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Low prevalence of SARS-CoV-2 infection in inflammatory bowel disease

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Abstract. – OBJECTIVE: Treatments used in Inflammatory Bowel Disease (IBD) have been associated with enhanced risk of viral infections and viral reactivation, however, it remains unclear whether IBD patients have increased risk of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. The aim of the study was to examine the prevalence of SARS-CoV-2 IgG positivity in IBD patients followed at our referral center. The role of treatments for IBD and risk factors for infection were also evaluated.

PATIENTS AND METHODS: In a prospective study, all IBD patients followed at our referral centre between May 27th and July 21st, 2020 and fulfilling the inclusion criteria were tested for SARS-CoV-2 IgG. Specific IgG antibodies were evaluated by a commercial ELISA kit and SARS-CoV-2 nasopharyngeal swab was performed in seropositive patients.

RESULTS: Two-hundred and eighteen patients, 128 Crohn's disease (CD) and 90 Ulcerative colitis (UC) [age 44, (19-77) years; ongoing biologics in 115 (52.7%)] were enrolled. No patient had major SARS-CoV-2-related symptoms. SARS-CoV-2 IgG were detected in 3 out of 218 (1.37%) patients with IBD (2 CD and 1 UC), all on biologics (2.6%). In all of the 3 seropositive patients, the nasopharyngeal swab was negative. There was no relationship between SARS-CoV-2 seroprevalence and the demographic/clinical characteristics of IBD patients. In contrast, history of recent travel was more frequent in the SARS-CoV-2 seropositive patients (2/3; 66.6%) than in SARS-CoV-2 seronegative patients [7/215 (3.25%); $p<0.0001$].

CONCLUSIONS: The prevalence of SARS-CoV-2 IgG seropositivity in IBD patients appears to be comparable to the non-IBD population and not influenced by ongoing treatments. Risk factors for infection common to the general non-IBD population should be considered when managing patients with IBD.

Key Words:
SARS-CoV-2 infection, Inflammatory bowel disease, Seroprevalence, Asymptomatic.

Introduction

The etiology of Inflammatory Bowel Disease (IBD) remains unknown. An inappropriate immune response towards luminal antigens appears involved in the pathogenesis of tissue damage. The proven efficacy of immunomodulators[1] supports this hypothesis. Conventional immunosuppressors (ISS) and biologics may determine an increased risk of both bacterial and viral infections and viral reactivation[1]. This issue is currently particularly relevant due to the pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2).

In the majority of patients, SARS-CoV-2 infection is asymptomatic or presents mild symptoms. However, one fifth of patients develop severe or fatal illness[2]. An excessive immunological response, characterized by a marked production of inflammatory cytokines (i.e., interleukin-6, TNF-α) has been shown in IBD[3]. Biologics blocking these cytokines have shown some efficacy in SARS-CoV-2-induced disease (COVID-19)[3]. These observations suggest that the use of biologics could help prevent, rath-

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er than promote, SARS-CoV-2 infection and/or COVID-19. The ECCO-COVID[4] task force and the SECURE-IBD registry[5] indicated that TNFα antagonists do not worsen the COVD-19 course, nor they increase the risk for SARS-CoV-2 infection. However, it remains plausible that IBD can influence the risk of SARS-CoV-2 infection, as well as COVID-19 be more common in patients with co-morbidities[5].

The present study was undertaken to assess IgG seroprevalence of SARS-CoV-2 in patients with Crohn's Disease (CD) and Ulcerative Colitis (UC). The role of treatments for IBD and risk factors for infection were also evaluated.

Patients and Methods

Study Design

In a prospective cohort study, all IBD patients showing no major signs or symptoms of SARS-CoV-2 infection and followed-up in our referral centre ("Tor Vergata University Hospital", Rome, Lazio, Italy), were asked to participate to the study. Patients were enrolled from May 27th to July 21st, 2020 during outpatient visit hospitalization or Day Hospital admission.

