Digestive and Liver Disease xxx (xxxx) xxx

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

The natural history of COVID-19 in vaccinated inflammatory bowel disease patients ☆

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ARTICLE INFO

Article history:
Received 26 September 2022
Accepted 15 December 2022
Available online xxx

Keywords:
COVID-19
Crohn's disease
Inflammatory bowel disease
Ulcerative colitis

ABSTRACT

Aim: Assess the characteristics of break through COVID-19 in Inflammatory Bowel Disease (IBD) patients, despite complete vaccination.
Methods: Patients who reported a COVID-19 at least 3 weeks after complete vaccination were asked to answer an on-line anonymous questionnaire which included patient and disease characteristics, vaccination history, and the evolution of COVID-19.
Results: Among 3240 IBD patients who reported complete vaccination between 1st May 2021 and 30thJune 2022, 402 (12.4%) were infected by SARS Cov-2 [223 male, 216 Crohn's disease (CD), 186 Ulcerative Colitis (UC), mean (SD) age 42.3 (14.9) years, mean (SD) IBD duration 10.1 (9.7) years]. Three hundred and sixty-nine patients (91.8%) were infected once and 33 (8.2%) twice. The mean (SD) time between last vaccination and infection was 4.1 (1.6) months. Overall, 351 (87.3%) patients reported mild constitutional and/or respiratory symptoms, 34 (8.4%) were asymptomatic and only 17 patients (4.2%) required hospitalization. Of hospitalized patients, 2 UC patients died of COVID-19 pneumonia. The remaining hospitalized patients did not need high flow oxygen supply or ICU admission.
Conclusions: A minority of completely vaccinated IBD patients developed COVID-19 which evolved with mild symptoms and a favorable outcome. These results reinforce the importance of vaccination especially in vulnerable populations.

1. Introduction

In December 2019, a novel coronavirus designated SARS-CoV-2, emerged from Wuhan, central Hubei Province, China [1]. The virus causes the disease COVID-19, which was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. COVID-19 manifests as a severe acute respiratory illness that can be complicated by acute respiratory distress syndrome (ARDS), multiorgan failure and even death [2].

Vaccines against COVID-19 became available in December 2020 and priority was given to vulnerable populations, including patients on immunosuppressive treatment, considering their

☆ No source of support and no grants have been received for this study.
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https://doi.org/10.1016/j.dld.2022.12.012
1590-8658/

Table 1
Characteristics and current treatment of the IBD patients included in the study.

Gender (male/female, n)	223/179
Type of disease (UC/CD, n)	186/216
Age, mean (SD), years	42.3 (14.9)
IBD duration, mean (SD), years	10.1 (9.7)
Smoking (n)	105
Obesity (BMI> 30 kg/m2, n)	49
Treatment (n)	
Biologic monotherapy	
i) Anti-TNF	148
ii) Vedolizumab	48
iii) Ustekinumab	32
iv) Tofacitinib	7
v) Rizakinzumab	1
Combination of biologics with conventional immunomodulators or corticosteroids	25
Immunomodulators monotherapy	46
Corticosteroids monotherapy	14
5-ASA only	78
No treatment	3

UC=Ulcerative colitis; CD=Crohn's disaese

susceptibility to infectious complications [3]. Inflammatory bowel diseases (IBD), namely ulcerative colitis (UC) and Crohn's disease (CD) are chronic immune-mediated diseases, with multifactorial pathogenesis. Corticosteroids, conventional Immunomodulators (azathioprine, methotrexate), biologic agents (anti-TNFα, anti-$\alpha 4\beta 7$ integrin, anti-IL12/23), and newer synthetic disease modifiers are the mainstay of treatment for patients with moderate and/or severe disease [4]. Initial reports have raised concerns that at least some these medications might impair the protective effect of the available SARS-CoV-2 vaccines. Indeed, the CLARITY-IBD study has shown that antibody responses following a single dose of either the BNT162b2 (Pfizer–BioNTech) or ChAdOx1 nCoV-19 (Oxford–AstraZeneca) vaccines are impaired in patients treated with anti-TNFα therapies compared with those treated with vedolizumab [5]; however, the response of these patient groups remains unknown compared to the non-immunosuppressed population, while data on the response rates of other IBD therapies are very limited.

