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SARS-CoV-2 Igg seroprevalence in IBD patients treated with biologics: first *vs.* second pandemic wave in a prospective study

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Abstract. – OBJECTIVE: In a prospective study, SARS-CoV-2 IgG seroprevalence was assessed during the second pandemic wave (W2) in a cohort of Inflammatory Bowel Disease (IBD) patients using biologics. The secondary aim was to compare, in the same cohort, the frequency of seropositivity and of COVID-19 during the second *vs.* the first (W1) wave.

PATIENTS AND METHODS: From November 2020 to March 2021, SARS-CoV-2 IgG seropositivity and the prevalence of COVID-19 were assessed in a cohort of IBD patients using biologics already studied at W1. Inclusion criteria: age ≥ 18 years; diagnosis of IBD; follow-up; written consent. Exclusion criteria: SARS-CoV-2 vaccination. Risk factors for infection, compatible symptoms, history of infection or COVID-19, nasopharyngeal swab test were recorded. Data were expressed as median [range]. The χ^2 test, Student's *t*-test, logistic regression analysis was used.

RESULTS: IBD cohort at W1 and W2 included 85 patients: 45 CD (52.9%), 40 UC (47.1%). When comparing the same 85 patients at W2 *vs.* W1, a higher SARS-CoV-2 seroprevalence at W2 was at the limit of the statistical significance (9.4% *vs.* 2.3%; *p*=0.05). The prevalence of COVID-19 at W2 *vs.* W1 was 3.5% (3/85) *vs.* 0% (0/85) (*p*=0.08). Contacts with COVID-19 patients and symptoms compatible with COVID-19 were more frequent at W2 *vs.* W1 (18.8 % *vs.* 0%; *p*=0.0001; 34.1% *vs.* 15.3%; *p*=0.004). At W2, history of contacts and new onset diarrhea were more frequent in seropositive patients [4/8 (50%) *vs.* 12/77 (15.6%); *p*=0.01 and 4/8 (50%) *vs.* 2/77 (2.6%); *p*=0.0001]. At W2, the risk factors for seropositivity included cough, fever, new onset diarrhea, rhinitis, arthromyalgia, dysgeusia/anosmia at univariate (*p*<0.05), but not at multivariate analysis. History of contacts was the only risk factor for seropositivity at univariate (*p*=0.03), but not at multivariate analysis (*p*=0.1).

CONCLUSIONS: During W2, characterized by a high viral spread, IBD and biologics appeared not to increase the prevalence of SARS-CoV-2 infection or COVID-19 disease. New onset diarrhea mimicking IBD relapse may be observed in patients with SARS-CoV-2 infection.

Key Words:
SARS-CoV-2 IgG seroprevalence, IBD, Biologic therapy, Second pandemic wave, Prospective study.

Introduction

Crohn's disease (CD) and Ulcerative Colitis (UC) are chronic inflammatory conditions highly responsive to immunomodulatory treatments[1]. Since March 2020, pandemic related to SARS-CoV-2 infection represented a worldwide health problem[2]. Whether this viral infection may influence the course of Inflammatory Bowel Disease (IBD), and whether a pre-existing IBD may increase the risk of SARS-CoV-2 infection and COVID-19 has been extensively investigated[3-7]. Corticosteroids, conventional immunosuppressors (ISS) and biologics used for treating IBD may increase the risk of viral and bacterial infections[8]. Nevertheless, biologics currently appear to not worsen the outcome of SARS-CoV-2 infection and, particularly anti-Tumor Necrosis factor-α (anti-TNF-α), may rather reduce the cytokine storm characterizing severe COVID-19[9,10].