Study Population

Inclusion criteria were: (1) age ≥18 years; (2) diagnosis of CD or UC[1]; (3) regular follow-up; (4) available demographic and clinical characteristics; (5) ability to understand the study design; (6) written informed consent. Exclusion criteria: (1) diagnosis or history of SARS-CoV-2 infection; (2) signs, symptoms and/or risk factors for SARS-CoV-2 infection ≤14 days before enrollment (≥2 among: sore-throat, weakness, fever, cough, arthralgias, weight loss, recent contacts with COVID-19 patients); (3) ongoing clinical trial; (4) pregnancy; (5) psychiatric or severe diseases. Demographic and clinical characteristics were reported in a database including: (1) age; (2) gender; (3) IBD type; (4) CD and UC extent[1]; (5) CD phenotype[1]; (6) clinical activity of CD (Harvey Bradshaw Index) and UC (Mayo score)[1]; (5) IBD-related surgery; (6) ongoing biologics: TNFα-antagonists (Infliximab, Adalimumab, Golimumab), anti-IL-12/IL-23 monoclonal antibody (Ustekinumab), anti-α4β7 integrin (Vedolizumab); (7) in patients on biologics: date of first administration, dosage, concomitant treatments; (8) ISS (thiopurines, methotrexate); (9) corticosteroids; (10) COVID-related symptoms, contacts with COVID-19 patients, travels outside the Lazio region within the previous 3 months.

SARS-CoV-2 Testing

Testing for SARS-CoV-2 IgG antibodies (Abbott Diagnostics, Chicago, IL, USA) was proposed to all eligible patients. Serum samples were frozen at -20°C until tested. A SARS-CoV-2 nasopharyngeal swab was performed in seropositive patients and, in case of positivity, patients were referred to infectivologists from the same University Hospital.

Statistical Analysis

The prevalence of SARS-CoV-2 IgG seropositivity in IBD remains undefined. Therefore, the sample size was not calculated, and SARS-CoV-2 seroprevalence was investigated in a cohort of IBD patients from May 27th to July 21st, 2020. Data were expressed and median [range]. The differences between IBD patients were sub-grouped according to clinical characteristics or treatments were assessed by using the χ^2 test (statistical significance: $p<0.05$).

Ethical Considerations

The protocol was approved by the local Ethics Committee ("Tor Vergata University Hospital", Rome, Italy; protocol 78/20). All enrolled patients gave written informed consent. The study protocol conforms to the Ethical Guidelines of the 1975 Declaration of Helsinki.

Results

Study Population

SARS-CoV-2 seroprevalence was assessed in 218 IBD patients: 128 CD, 90 UC. Demographics and clinical characteristics are reported in Table I. Testing was refused by <5% of patients. History of appendectomy and smokers were more frequent in CD than in UC patients [37 (23.4%) *vs.* 7 (7.7%); $p=0.0001$ and 44 (34.3%) *vs.* 8 (8.8%); $p<0.0001$, respectively]. Aminosalicylates were used in a higher proportion of UC than CD patients [83 (92.2%) *vs.* 82 (72.6%); $p<0.0001$].

Biologics were used by115 (52.7%) IBD patients, including 69/128 (53.9%) CD and 46/90 (51.1%) UC patients (Table II). Other treatments are reported in Table II.

Table I. Study population clinical IBD characteristics.