Given the above uncertainties, IBD patients were advised to receive an extra fourth dose of vaccination, beyond the 3-dose schedule that was set for the general population. However, data on the effectiveness of this strategy are lacking. We have therefore conducted a prospective study to assess the proportion of IBD patients who despite complete vaccination developed COVID-19, as well as the course of the infection.

2. Methods

This study was an initiative of the Hellenic Group for the study of IBD (EOMIFNE) which involved 12 referral IBD centers. Patients attending these centers who reported a COVID-19 at least 3 weeks after completion of vaccination were asked to fulfill an on-line anonymous questionnaire which included patient and IBD characteristics, a detailed vaccination history, and the outcome of COVID-19, especially the need for hospitalization, oxygen supply, and admission to ICU. Information was sought by family members in patients with grave outcome. Co-morbidities, such as cardiovascular (coronary heart disease, hypertension, cerebrovascular disease) and respiratory (asthma, emphysema, chronic bronchitis) diseases, diabetes mellitus, chronic renal and liver disease and history of malignancies were also recorded.

IBD treatment was classified into five categories: biologic monotherapy, combination of a biologic with conventional immunomodulator or corticosteroids, immunomodulator monotherapy, corticosteroid monotherapy and 5-ASA only (non immunosuppressive group). Biologics included anti-TNFα, anti-$\alpha 4\beta 7$integrin, anti-IL-12/23 and JAK inhibitors, whereas immunomodulators included azathioprine and methotrexate.

IBD patients in Greece were offered either the Vaxzevria® (AstraZeneca AB) or the Comirnaty® (BioNTech Manufacturing GmbH) vaccine. Complete vaccination was defined differently based on the time period of the occurrence of COVID-19: from May 1 to November 19, 2021 administration of two doses, November 20, 2021 till April 5, 2022 administration of three doses and April 6 until June 30, 2022 (recruitment completion) administration of an extra optional fourth dose as local authorities advised. Patients who reported a confirmed COVID-19 infection, defined as a positive PCR or rapid antigen test for SARS-CoV-2 obtained through a nasopharyngeal swab at least 3 weeks after vaccination completion were included in the study.

The study was approved by the ethical committees of all participating hospitals according to national legislation, and informed consent was obtained in all cases.

2.1. Statistical analysis

Data are expressed as percentages for qualitative data and as means ± standard deviation (SD) or medians [interquartile range, IQR] for quantitative data. Qualitative variables were compared using Chi² test or Fisher's exact test, and quantitative variables using Mann-Whitney test. A result was considered significant if the p value was less than 0.05. SPSS Statistics v23® software was used for all analyses.

3. Results

On estimate, 3240 patients reported full vaccination in the 12 centers during the study period. Among them, 402 (12.4%) reported COVID-19. Three hundred and sixty-nine patients (91.8%) were infected once and 33 (8.2%) twice. COVID-19 diagnosis was made by PCR amplification of nasal swabs in 339 (84.3%) cases, whereas 63 (15.7%) patients were diagnosed via a rapid antigen test. The mean (SD) time between last vaccination dose and infection was 4.1 (1.6) months. Among all verified cases, 105 (26.2%) reported exposure to a known COVID-19 case, whereas the remaining297 (73.8%) had no such recollection.

Information about patient characteristics and IBD treatment at the time of inclusion in the study is presented in Table 1. Most of the patients were receiving anti-TNFα either as monotherapy or in combination with immunomodulators or corticosteroids. IBD

Table 2
Characteristics of the IBD patients hospitalized for COVID-19 despite complete vaccination.