Several studies investigated the frequency of SARS-CoV-2 infection in IBD patients during the first pandemic wave, showing marked variations[3,11-13]. In a previous prospective study[14], we reported a low SARS-CoV-2 IgG seroprevalence in IBD patients enrolled in central Italy (Lazio) during the first wave. From May 2020 to July 2020, seropositivity was observed in 3 out of 218 (1.37%) IBD tested patients, all 3 included in the group of 115 patients treated with

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biologics. SARS-CoV-2 seroprevalence was comparable between the tested IBD population and the general non-IBD population from the same area, as also between IBD patients using or not biologics[14]. These findings added support to the hypothesis that biologics do not increase the risk of SARS-CoV-2 infection in IBD[15]. However, the relevance of our findings was limited by the relatively low proportion of patients with SARS-CoV-2 infection occurring at that time in the general population from the same area[16]. More recently, the second pandemic wave has been characterized by a worldwide increased prevalence of SARS-CoV-2 infection. Despite the huge amount of epidemiologic studies investigating the prevalence of SARS-CoV-2 infection in IBD, to our knowledge findings from prospective studies assessing this issue in the same cohort of IBD patients during first *vs.* second wave are lacking.

Based on these findings, in a prospective single center study, we aimed to evaluate the frequency of SARS-CoV-2 IgG seropositivity and COVID-19 in a cohort of IBD patients treated with biologics during the second wave. We also aimed to compare these outcomes with those from the same cohort of IBD patients assessed during the first wave.

Patients and Methods

Study Population

In a prospective single-center study, all IBD patients treated with biologics enrolled in our previous study[14] assessing the SARS-CoV-2 IgG seroprevalence (from May to July 2020), were asked to participate. For this purpose, from November 2020 to March 2021 IBD patients under regular follow-up at our referral center ("Tor Vergata" University Hospital, Rome, Lazio, Italy) were considered. Inclusion criteria were: 1) age $\geq$ 18 years; 2) well defined diagnosis of IBD, according to current guidelines[17,18]; 3) regular follow-up; 4) inclusion in our previous study[14]; 5) biologic treatment at the time of enrollment in the previous study ($\geq$ 6 months duration)[14], including either intravenous or subcutaneous administration (i.e., infliximab, adalimumab, golimumab, vedolizumab, ustekinumab); 6) written informed consent.

The only exclusion criterium was SARS-CoV-2 vaccination.

Study Design

The day of enrollment, all patients fulfilling the inclusion criteria were asked to fill a questionnaire. The following parameters were included: known risk factors for SARS-CoV-2 infection [contact with COVID-19 patients, travel, hospitalization, emergency room (ER) admission], symptoms compatible with COVID-19 (cough, fever, dysgeusia/anosmia, dyspnea, weakness, diarrhea, pharyngodynia, conjunctivitis, rhinitis, arthromyalgia) during the 6 months before enrollment, history of previous SARS-CoV-2 infection (not representing an exclusion criterium) or of nasopharyngeal swab testing (number, data, indication). Demographic and clinical characteristics of each patient were prospectively collected and reported in a database including: 1. age; 2. gender; 3. IBD characteristics (IBD type, disease duration, CD and UC extent, CD phenotype, IBD related surgery)[17,18]; 4. smoking habits; 5. ongoing biologic (type); 6. concomitant medications (ISS, corticosteroids); 7. COVID-19-related symptoms; 8. risk factors for SARS-CoV-2 infection. During the second wave, data from IBD patients fulfilling the inclusion criteria were prospectively collected and compared with data from the same patients assessed during the first wave[14].

SARS-CoV-2 Testing

At entrance, a blood sample (5 mL) for testing SARS-CoV-2 IgG antibodies (Abbott Diagnostics, Chicago, IL, USA) was collected in each patient. Serum samples were frozen at -20°C until tested.

Ethical Considerations

All patients gave their written informed consent before enrollment. The study was approved by the Local Independent Ethic Committee of the University "Tor Vergata" of Rome, Italy (protocol n. 78/20). The study protocol conforms to the Ethical Guidelines of the 1975 Declaration of Helsinki.

