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ABOUT COVER

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AIMS AND SCOPE

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ORIGINAL ARTICLE

Observational Study

SARS-CoV-2 in inflammatory bowel disease population: Antibodies, disease and correlation with therapy

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Abstract

BACKGROUND
Guidelines recommend to cease inflammatory bowel disease (IBD) biologic therapy during coronavirus disease 2019 (COVID-19).

AIM
To investigate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibody positivity in an IBD cohort, COVID-19 disease severity and to evaluate the correlation with clinical/therapeutic variables.

METHODS
Prospective observational cohort study. IBD patients were tested for SARS-CoV-2 IgG. Data on COVID-19 disease, demographics/therapeutics and clinical features of the IBD population were collected. IgG ≥ 7 was set for SARS-CoV-2 antibody positivity. Throat swab was performed in cases of IgG positivity. Correlations between antibody positivity or COVID-19 symptoms and therapeutic/clinical data were assessed.

RESULTS
In total, 103 IBD patients were enrolled. Among them, 18.4% had IgG ≥ 7. Multivariate analysis of antibody positivity correlated only with IBD treatment. For IgG ≥ 7, the odds ratio was 1.44 and 0.16 for azathioprine and mesalazine, respectively, *vs* biologic drugs (*P* = 0.0157 between them). COVID-19 related symptoms were reported in 63% of patients with IgG positivity. All but one

patient with COVID-19 symptoms did not require ceasing IBD treatment or hospitalization. IBD treatment and body mass index correlated with COVID-19 disease development with symptoms.

CONCLUSION
The IBD population does not have a higher risk of severe COVID-19. The relative risk of having SARS-CoV-2 antibodies and symptoms was higher for patients taking azathioprine, then biologic therapy and lastly mesalazine. None of the patients under biologic therapy developed severe COVID-19.

Key Words: Inflammatory bowel disease; SARS-CoV-2; COVID-19; Biologic treatment; SARS-CoV-2 antibody; Inflammatory bowel disease therapy

Core Tip: Guidelines recommend ceasing inflammatory bowel disease (IBD) biologic therapy during coronavirus disease 2019 (COVID-19). IBD patients were prospectively tested for severe acute respiratory syndrome coronavirus 2 IgG. In total, 103 IBD patients were enrolled. We found that 18.4% had IgG positivity, and 63% developed COVID-19 disease with symptoms. However, all but one patient with symptoms did not require ceasing IBD treatment no hospitalization. None of the patients under biologic therapy developed severe COVID-19. Therefore, the IBD population does not seem to have a high risk of severe COVID-19, particularly if under biological treatment or mesalazine.

INTRODUCTION

A new β-coronavirus (SARS-CoV-2) spread in November 2019 in China and then worldwide, becoming a pandemic. The related disease, known as coronavirus disease 2019 (COVID-19), mainly involves the respiratory system. The elderly and patients affected by chronic diseases seem to be at a higher risk to develop severe pneumonia and acute distress syndrome[1]. In this scenario, the patients affected by inflammatory bowel diseases (IBD) appeared to be an at-risk population for severe COVID-19, considering the possible gastrointestinal system involvement[2-6]. Indeed, it seems that the high expression of angiotensin-converting enzyme 2 in the intestinal tract, above all in the absorptive enterocytes of the ileum and colon and in the epithelial cells of the esophagus, makes these tissues highly susceptible to SARS-CoV-2 infection. Mucosal damage was observed in the esophagus, stomach, duodenum and rectum by histological examinations as plasma cells and lymphocytes infiltrated the lamina propria. Approximately 3% of COVID-19 cases have only digestive symptoms. Moreover, the detection of SARS-CoV-2 in the stool suggested that the virus could replicate in the digestive tract[6].

Initial indications from an IBD center in Wuhan, China was to discontinue all biological and immunosuppressive treatments. They reported that among 318 registered IBD patients, none developed COVID-19[7]. Nevertheless, scientific societies suggested that IBD patients should continue the ongoing treatment to avoid relapse, including the biological therapies[1]. However, regarding IBD patients affected by COVID-19, guidelines suggest handling the treatments with more caution. In particular, the American Gastroenterological Association guidelines divided them into three different categories: IBD patients without SARS-CoV-2 infection; IBD patients with SARS-CoV-2 infection but no symptoms of COVID-19; and IBD patients with COVID-19 symptoms. The first category should continue all treatments. The second category should discontinue thiopurines, methotrexate and tofacitinib and delay biological therapies for 2 wk while monitoring symptoms of COVID-19. The third category should discontinue thiopurines, methotrexate, tofacitinib and biological therapy during the illness[1].