Patient	Gender	Age at COVID-19 (years)	Type of disease	Co-morbidities	Therapy	Active disease	Vaccination doses (n)	Hospitalization (days)	High flow oxygen or ICU admission	Outcome
1	M	36	UC	None	IFX	No	2	2	No	Recovered
2	F	29	UC	None	AZA	No	3	3	No	Recovered
3	M	55	CD	None	USTE	No	3	5	No	Recovered
4	M	62	UC	Thyroid disease	VEDO	No	2	4	No	Recovered
5	M	67	UC	Diabetes	IFX	No	3	21	Yes	Deceased
6	F	59	CD	None	ADA	No	2	12	No	Recovered
7	F	52	CD	None	ADA	No	2	9	No	Recovered
8	M	61	CD	CHD	VEDO	No	2	5	No	Recovered
9	M	47	UC	None	IFX	No	3	4	No	Recovered
10	M	73	UC	Hypertension	5-ASA	No	3	3	No	Recovered
11	M	45	CD	Thyroid disease	ADA	No	2	3	No	Recovered
12	F	39	CD	None	USTE	No	3	4	No	Recovered
13	F	24	CD	None	ADA	Yes	2	4	No	Recovered
14	F	80	UC	Prior cancer	5-ASA	No	2	16	Yes	Deceased
15	M	44	CD	Thyroid disease	AZA	No	3	7	No	Recovered
16	M	57	UC	Diabetes	IFX	No	3	3	No	Recovered
17	F	69	UC	Hypertension	5-ASA	No	2	5	No	Recovered

M=Male; F=Female; UC=Ulcerative Colitis; CD=Crohn's Disease; IFX=Infliximab; ADA=Adalimumab; VEDO=Vedolizumab; USTE=Ustekinumab; AZA=Azathioprine; CHD=Coronary Heart Disease

was in remission in 322 patients (80.1%). Among the 402 patients included in the study, 81 were not on an immunosuppressant therapy, while the remaining 321 were receiving immunosuppressants. Among the 81 patients that were not receiving immunosuppressants, 3 were diagnosed with COVID-19, while among the 324 on immunosuppressants, 14 patients were diagnosed with COVID-19 ($p = 0.79$). Among the 236 patients receiving biological treatment, there were 48 patients on vedolizumab, while the remaining 188 patients were receiving other biologics. From the patients on vedolizumab, 2 were diagnosed with COVID-19, whereas from those on other biologics, 10 were diagnosed with COVID-19 ($p = 0.74$).

Overall, 149 patients (37.1%) reported at least one co-morbidity: thyroid disease 62; hypertension 54; diabetes mellitus 12; coronary heart disease 11; cancer 4; psoriasis 2; spondyloarthropathy 2; dyslipidemia 1; and PSC 1 patient.

Thirty-four patients (8.4%) were asymptomatic, 351 (87.3%) reported mild constitutional and respiratory symptoms and 17 patients (4.2%) required hospitalization. The characteristics of the hospitalized patients are presented in Table 2. The rate of hospitalization did not differ between the period before and after January 2022, when SARS-CoV-2 omicron variant became prevalent in Greece [12 patients out of 291 (4.1%) vs 5 patients out of 111 (4.5%), p=NS]. The most common symptoms reported were fever ($n = 107$, 30.5%), fatigue ($n = 191$, 54.4%), headache ($n = 98$, 27.9%) and cough ($n = 172$, 49.0%). Interestingly, 75 patients (21.4%) reported gastrointestinal symptoms, the most common being diarrhea ($n = 67$, 19.1%) followed by abdominal pain ($n = 24$, 6.8%) and nausea with or without vomiting ($n = 10$, 2.8%). Of those hospitalized, 2 patients, both with UC, died because of COVID-19 pneumonia (a male aged 67, on infliximab, with diabetes mellitus, and a female aged 80, on 5-ASA, with a history of laryngeal cancer); the remaining 15 hospitalized patients did not need high flow oxygen supply or ICU admission, and none reported symptoms of long COVID-19 (Table 2).