Statistical Analysis

Data were expressed as median [range]. The student's *t*-test and the χ^2 test were used to compare both characteristics of the study population assessed during the first and second pandemic waves, and characteristics of seropositive *vs.* seronegative patients studied during the second period. In order to evaluate risk factors for SARS-CoV-2 infection, logistic regression and multinomial logistic regression were used for univariate and multivariate analysis, respectively (a statistical significance of $p<0.05$ was considered for all tests). Sample size was not assessed as the

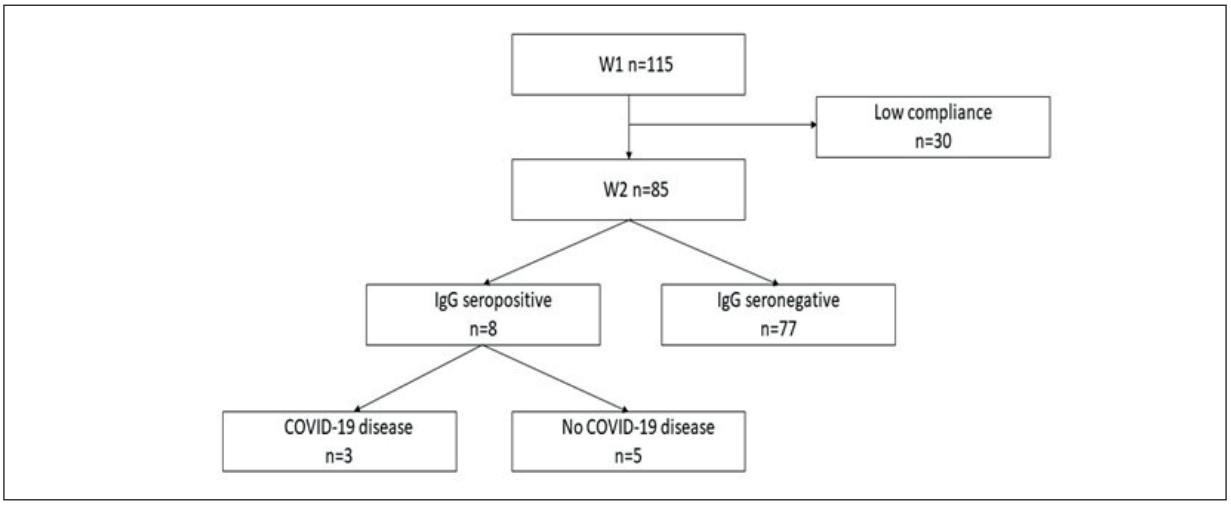

Figure 1. Flow chart of the IBD study population assessed during the first and second pandemic wave.
Abbreviations: W1=first pandemic wave; W2=second pandemic wave; n=number of patients.

study population included all the IBD patients using biologics already enrolled in the previously reported study[14].

Results

During the second wave, the study population included 85 out of the 115 (73.9%) IBD patients treated with biologics, already assessed for SARS-CoV-2 IgG seropositivity during the first wave[14]. The remaining 30 out of the 115 (26.1%) patients were not enrolled due to low compliance (Figure 1). The IBD population included 45 CD (52.9%) and 40 UC (47.1%) patients studied during both the first and second wave. Table I summarizes demographic and clinical characteristics, medications, risk factors for SARS-CoV-2 infection and symptoms compatible with COVID-19 in the tested IBD cohort.

Characteristics of IBD Patients

When comparing demographic and clinical characteristics of IBD patients detected during the two waves, no differences were found in terms of IBD-related surgery, smoking habits, corticosteroids, ISS and biologic use (Table I). Before enrollment, biologics were discontinued in 2 out of the 85 (2.3%) patients.

Overall, symptoms potentially compatible with SARS-CoV-2 infection were recorded in a higher proportion of patients during the second wave [29 out of 85 (34.1%) *vs.* 13 out of 85 (15.3%); p=0.004] (Table I). Comparison between the first *vs.* the second pandemic wave, in terms of COVID-19 compatible symptoms, showed a higher occurrence of cough (p=0.01), weakness (p=0.02), pharyngodynia (p=0.001) and rhinitis (p=0.06) in patients assessed during the second period (Table I). The frequency of other COVID-19 compatible symptoms was comparable between the two groups (Table I).