Since the scientific community had to develop new guidelines in a short time with a new and unknown disease, the recommendations carry a low grade of evidence. In an Italian cohort of 522 IBD patients, none were hospitalized for SARS-CoV-2 infection, and 16% of the patients were under biologic treatment. However, 11% of the patients were children, a population with an unclear susceptibility to the virus[8]. Moreover, some interesting observational studies report COVID-19 prevalence and symptoms/outcomes in IBD cohorts[9,10]. However, little is known about the possible role of IBD treatments in the development of severe COVID-19 disease. Importantly, it remains unclear whether

IBD patients are at a higher or lower risk of severe COVID-19.

Systemic inflammation is a crucial target for the treatment of COVID-19 pneumonia, as the severity of the respiratory disease seems to be linked to the upregulation of inflammatory cytokines by creating a "cytokine storm," producing interleukin (IL)-6, IL-1, tumor necrosis factor (TNF) and interferon-γ. The exaggerated synthesis of IL-6 can lead to an acute severe systemic inflammatory response. It should be noted that cytokine blockers and Jak inhibitors were considered for clinical therapy of COVID-19 acute respiratory distress syndrome[11-13]. Interestingly, TNF inhibition has also been suggested in selected patients with high IL-6 levels. Indeed, when TNF is blocked, there is a serial decrease of IL-6 and IL-1 within 12 h in patients with active rheumatoid arthritis. A reduction of adhesion molecules and vascular endothelial growth factor was observed as well[14]. Nevertheless, no definitive treatment has been approved. Therefore, many hypotheses but few certainties are present. In particular, COVID-19 outcomes in patients with IBD immunomodulant/immunosuppressive treatments remains under debate.

The present study aimed to investigate the prevalence of SARS-CoV-2 antibody positivity and COVID-19 disease severity in an IBD cohort, in both symptomatic and asymptomatic patients and to evaluate the correlation with clinical/therapeutic variables.

MATERIALS AND METHODS

Study design
We conducted a prospective cohort study. The informed consent for the study was obtained from all the patients in accordance with the World Medical Association's 2008 Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. The privacy rights of patients were always observed. All authors had access to the study data and reviewed and approved the final manuscript.

Patients
Cohort of patients affected by IBD (Crohn's disease or ulcerative colitis). From April 22, 2020 to May 31, 2020, each IBD patient followed-up at ASST Cremona was offered to participate in the study. The patients were consecutively enrolled.

Data collection
Each IBD patient was asked about his/her recent clinical history (respiratory and gastrointestinal symptoms) from the beginning of the COVID-19 pandemic in Europe (February 21, 2020) by completing a questionnaire, and all the information was validated with the doctor who conducted the interview. Data collected in the questionnaire were summarized in the Supplementary Material.

Age, sex, body mass index (BMI), IBD type, treatments and clinical activity and other comorbidities were anonymously collected in a database. Charlson Comorbidity Index was calculated for each patient.

Antibody testing
A single blood test was performed for each patient to search for anti-SARS-CoV-2 IgG. The LIAISON® SARS-CoV-2 S1/S2 IgG test [Diasorin S.p.A, Saluggia (VC) – Italy] was used according to manufacturer's instructions. S1 and S2 are subunits of the spike protein and are responsible for binding (S1) and fusion (S2) of the virus to cells. The spike protein is the target of neutralizing antibodies. They are defined as antibodies that protect cells from pathogens or infectious particles by neutralizing their biological effects. The manufacturer reports a positive agreement of 94.4% [95% confidence interval (CI): 88.8%-97.2%] with the plaque reduction neutralization test. The IgG test has diagnostic specificity of 98.5% (95%CI: 97.5%-99.2%) in blood donors and 98.9% in presumably SARS-Cov-2 negative diagnostic routine samples. The IgG values are considered negative when < 12.0 kAU/L, equivocal from 12 kAU/L to 15.0 kAU/L and positive when ≥ 15.0 kAU/L. When applying a cutoff of >15 kAU/L, the reported test's sensitivity is time-dependent: 25% (14.6%-39.4%) ≤ 5 d after reverse transcriptase-PCR-confirmed diagnosis; 90.4% (79.4%-95.8%) from day 5 to day 15; and 97.4% (86.8%-99.5%) after > 15 d from PCR diagnosis[15]. However, Plebani *et al*[16] found that 6.2 kAU/L was the appropriate cutoff for the DiaSorin method to reach a sensitivity of 97.1% and a specificity of 88.9%. Moreover, in our hospital, all health care workers (HCW) were tested for serology immediately after the first 2 mo of pandemic (between April and May 2020). Among the HCW who were previously confirmed ill, only the 85% of them resulted having IgG value > 15, whereas 14% of them had values between 7 and 15 (data from National Institute of Heath, 2020).