IBD medications were temporarily halted in 105 patients (26.1%) during the infection. Patients on biologic monotherapy were less likely to stop their treatment as compared to patients receiving combination of biologics with immunomodulators or corticosteroids (OR = 0.0148, 95% CI, 0.0020–0.1121, $p<0.0001$).

4. Discussion

This study aimed to assess the characteristics of break-through COVID-19 in IBD patients after complete vaccination. Our results clearly show that a minority of completely vaccinated IBD patients developed COVID-19, which was relatively mild and uneventful, further emphasizing the importance of vaccination in this patient population.

Numerous groups and experts support the importance of adequate vaccination of IBD patients for the prevention of COVID-19, since the existing vaccines appear to be safe for this population and not associated with onset and/or exacerbations of IBD [6–8]. Initial concerns that immunosuppressive treatments might abrogate the development of anti–SARS-COV2 antibodies and impair the protective effect of the available SARS-CoV-2 vaccines in IBD patients, were not further supported by published data. Indeed, although infliximab was shown to be associated with an attenuated immunogenicity to a single dose of the BNT162b2 or the ChAdOx1 nCoV-19 SARS-CoV-2 vaccines in patients with IBD and immunomodulators further blunted immunogenicity rates to both vaccines, vaccination after infection or a second dose of vaccine led to seroconversion in most patients [5]. In another study it was shown that IBD patients who were treated with infliximab or tofacitinib had lower anti-SARS-CoV-2 spike protein antibody concentrations after two doses of vaccine than did healthy controls [9]. Overall, 55% of patients on infliximab monotherapy and 48% on thiopurine and infliximab combination therapy had antibody concentrations greater than 2 geometric SD below the geometric mean of control participants within 92 days after two doses of a COVID-19 vaccine; 10% and 13%, respectively, did not mount antibody responses at concentrations of 15 U/mL or more, which correlate with viral neutralization in functional assays [5]. No significant reductions in antibody responses were observed in patients with IBD treated with thiopurines, ustekinumab, or vedolizumab relative to control participants [9]. Further to these reports many countries and among them Greece have embarked on three primary doses and booster vaccination programs, especially for IBD patients. Unfortunately, the outcome of such a strategy remains largely unknown. A recent meta-analysis reported that the pooled seroconversion rate after complete vaccination (31 studies, 9447 patients)

was 0.96 (95% confidence interval [CI], 0.94–0.97; I^2 =90%), concluding that this strategy is associated with seroconversion in most patients with IBD [10]. Since no solid data are available regarding antibody concentrations, we believe that the only possible way to detect the efficacy of vaccination is to examine clinical data and outcomes of IBD patients vaccinated against COVID-19.

Our results clearly show that a complete vaccination program provides adequate protection against COVID-19, since only 2 out of the 402 infected IBD patients (0.49%) had a fatal outcome. The overall favorable outcome has also been reported in previous studies not only in the Greek IBD population (1.3% mortality rate) [11], but also in a European cohort [12], as well as in the population registered in the SECURE-IBD database (2% mortality rate) [13]. The mortality rate from COVID-19 in the general population in Greece has been reported to be 3.1% [14], higher than that reported in the IBD population. It must be noted that these data do not distinguish whether patients have been vaccinated against COVID-19 or not. It is also of interest that 95.7% of the Greek patients who died because of COVID-19 had either a co-morbidity or/and were over 70 years of age [14]. Although in our study only 2 patients died and therefore our data cannot be generalized, those two patients exhibited a co-morbidity (diabetes and laryngeal cancer respectively) and one of them was over 70 years of age.