When considering risk factors for infection, contacts with well-defined cases of COVID-19 were reported by 18.8% of patients during the second wave, while no patients referred contacts during the first wave (p=0.0001) (Table I). The frequency of IBD-related hospitalizations was significantly higher during the second than the first wave (12.9% *vs.* 3.5%; p=0.02) (Table I). No differences were observed between the two waves in terms of frequency of history of recent travels or ER admissions (Table I).

SARS-CoV-2 Seropositivity and Prevalence of COVID-19

The prevalence of SARS-CoV-2 IgG seropositivity and COVID-19 in the 85 IBD patients assessed during both the first and second wave is reported in Figure 2. As shown, seropositivity was detected in 8 out of 85 (9.4%) patients during the second wave and in 2 out of the same 85 (2.3%) patients during the first wave (p=0.05) (Figure 2). In the same cohort, COVID-19 was diagnosed in 3 (3.5%) patients (2 CD, 1 UC) during the second wave, and in no patients (0%) during the first wave (p=0.08) (Figure 1). None of the 3 COVID-19 patients required hospitalization related to infection or developed pneumonia.

Table I. Symptoms and risk factors for SARS-CoV-2 infection and characteristics of IBD: first *vs.* second wave.
Abbreviations: IBD= Inflammatory bowel disease; ISS= Immunosuppressants; n= Number; n.a.= Not applicable.

IBD population	First wave (n= 85)	Second wave (n=85)	*p*
IBD-related surgery, n (%)	22 (25.9%)	24 (28.2%)	0.72
Smoking habit, n (%)			
Yes	19 (22.4%)	20 (23.5%)	0.85
No/ex	66 (77.6%)	65 (76.5%)	
Current ISS use, n (%)	2 (2.4%)	3 (3.5%)	0.64
Current biologic use, n (%)			
Overall biologics	85 (100%)	83 (97.6%)	
Infliximab	48 (56.5%)	42 (50.6%)	0.35
Adalimumab	8 (9.4%)	9 (10.8 %)	0.79
Golimumab	1 (1.1%)	1 (1.2%)	1
Ustekinumab	10 (11.8%)	13 (15.6%)	0.50
Vedolizumab	18 (21.2%)	18 (21.6%)	1
Systemic corticosteroid use, n (%)	4 (4.7%)	5 (5.8%)	0.73
COVID-19 compatible symptoms, n (%)			
Overall symptoms	13 (15.3%)	29 (34.1%)	0.004
Cough	1 (1.2%)	8 (9.4%)	0.01
Fever	3 (3.5%)	7 (8.2%)	0.19
Dysgeusia/Anosmia	0	2 (2.3%)	0.15
Dyspnea	0	0 (0%)	n.a.
Weakness	4 (4.7%%)	13 (15.3%)	0.02
Diarrhea	4 (4.7%%)	6 (7.1%)	0,51
Pharyngodynia	1 (1.2%)	12 (14.1%)	0.001
Conjunctivitis	1 (1.2%%)	1 (1.2%)	1
Rhinitis	0	7 (8.2%)	0.006
Arthromyalgia	4 (4.7%)	9 (10.6%)	0.14
Risk factors for SARS-CoV-2 infection, n (%)			
Contacts	0	16 (18.8%)	0.0001
Travels	8 (9.4%)	10 (11.8%)	0.61
Hospitalizations	3 (3.5%)	11 (12.9%)	0.02
Emergency Room Admission	2 (2.3%)	7 (8.2%)	0.08
SARS-CoV-2 IgG seropositivity n, (%)	2 (2.3%)	8 (9.4%)	0.05
COVID-19 disease	0 (0%)	3 (3.5%)	0.08

The flow chart in Figure 1 summarizes findings regarding SARS-CoV-2 IgG seropositivity and diagnosis of COVID-19 in the 8 seropositive patients during the second pandemic wave. Among these 8 patients, 3 developed COVID-19 disease, 4 showed seropositivity associated with a negative nasopharyngeal test (2 asymptomatic during the first wave, 2 symptomatic in the second wave), while the remaining asymptomatic patient showed a positive nasopharyngeal test.