Thus, in the present study we decided to perform the analysis using both 15 and 7 as cutoffs, considering 7 as the most reliable value.

Swab throat test
All patients who resulted positive for SARS-CoV-2 IgG were tested with a SARS-CoV-2 swab throat test during the same week using the Allplex 2019-nCoV assay (Arrow Diagnostics S.r.l., Genova, Italy),

which is a single-tube assay able to detect the three target genes (*E* gene, *RdRP* gene and *N* gene) as recommended by the World Health Organization.

Statistical analysis

Categorical variables were described as count and percentage and compared between groups with the χ^2 test. Continuous variables were described as mean and standard deviation or median and interquartile range if not normally distributed (Shapiro-Wilks test) and compared with independent *t*-test or Mann-Whitney.

Univariate and multivariate logistic regression models were used to assess: (1) Association between age, sex, BMI, IBD type, IBD treatments, IBD clinical activity, Charlson Comorbidity Index and SARS-CoV-2 IgG positivity; and (2) Association between age, sex, BMI, IBD type, IBD treatments, IBD clinical activity, Charlson Comorbidity Index and presence of COVID-19 symptoms.

The analysis was performed using SARS-CoV-2 IgG value cutoff of > 7 kAU/L (15-16).

RESULTS

In total, 103 IBD patients were consecutively enrolled; 54 had Crohn's disease and 49 ulcerative colitis. Among these, 36 patients (35.0%) were treated with biologic treatment, 14 (13.6%) with azathioprine (AZA) and 53 (51.4%) with mesalazine. Demographic, clinical and therapeutic characteristics of the cohort were summarized in Table 1. The survey's results were summarized in Table 2.

Prevalence of SARS-CoV-2 IgG positivity in IBD cohort

SARS-CoV-2 IgG positivity with value > 7 was found in 19 out of 103 patients (18.4%). Among them: 10 were under biological treatment; 5 under AZA; and 4 under mesalazine. Symptoms related to COVID-19 disease were reported in 12 out of 19 patients (63%). Among them, 2 were treated with mesalazine, 4 with AZA and 6 with biologic treatment. Among the 7 out of 19 patients without a history of COVID-19-related symptoms but positive for antibodies, 2 were treated with mesalazine, 1 with AZA and 4 with biologic therapy. All but one patient, who had pneumonia and was under AZA treatment, did not require hospitalization. Data regarding the patients with IgG > 7 were summarized in Table 3.

Swab throat test

All the patients with IgG > 7 were tested with a swab throat test. All of them were negative. The patient with a history of COVID-19 pneumonia had tested positive before the enrollment and tested negative after enrollment.

Correlation between SARS-CoV-2 IgG positivity and clinical/therapeutic variables in the IBD cohort

SARS-CoV-2 IgG value ≥ 7 correlated at multivariate analysis only with IBD treatment. In detail, stratifying the population for treatment, the relative risk of having SARS-COV-2 IgG ≥ 7 was higher for patients treated with AZA and lower with mesalazine. The odds ratios for AZA was 1.44 (95%CI: 0.27-7.56) and 0.16 (95%CI: 0.03-0.71) for mesalazine *vs* biologic drug (P = 0.0157 between them). The relative risk for patients under mesalazine was lower than for those under biologic therapy (P = 0.016).

Correlation between the presence of COVID-19-related symptoms and clinical/therapeutic variables in IBD cohort

The presence of COVID-19-related symptoms were correlated after multivariate analysis with BMI (P = 0.05) and with IBD therapy. The relative risk of having symptoms was higher for patients treated with AZA and lower with mesalazine *vs* biologic drug: odds ratios 7.47 (95%CI: 1.22-45.73) and 0.52 (95%CI: 0.17-1.72, P = 0.03) for AZA and mesalazine, respectively (P = 0.004 between them).