At the same time current guidelines and expert advice [15–17] as well as Greek Society for the study of IBD recommendations suggested that IBD patients should continue their therapy during COVID-19 [11]. Indeed, 73.9% of our study population continued their IBD medication despite COVID-19 and this did not lead to an adverse outcome. Several studies have clearly demonstrated the safety of biological therapy in patients with IBD infected with SARS-CoV-2. In line, Greek IBD patients on biological therapy had a significantly lower probability for adverse outcomes, namely hospital or ICU admission and death, while anti-TNFα treatment exerted a protective effect [11]. Of note, anti-TNFα therapy has been employed in the management of severe sepsis, with a meta-analysis demonstrating reduced overall mortality when used in severe sepsis before shock, and improved survival at 30 days in patients with shock or high baseline levels of IL-6 [18]. Another recent meta-analysis reported that patients on anti-TNFαtherapy had a lower risk of hospitalization (risk ratio [RR], 0.24; 95% CI, 0.16–0.35; $P < 0.01$; I2 = 0%) and ICU admission (RR, 0.10; 95% CI, 0.03–0.37; $P < 0.01$) but not death (RR, 0.16; 95% CI, 0.02–1.71; $P = 0.13$; I2 = 39%) compared with patients on corticosteroids and a lower risk of hospitalization (RR, 0.37; 95% CI, 0.25–0.54), ICU admission (RR, 0.20; 95% CI, 0.07–0.58), and death (0.21; 95% CI, 0.04–1.00) compared to those treated with mesalamine. Comparing patients on immunomodulators vs mesalamine or anti-TNFα therapy, there was no difference in these outcomes [19].

The risk of severe infections in general does not appear to be increased in patients treated with ustekinumab [20] and rates of hospitalization, severe COVID-19 and death were not impacted, according to the SECURE-IBD database [21]. On the other hand, there has been a theoretical concern of an increased risk of respiratory infections, and, hence, COVID-19, with vedolizumab use [22]. Reassuringly though, several studies have demonstrated that there is no increased risk of respiratory, systemic, or serious infections in patients on vedolizumab over placebo or other IBD related therapies [23–25]. Although hospitalization was more likely with vedolizumab than with anti-TNFα monotherapy, this was not the case for severe COVID-19 and overall vedolizumab appears to be safe in IBD patients with COVID-19 [25]. Data on the association of tofacitinib with COVID-19 are very limited; Tofacitinib dose of 10 mg as opposed to 5 mg twice daily, age >65 years, corticosteroids >7.5 mg/d and diabetes were independent factors associated with increased serious infection risk [26]. Therefore, patients on tofacitinib who contract COVID-19 should be maintained on the lower dose where possible and weaned off corticosteroids [27]. It should be noted though that according to a recent observational study, no single IBD medication (including tofacitinib) was associated with poor COVID-19 outcomes in multivariable analyses [28], data further supported by those of the IBD-SECURE registry [21].

This is the largest cohort to report data on the clinical outcome of COVID-19 in completely vaccinated IBD patients to the best of our knowledge. Among the strengths of the present study are its prospective design and the simultaneous inclusion of patients in several IBD referral centers. Among its limitations is the fact that data on COVID-19 were self-reported by patients which might introduce recall bias. However, data on hospitalization were reported by the attending physicians without any discrepancy. Also, we have to mention that the number of patients receiving conventional, non-immunosuppressant therapy is low. This can be attributed to the fact that all 12 hospitals that participated in this study are tertiary referral centers for IBD patients and therefore their cohorts are not completely representative of the general IBD population in Greece. Besides, and even though this might be a non-representative cohort study there is a lack of statistical significance on patients who were diagnosed with COVID −19 between those who were on immunosuppressants versus those who were on conventional therapy. This is also partly attributed to the considerable low number of patients with an undesirable outcome in a cohort that predominantly consists of immunocompromised patients. Thus, we feel that the inclusion of more immunocompetent patients would not significantly alter the results. Finally, a limitation of our study is the fact that a comparison control group is lacking, since our study was designed as an observational one. Such a group would be important in order to further demonstrate that vaccinated IBD patients are really protected from COVID-19. However, indirect comparisons can be made with studies reporting the re-infection rates in fully vaccinated subjects in the general population, where similar results are noted [29,30].

In conclusion, only a minority of completely vaccinated IBD patients developed COVID-19 which was relatively mild and uneventful. These results justify the strategy for the intensified vaccination schemes implemented in this vulnerable population.

Conflict of Interest

There are no conflicts of interest to declare regarding this study

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