Demographic Characteristics of Seropositive vs. Seronegative IBD Patients

Characteristics of IBD patients subgrouped according to SARS-CoV-2 seropositivity during the second pandemic period are summarized in Table II. As shown, the 8 seropositive patients included 5 CD and 3 UC. All these 8 seropositive patients were still using biologics during the second wave, and none was using ISS or corticosteroids. Comparable clinical and demographic characteristics and treatments (including corticosteroids, ISS, biologics) were observed in seropositive *vs.* seronegative patients (Table II). Symptoms compatible with COVID-19 occurred more frequently in seropositive patients (i.e., cough p=0.004; fever p=0.001; dysgeusia/anosmia p=0.0001; new onset diarrhea p=0.0001; pharyngodynia p=0.04; rhinitis p=0.001; arthromyalgia p=0.009) (Table II).

Among symptoms considered, only cough, fever, new onset diarrhea, rhinitis, dysgeusia/anosmia and arthromyalgia were identified as risk factors for SARS-CoV-2 IgG seropositivity at univariate (p<0.05), but not at multivariate analysis (Table III).

Regarding risk factors, the frequency of patients referring history of contacts at risk was

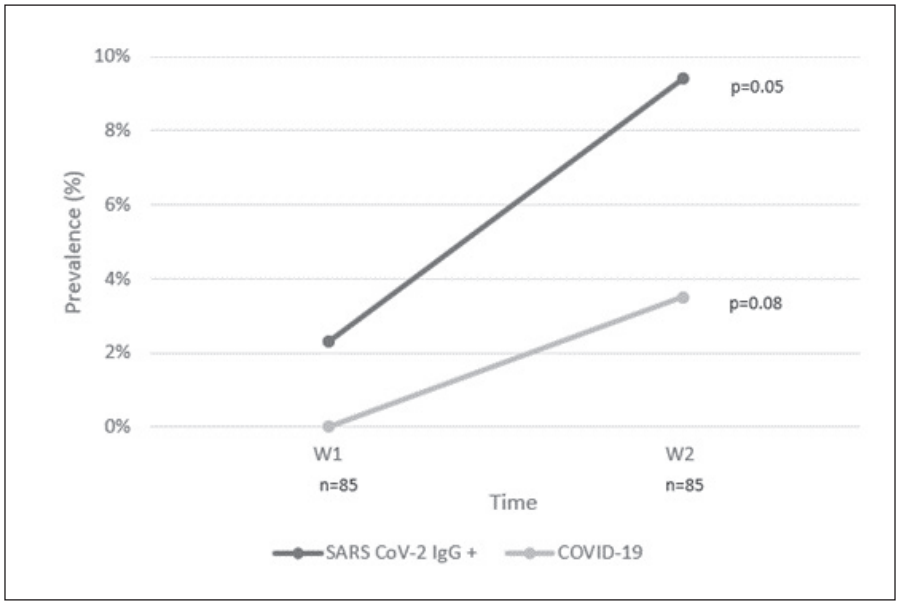

Figure 2. Prevalence of SARS-CoV-2 seropositivity and of COVID-19 in 85 IBD patients prospectively assessed during both the first and the second pandemic wave. A trend at the limit of the statistical significance (p=0.05) for a higher seroprevalence during the second *vs.* the first pandemic was observed.
Abbreviations: W1=first pandemic wave; W2=second pandemic wave; n=number of patients.

significantly higher in SARS-CoV-2 seropositive patients (p=0.01) (Table II). History of contacts at risk for infection indeed represented the only significant risk factor for IgG seropositivity at univariate analysis (p=0.03), but not at multivariate analysis (p=0.1).