DISCUSSION

The use of SARS-Cov-2 antibodies to monitor the immunity against COVID-19 remains a matter of debate in the general population. However, the presence of SARS-CoV-2 IgG antibodies certify the previous or recent infection[17]. In our hospital, all health care workers (HCW) were tested for serology immediately after the first 2 mo of pandemic, in the same week of the start of our study on IBD cohort. 364 out of 1600 operators were diagnosed as affected by COVID-19 between February 21 and April 22 and all of them tested positive for SARS-CoV-2 swab throat test. Among the HCWs who were previously confirmed ill, the 99% resulted having IgG3 value > 7. Interestingly, 20% of operators who did not report symptoms suggestive for COVID-19 resulted having SARS-CoV-2 antibodies ≥ 7. (data from National Institute of Health, 2020). This observation confirms the presence of an unknown number of asymptomatic infected people[18]. The available studies on the serum concentration of IgG after

Table 1 Demographic, clinical and therapeutic characteristics of the inflammatory bowel disease cohort

Therapy	Characteristics (*n*, %)	Disease		Total (*n*)
		CD (*n*)	UC (*n*)	
Biologic treatment	Male (15, 41.6)	13	3	36
	Woman (20, 55.5)	15	5	
	BMI > 30 (5, 13.8)	3	2	
	BMI < 30 (31, 82.2)	25	6	
	Comorbidities yes (14, 38.8)	11	3	
	Comorbidities no (22, 61.2)	17	5	
	Age > 65 (5, 13.8)	2	3	
	Age < 65 (31, 86.2)	26	5	
Azathioprine	Male (9, 64.2)	3	6	14
	Woman (5, 35.7)	2	3	
	BMI > 30 (1, 7.1)	1	0	
	BMI < 30 (13, 92.8)	4	9	
	Comorbidities yes (6, 42.8)	2	4	
	Comorbidities no (8, 57.1)	3	5	
	Age > 65 (3, 21.4)	1	2	
	Age < 65 (11, 78.6)	4	7	
Mesalazine	Male (23, 43.4)	10	13	53
	Woman (30, 56.6)	11	19	
	BMI > 30 (6, 11.3)	2	4	
	BMI < 30 (47, 88.7)	19	28	
	Comorbidities yes (30, 56.6)	10	20	
	Comorbidities no (23, 43.3)	11	12	
	Age > 65 (19, 35.8)	10	9	
	Age < 65 (34, 64.2)	11	23	
		54	49	103

BMI: Body mass index; CD: Crohn's disease; UC: Ulcerative colitis.

COVID-19 infection revealed conflicting results and the duration of antibodies rises is currently unknown, but is estimated around 9 mo (data from National Institute of Health, 2021). There is a possible decrease of IgG title after the first two wk of infection and it is unclear whether the test is able to detect lower antibody levels in milder and asymptomatic COVID-19 disease[17-20]. Plebani group tried to harmonize the thresholds to allow a larger agreement on IgG anti Sars-Cov-2 antibodies determination. They found 6.2 KAU/L as the cut off for Diasorin method to reach a sensitivity of 97.1% and a specificity of 88.9% for the diagnosis of SARS-CoV-2 infection[16]. Our data are thus in line with this latter observation. The COVID-19 symptoms occurred in IBD patients at least 1 mo before the interview. During the time between the symptoms and the enrollment, they lived the complete lock down, established in Italy from March 9 to May 18. They tested all negative at the swab test performed at the enrollment. This is in line with the overall sensitivity of the test, ranging from 56 to 83%: 66.7% in the first week of the infection and lower in the following wk observation that the SARS-CoV-2 positivity in the swab[21].

Prevalence of patients with SARS-CoV-2 IgG positivity in our cohort was 18.4%. This means that those patients got infected with SARS-CoV-2 virus in the previous period, but only 63% of them developed the disease, reporting symptoms. Moreover, only one patient required hospitalization for pneumonia. The patients with history of COVID-19 related symptoms mainly had mild respiratory symptoms or minor manifestations. None but one patient (5%) required hospitalization, but without the need of intensive care unit. Conversely, in the general population, during both the first and the second

Table 2 Survey responses of 103 inflammatory bowel disease patients

Survey answers					
Close contacts with positive patients (*n*, %)		Yes	17, 16.5		
		No	85, 82.5		
		Nd	1, 1		
Tested for swab (*n*, %)		Yes	13, 12.5	Positive	1, 1
				Negative	12, 11.5
		No	90, 87.5		
Symptoms (*n*, %)	No symptoms		49, 47.5		
	Mild	Cough	19, 18.4		
		Changes in taste/smell	6, 5.8		
		Muscle and joint pain	12, 11.6		
		Asthenia	11, 10.6		
		Fever	18, 17.4		
		GI symptoms	23, 22.3		
	Severe	Mild dyspnea	4, 3.8		
		Pneumonia	1, 0.9		
Total number of patients (*n*)					103

GI: Gastrointestinal; Nd: Not determined.