	IBD Total (n = 218)	IBD SARS-Cov2+ (n = 3)	IBD SARS-Cov2- (n = 215)	CD Total (n = 128)	CD SARS-Cov2+ (n = 2)	CD SARS-Cov2- (n = 126)	UC Total (n = 90)	UC SARS-Cov2+ (n = 1)	UC SARS-Cov2- (n = 89)
Age Median [range]	44 [19-77]	32 [32-55]	44 [19-77]	44 [21-77]	32 [32-32]	44 [21-77]	44.5 [19-72]	55 [55-55]	44 [19-72]
Gender, n (%) Female Male	100 (45.8%) 118 (54.2%)	2 (66.6%) 1 (33.4%)	98 (45.5%) 117 (55.5%)	56 (43.8%) 72 (56.2)	1 (50%) 1 (50%)	55 (43.6%) 71 (56.4%)	44 (49.9%) 46 (51.1%)	1 (100%) 0 (0%)	43 (48.3%) 46 (51.7%)
IBD duration Median [range]	11 [1-52]	11 [7-14]	11 [1-52]	12 [1-52]	12.5 [11-14]	12 [1-52]	8 [1-40]	7 [7-7]	7 [1-40]
CD localization Ileum Colon Ileum-colon Upper GI	N/A	N/A	N/A	60 (46.8%) 15 (11,7%) 45 (35.1%) 8 (6.2%)	1 (50%) 1 (50%)	59 (46.8%) 15 (11.9%) 44 (34.9%) 8 (6.3%)	N/A	N/A	N/A
Behaviour non stricturing-non penetrating Stricturing Penetrating	N/A	N/A	N/A	52 (40.6%) 51 (39.8%) 25(19.5%)	1 (50%) 1 (50%) 0 (0%)	51 (40.5%) 50 (39.7%) 25 (19.8%)			
UC extension Proctitis Lleft-sided Ppancolitis	N/A	N/A	N/A	N/A	N/A	N/A	10 (11.1%) 21 (23.3%) 59 (65.6%)	0 (0%) 1 (100%) 0 (0%)	10 (11.2%) 20 (22.4%) 59 (66.4%)
Appendectomy n (%)	44 (20.2%)	1 (33.3%)	43 (20%)	37 (23.4%)	1 (50%)	36 (28.5%)	7 (7.7%)	0 (0%)	7 (7.8%)
IBD-related surgeryn (%)	60 (27.5%)	1 (33.4%)	59 (27.4%)	53 (41.4%)	1 (50%)	52 (41.2%)	7 (7.7%)	0 (0%)	7 (7.8%)
Smoking Habits n, (%) Yes No/ex	52 (23.8%) 166 (76.2%)	0 (0%) 3 (100%)	52 (24.1%) 163 (65.9%)	44 (34.3%) 84 (65.7%)	0 (0%) 2 (100%)	44 (34.9%) 82 (65.1%)	8 (8.8%) 82 (91.2%)	0 (0%) 1 (100%)	8 (8.9%) 81 (91.1%)

IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; ISS: immunosuppressors; TNF: tumor necrosis factor.

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Table II. Study population treatments and risk factors.

	IBD Total (n = 218)	IBD SARS-Cov2+ (n = 3)	IBD SARS-Cov2- (n = 215)	CD Total (n = 128)	CD SARS-Cov2+ (n = 2)	CD SARS-Cov2- (n = 126)	UC Total (n = 90)	UC SARS-Cov2+ (n = 1)	UC SARS-Cov2- (n = 89)
Current ISS use, n (%)	16 (7.4%)	0 (0%)	16 (7.4%)	9 (7%)	0 (0%)	9 (7.1%)	7 (7.7%)	0	7 (7.8%)
Current biologic use, n (%)	115 (52.7%)	3 (100%)	112 (52.1%)	69 (53.9%)	2 (100%)	67 (54.7%)	46 (51.1%)	1 (100%)	45 (50.5%)
Anti-TNFs									
Infliximab	72 (62.7%)	2 (66.6%)	70 (62.6%)	44 (64.7%)	1 (50%)	43 (64.2%)	28 (61%)	1 (100%)	27 (60%)
Adalimumab	56 (48.6%)	2 (66.6%)	54 (48.2%)	33 (47.8%)	1 (50%)	32 (47.7%)	23 (50%)	0 (0%)	23 (51.1%)
Biosimilars	14 (12.1 %)	0 (0%)	14 (12.5%)	11 (15.9%)	0 (0%)	11 (16.4%)	3 (6.5%)	0 (0%)	3 (6.6%)
Golimumab	2 (1.7%)	0 (0%)	2 (1.7%)	0 (0%)	0 (0%)	0 (0%)	2 (4.3%)	0 (0%)	2 (4.4%)
Ustekinumab	22 (19.1%)	1 (33.4%)	21 (18.7%)	21 (30.4%)	1 (50%)	20 (29.9%)	1 (2.1%)	0 (0%)	1 (2.2%)
Vedolizumab	21 (18.2%)	0 (0%)	21 (18.7%)	4 (5.7%)	0 (0%)	4 (5.9%)	17 (36.9%)	0 (0%)	17 (37.8%)
Contacts, n (%)	1 (0.4%)	0 (0%)	1 (0.4%)	1	0	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)
Symptoms, n (%)	37 (16.9%)	0 (0%)	37 (17.3%)	17 (13.3%)	0 (0%)	17 (13.4%)	20 (22.2%)	0 (0%)	20 (22.4%)
Cough	4 (1.8%)	0 (0%)	4 (1.8%)	0 (0%)	0 (0%)	0 (0%)	4 (4.4%)	0 (0%)	4 (44.9%)
Fever	5 (2.3%)	0 (0%)	5 (2.3%)	2 (1.5%)	0 (0%)	2 (1.5%)	3 (3.3%)	0 (0%)	3 (3.3%)
Dysgeusia/Anosmia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dyspnea	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Weakness	9 (4.1%)	0 (0%)	9 (4.1%)	5 (3.9%)	0 (0%)	5 (3.9%)	4 (4.4%)	0 (0%)	4 (4.4%)
Diarrhea	15 (6.8%)	0 (0%)	15 (6.9%)	7 (5.4%)	0 (0%)	7 (5.5%)	8 (8.8%)	0 (0%)	8 (8.9%)
Pharyngodynia	3 (1.3%)	0 (0%)	3 (1.3%)	1 (0.7%)	0 (0%)	1 (0.7%)	2 (2.2%)	0 (0%)	2 (2.2%)
Conjunctivitis	2 (0.9%)	0 (0%)	2 (0.9%)	1 (0.7%)	0 (0%)	1 (0.7%)	1 (1.1%)	0 (0%)	1 (1.1%)
Rhynitis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; ISS: immunosuppressors; TNF: tumor necrosis factor.