Discussion

IBD currently appears to not increase the risk of SARS-CoV-2 infection, even in the subgroups of patients treated with biologics[15]. Due to the role played by TNFα during SARS-CoV-2 infection, TNFα antagonists blocking the cytokine storm have been suggested to protect patients from severe forms of COVID-19[19]. No significant differences in COVID-19 outcomes when using different types of biologics, including TNFα antagonists, IL-12/23 and integrin antagonists have been reported[20].

Since the advent of the COVID-19 outbreak, the prevalence and impact of SARS-CoV-2 infection in IBD patients during the first pandemic period has been extensively investigated, particularly in patients using biologics[21-23]. Marked variations, in terms of prevalence of infection, have been observed worldwide[13], thus suggesting the usefulness of epidemiological studies from different geographical areas. In the present study we therefore addressed this issue in a region of central Italy (Lazio). The COVID-19 outbreak in Italy has currently included three phases: 1) the first wave (March 2020-May 2020), characterized by a rapid spread of SARS-CoV-2 infection and a high mortality rate; 2) the transition period (June 2020- September 2020) characterized by a low spread of this infection; 3) the second wave (September 2020-January 2021), characterized by an exponential increase of new cases in few weeks, also related to an increased detection rate. In the Lazio region, the number of patients with SARS-CoV-2 infection in the general population raised from 7,545 during the first wave to 14,6417 during the second pandemic wave[24].

In relation to the need to further address whether IBD may impact the risk of developing SARS-CoV-2 infection and COVID-19, particularly in patients using biologics, this issue was prospectively investigated. An increased incidence of infection during the second wave in the general non-IBD population has indeed been observed. Moreover, at the best of our knowledge, prospective studies comparing the two pandemic periods in terms of SARS-CoV-2 prevalence in IBD are currently lacking.

In the tested IBD population, a trend at the limit of the statistical significance for a higher

Table II. Characteristics of IBD, SARS-CoV-2-related symptoms and risk factors for infection in seropositive *vs.* seronegative patients. *Abbreviations:* IBD= Inflammatory bowel disease; CD= Crohn disease; UC= Ulcerative Colitis; ISS= Immunosuppressants.

IBD population	IgG seropositivity (n= 8)	IgG seronegativity (n=77)	p
Age			
Median [range]	54 [27-63]	43 [21-67]	0.17
Gender, n (%)			
Female	3 (37.5%)	29 (37.7%)	0.99
Male	5 (62.5%)	48 (62.3%)	
IBD type, n (%)			
CD	5 (62.5%)	40 (51.9%)	0.56
UC	3 (37.5%)	37 (48.1%)	
IBD duration			
Median [range]	9.5 [2-24]	11 [1-34]	0.57
CD localization, n (%)			
Ileum	4 (80%)	19 (47.5%)	0.12
Colon	1 (20%)	5 (12.5%)	0.52
Ileum-colon	0	14 (35%)	0.18
Upper GI	0	2 (5%)	0.64
CD Behavior, n (%)			
Non stricturing-non penetrating	2 (40%)	17 (42.5%)	0.85
Stricturing	3 (60%)	15 (37.5%)	0.23
Penetrating	0	8 (20%)	0.33
UC extension, n (%)			
Proctitis	0	2 (5.4%)	0.64
Left-sided	1 (33.3%)	7 (18.9%)	0.75
Pancolitis	2 (66.7%)	28 (75.7%)	0.52
IBD-related surgery, n (%)	3 (37.5%)	21 (27.3%)	0.54
Smoking Habits n, (%)			
Yes	2 (25%)	18 (23.4%)	0.91
No/ex	6 (75%)	59 (76.6%)	
Current ISS use, n (%)	0	3 (3.9%)	0.56
Current biologic use, n (%)			
Overall biologics	8 (100%)	75 (97.4%)	0.14
Infliximab	6 (75%)	36 (48%)	0.29
Adalimumab	0	9 (12%)	0.74
Golimumab	0	1 (1.3%)	0.44
Ustekinumab	2 (25%)	11 (14.7%)	0.11
Vedolizumab	0	18 (24%)	
Systemic corticosteroids, n (%)	0	5 (6,5%)	0.45
COVID-19 compatible symptoms, n (%)			
Overall symptoms	5 (62.5%)	24 (31.2%)	0.07
Cough	3 (37.5%)	5 (6.5%)	0.004
Fever	3 (37.5%)	4 (5.2%)	0.001
Dysgeusia/Anosmia	2 (25%)	0	0.0001
Dyspnea	0	0	-
Weakness	3 (37.5%)	10 (13%)	0.06
Diarrhea	4 (50%)	2 (2.6%)	0.0001
Pharyngodynia	3 (37.5%)	9 (11.7%)	0.04
Conjunctivitis	0	1 (1.3%)	0.74
Rhinitis	3 (37.5%)	4 (5.2%)	0.001
Arthromyalgia	3 (37.5%)	6 (7.8%)	0.009
Risk factors for SARS-CoV-2 infection, n (%)			
Contacts	4 (50%)	12 (15.6%)	0.01
Travels	1 (12.5%)	9 (11.7%)	0.94
Hospitalizations	0	11 (14.3%)	0.25
ER admission	0	7 (9.1%)	0.37

