of manuscript. GJM: translating questionnaire to native language, promotion of study and local data collection, review of manuscript. IK: reviewing questionnaire to native language, promotion of study and local data collection, review of manuscript. KK: reviewing questionnaire to native language, promotion of study and local data collection, review of manuscript. KHK: reviewing questionnaire to native language, promotion of study and local data collection, review of manuscript. DD: translating questionnaire to native language, promotion of study and local data collection, review of manuscript. JB: translating questionnaire to native language, promotion of study and local data collection, review of manuscript. GRM: translating questionnaire to native language, promotion of study and local data collection, review of manuscript. CM: translating questionnaire to native language, promotion of study and local data collection, review of manuscript. NA: reviewing and formulation of questionnaire, promotion of study and local data collection, review of manuscript. EO: translating questionnaire to native language, promotion of study and local data collection, review of manuscript. VM: translating questionnaire to native language, promotion of study and local data collection, review of manuscript. AB: translating questionnaire to native language, promotion of study and local data collection, review of manuscript. LA: reviewing and formulation of the questionnaire, promotion of survey, through EFCCA. SL: reviewing and formulation of the questionnaire, promotion of survey, through EFCCA. JT: study design, formulation of questionnaire, writing of manuscript.

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