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SARS-CoV-2 IgG Seroprevalence

IgG seropositivity for SARS-CoV-2 was detected in 3/218 (1.37%) patients, all showing a negative nasopharyngeal swab. SARS-CoV-2 IgG seropositivity was observed in 2/128 (1.56%) CD and in 1/90 (1.11%) UC patients (p=0.07) (Table I).

Symptoms compatible with SARS-CoV-2 infection (≤3 months) were referred by 37 (16.9%) patients, all seronegative. Recent contacts with a SARS-CoV-2 positive subjects were reported by 1/218 (0.86%) IBD patients (seronegative) (Table II).

Biologics and SARS-COV-2 IgG Seropositivity

All the 3 IBD patients showing SARS-CoV-2 IgG seropositivity were using biologics (2 Infliximab,1 Ustekinumab). SARS-CoV-2 IgG seroprevalence did not significantly differ between patients using or not biologics (3/115 *vs.* 0/103; p=0.09) (Table II).

Steroids, Conventional Immunomodulators and SARS-COV-2 IgG Seropositivity

Sixteen (7.4%) IBD patients (9 CD,7 UC) were on conventional ISS and 49 (22.4%) (30 CD, 19 UC) on steroids: none of them showed SARS-CoV-2 seropositivity (Table II).

Clinical Characteristics and SARS-COV-2 Seropositivity

SARS-CoV-2 IgG seropositivity was observed in only 3 IBD patients, thus limiting statistical comparisons according to demographic and clinical characteristics (Tables I and II). However, a history of recent travels was referred by 9/218 (4.12%) patients. Although only 9 IBD patients referred this risk factor, the proportion of patients referring recent travels was significantly higher in the subgroup of SARS-CoV-2 IgG seropositive than seronegative patients [2/3 (66.6%) *vs.* 7/215 (3.25%), respectively; p<0.0001].

Discussion

In our prospective study, a low SARS-CoV-2 IgG seroprevalence (1.37%) was observed in IBD, with no cases of COVID-19. Interestingly, all 3 patients with SARS-CoV-2 IgG seropositivity were on biologics, although seroprevalence was comparable between treated and untreated patients.

Clinical characteristics appeared representative of the general IBD population[1], thus supporting the absence of selection biases.

Our data expand findings from an epidemiological study using telephone interview, reporting a low prevalence of COVID-19 in IBD (3/672 patients: 0.44%)[6]. Present results mirror those reported by the National Institute of Statistic of the Italian Health Minister (ISTAT)[7]. During the same study period (May 25th-July 15th, 2020), ISTAT reported that the Lazio region had an overall SARS-CoV-2 IgG seroprevalence in the general population from the Lazio region of 1.0% (56.093/5.843.220 residents)[7], thus comparable to our findings in IBD (1.37%).