Table III. Univariate and multivariate analysis of variables associated with a SARS-CoV-2 IgG seropositivity.
Abbreviations: OR= Odds Ratio; CI= Confidence Interval.

Variable	Univariate analysis		Multivariate analysis	
	OR [95% CI]	*p*	OR [95% CI]	*p*
Age	1.044 [0.98-1.11]	0.18	-	-
Gender	1.01 [0.22-4.53]	0.99	-	-
IBD type	1.54 [0.34-6.91]	0.57	-	-
Smoking habit	1.09 [0.20-5.90]	0.92	-	-
Cough	8.64 [1.60-47]	0.013	4.90, [0.34-69.75]	0.24
Fever	10.95 [1.90-63]	0.007	1.57 [0.05-47.62]	0.79
Asthenia	4.02 [0.83-19.5]	0.08		-
Diarrhea	37.5 [5.21-269.7]	0.0001	3.9 [0.11-134.68]	0.44
Pharyngodynia	4.53 [0.92-22.26]	0.06	-	-
Rhinitis	10.95 [1.90-63]	0.007	2.90, [0.05-144.03]	0.59
Arthromyalgia	7.1 [1.36-37.2]	0.02	6.65 [0.34-127.29]	0.20
Disgeusia/anosmia	45.6 [3.98-521.79]	0.002	13.5 [0.35-517.78]	0.16
Travels	1.08, [0.12-9.82]	0.94	-	-
Contact with COVID-19 positive patients	5.42 [1.20-24.7]	0.03	5.88 [0.62-55.45]	0.12

prevalence of infection and COVID-19 was observed in the same IBD cohort during the second *vs*. the first pandemic wave. This agrees with data deriving from the general non-IBD population coming from the same region[24], supporting that the observed increased SARS-CoV-2 prevalence during the second period was not related to the characteristics of IBD or to the use and type of biologics. The observed trend for a higher seroprevalence observed during the second wave in the tested IBD population is in agreement with previous independent studies[13,25]. This finding further supports that using biologics in IBD does not increase the risk of infection or worsen its course also when considering a study period characterized by a high spread of SARS-CoV-2 infection.

The observed finding that both IBD and biologics did not increase the risk of developing SARS-CoV-2 infection and severe COVID-19 is in agreement with several worldwide studies[15,20], including those from the same geographic area. In northern Italy (Bergamo) indeed, a large study from Norsa et al[21] during the early outbreak in 2020, reported a seroprevalence of 21% in IBD patients, comparable to that of the general local population. Immunosuppression appeared not to represent an additional risk factor for severe COVID-19, as most patients were pauci- or asymptomatic[21], as observed in the present study. The same observation derives from a subsequent multicenter study[22] including the Italian population, showing a low overall seroprevalence (2.3%) and frequency of severe COVID-19 in IBD patients using biologics. Comparable findings were reported in a large monocentric study[23] including 259 IBD patients using biologics studied during the first pandemic wave.