Present observations are in agreement with a multicentric study from high-risk regions (France, Northern Italy)[8] reporting a low incidence of COVID-19 in a large cohort of 6000 IBD patients.

The impact of biologic therapies on the risk of SARS-CoV-2 infection and COVID-19 is under evaluation[3]. The viral entry molecules ACE2 and TMPRSS2 have been found to be normally expressed in the intestine[9]. Neither inflammation nor biologics appeared to increase the expression of ACE2 and TMPRSS2 in the gut. By contrast, biologics (anti-TNFα, antiIL-12/23, anti-integrins) appeared to downregulate ACE2 expression. This evidence[9] provides a background supporting why biologics should not increase the risk of SARS-CoV-2 infection.

When compared to our findings, a higher SARS-CoV-2 seroprevalence (21% *vs.* 1.37%) was observed in an Italian study during pandemic[10]. Norsa et al[10] however included IBD patients from Bergamo (Lombardy region), the second epicenter of SARS-CoV-2 infection after China. Differently, our study considered only patients from Lazio, region characterized during the study period by a lower seroprevalence (1%) than Lombardy (7.5%)[7]. Present findings further support a comparable prevalence of SARS-CoV-2 infection in IBD *vs.* non-IBD population from the same area[5,6,8,10].

Although in our cohort only 3 patients showed SARS-CoV-2 seropositivity (all on biologics), the overall number of patients using immunomodulators was quite high,as more than half of the population study was on biologics (52%), and less on ISS (7.4%). All the 3 SARS-CoV-2 IgG se-

ropositive patients were asymptomatic. Overall, present findings add support to the few available data suggesting that immunomodulators do not increase the risk nor worsen the outcome of SARS-CoV-2 infection in IBD[4]. Current recommendations[4] indeed suggest not to stop immunomodulators in SARS-CoV-2 infected patients.

In our series, 66% of SARS-CoV-2 seropositive patients had a recent history of travel, while the same was observed in only 3% of seronegative patients. Despite the limited number of patients showing IgG seropositivity (n=3) or history of travel (n=9), this known risk factor for infection was significantly more frequent in SARS-CoV-2 seropositive than seronegative patients ($p<0.0001$). This finding strongly suggests that when assessing risk factors for SARS-CoV-2 infection in IBD, variables common to the general non-IBD population rather than to IBD itself should be considered. Although our limited series does not allow conclusive statements, by our knowledge this known risk factor has not been considered in similar studies[5,6,8,10].

Among limitations of our study, here is the absence of a non-IBD control group, thus not allowing statistical comparisons in terms of SARS-CoV-2 seroprevalence. However, the availability of national ISTAT data[7] on SARS-CoV-2 seroprevalence referring to the same period and geographic area, may provide a referral non-IBD population for comparisons.

Strengths of this study include the quite large population, which appears not burdened by selection biases, the prospective study design and the accurate selection of risk factors for SARS-CoV-2 infection.

Conclusions

Present findings from a prospective study support that the prevalence of SARS-CoV-2 IgG seropositivity in IBD patients is comparable to the non-IBD population and not influenced by ongoing treatments, including TNFα antagonists. Risk factors for SARS-CoV-2 infection common to the general non-IBD population (i.e., recent history of travel) should be considered for a proper assessment of the impact of this new virus in clinical management of IBD. To our knowledge, this is one of the few prospective studies aimed to assess SARS-CoV-2 seroprevalence in IBD, thus providing new data regarding this still undefined issue.

Conflict of Interest

All authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article. BL has served as a speaker for Takeda, Zambon, AbbVie, Janssen; EC has served as a speaker for Takeda, AbbVie, Janssen.

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Statement Authorship

LB, LS, BN, GM: wrote the manuscript; LB: concept, study design, clinical assessments; LB, CP, MM, IM: Clinical assessments; LS, MA revised findings and assessed seropositive patients: RM, SB: testing for SARS-CoV-2 seropositivity. All authors read and approved the final manuscript..

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