The assessment of SARS-CoV-2 seroprevalence in IBD patients evaluated during the second wave can be considered as one of the strengths of the present study. Additional strength includes comparisons in terms of seroprevalence and frequency of COVID-19 in the same IBD population considered during the first *vs.* the second pandemic wave. Data from the second wave[25,26], as also prospective studies comparing the prevalence of infection and COVID-19 in the same IBD patients assessed during both pandemic periods, are indeed lacking. A prospective monocentric study[25] during the second wave reported a comparable SARS-CoV-2 IgM and IgG seroprevalence in 386 IBD patients using or not biologics (10.3% *vs.* 10.7%; p=0.92) and in IBD patients *vs.* controls (13%; p=0.14). Close contact with SARS-CoV-2 positive IBD patients represented a risk factor for infection[25]. This is in agreement with the univariate analysis reported in the present study, including a different IBD population using biologics. This observation further supports the role of risk factors for infection common to the general population, rather than to IBD-related conditions and biologics, also during the second wave, characterized by a higher viral spread. Serological response to COVID-19 vaccines in IBD patients has recently been reported to be further diminished by TNF-antagonists[27].

However, this issue was not assessed in the present study, as SARS-CoV-2 vaccination was the only exclusion criterium.

The higher frequency of recent history of travels in seropositive IBD patients reported in our previous study[14] was not confirmed during the second wave.

Among the main findings, the frequency of new-onset diarrhea was significantly higher in seropositive *vs.* seronegative IBD patients (p=0.0001). In agreement with this observation, a single-center study[28] including 80 IBD patients with COVID-19 reported that diarrhea was more frequent in IBD patients than in non-IBD controls. Accordingly, data from a global registry (SECURE-IBD)[29] reported that new gastrointestinal symptoms, particularly diarrhea (observed in almost 20% of cases), are common among IBD patients with COVID-19, regardless of IBD activity.

As COVID-19 and IBD may share symptoms involving the gastrointestinal tract, including diarrhea, a differential diagnosis should be considered.

The relatively limited sample size and the absence of a non-IBD control group represent the main limitations of the present study. However, we aimed to compare the frequency and risk factors for SARS-CoV-2 infection and COVID-19, in a cohort of IBD patients using biologics and prospectively followed up during the two pandemic waves.

Conclusions

To the best of our knowledge, present findings provide new data regarding comparisons in terms of SARS-CoV-2 prevalence and COVID-19 in the same IBD patients treated with biologics, assessed during the first *vs.* the second pandemic wave. Taken together, the reported findings add support to the concept that having IBD does not represent a risk factor for either SARS-CoV-2 infection or COVID-19, even when considering patients treated with biologics during the second pandemic wave, characterized by a high viral spread. Present findings also add strengths to the concept that new onset diarrhea mimicking IBD relapse may be observed in patients with SARS-CoV-2 infection.

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Authors' Contributions

LB, MM, BN: concept, study design; LB, MM: drafting the manuscript; LB, MM, BN, LM, SS, IM, LS, EL, CP, EC, GM: clinical assessments; MM, BN, LM, LS: data entry; MM, LM revised findings and assessed seropositive patients; RM, SB: testing for SARS-CoV-2 seropositivity. All authors read and approved the final manuscript.

Conflict of Interest

All authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article. LB has served as a speaker for Takeda, Zambon, Janssen, Vifor Pharma, Ferring; GM received grant support from Giuliani SpA, Broad Medical Research Foundation, Novo Nordisk, Teva, Sirtris, Lycera, Sofar and speaker fees from AbbVie and Zambon and reported a patent related to the use of Smad7 antisense oligonucleotides in Crohn's disease (PCT Pub. No. WO2004/087920). EC has served as a speaker for Takeda, Janssen, Sandoz; IM has served as a speaker for Janssen.

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