Table 3 Severe acute respiratory syndrome coronavirus 2 IgG positive inflammatory bowel disease patients divided by presence or absence of COVID-19 symptoms and ongoing therapy

SARS-CoV-2 IgG value > 7				
SARS-CoV-2 IgG positive patients (*n*, %)	Therapy (patients, *n*, %)	Disease		Total *n* (%)
		CD (*n*)	UC (*n*)	
COVID-19 symptoms yes (12, 63.2)	Biologic drug (6, 50.0)	5	1	6
	Azathioprine (4, 33.3)	1	3	4
	Mesalazine (2, 16.6)	0	2	2
COVID-19 symptoms no (7, 36.8)	Biologic treatment (4, 57.1)	4	0	4
	Azathioprine (1, 14.3)	0	1	1
	Mesalazine (2, 28.6)	0	2	2
		12	7	19

CD: Crohn' s disease; COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; UC: Ulcerative colitis.

wave of the pandemic, 10% of people required hospitalization in intensive care unit (data from the National Institute of Health, 2021). Half of the IBD patients that resulted positive to antibody test remained asymptomatic and in 48% of cases they developed only mild symptoms. We can thus conclude that the IBD population does not seem at higher risk to develop severe COVID-19 disease in comparison with the general population, confirming the observation of Bezzio *et al*[9]. Only the patient with pneumonia hold the IBD treatment. This happened because, due to the mildness of the disease, the patients informed the general practitioner but not the IBD center about the symptoms. These data, even if do not confirm the American Gastroenterological Association guidelines strategy, gave us the opportunity to evaluate the cohort[1]. The results obtained are encouraging, as it seems that IBD patients with COVID-19 ongoing disease with symptoms could continue any treatments both avoiding IBD relapse and without a significant higher risk of developing severe COVID-19 requiring hospitalization. Differently from Bezzio *et al*[9], nobody died in our cohort; moreover, nor age neither active IBD

were significantly associated with a COVID-19 worse prognosis.

SARS-coV-2 serology resulted associated only with the ongoing IBD treatment. Among the patients having a positive serology there was a prevalence of biologic therapy. The presence of COVID-19 disease was associated with both IBD therapy and BMI. The patients who reported previous symptoms were treated with mesalazine in 2 cases, with AZA in 4 and with biological treatment in 6; the only patient with pneumonia was treated with AZA. The calculated relative risk of being infected was higher for patients treated with AZA, then for patients treated with biologic drugs and the lowest risk was found for patients treated with mesalazine. We decided to separate the different treatments in the analysis, as the AZA and the biologic therapy have a different mechanism of action: AZA is an immunosuppressive agent, whereas the biologic therapies are known as immunomodulating agents. None of the patients treated with biologic therapy developed a severe COVID-19 disease. Our results show that the use of biologic therapy does not seem to expose the patients to higher risk of severe COVID-19 disease, even when the infection is present. We did not perform a sub-analysis of the different type of biologic treatment for the small sample size. However, we report that the 80% of patients was treated with anti-TNF agents. More studies are needed to confirm whether it is appropriate to continue biological drugs for IBD patients who are affected with Sars-cov-2. The other variable associated with the presence of COVID-19 related symptoms was the BMI. This data is supported by the literature, as obesity is a factor associated with bad prognosis in the patients with COVID-19 pneumonia [22]. Interestingly, nor the old age neither the comorbidities or the type of IBD were associated with the antibody positivity or the development of COVID-19 symptoms in our study. This could be explained by the fact that these variables were associated in literature to death or very bad outcome, and none of our patients reported such complication[23].

All the 103 patients of the study had been clinically followed up for 10 mo after the beginning of the study. None of them hold the IBD treatments or developed new symptoms of COVID-19 until April 2021. After this period of time all our IBD patients had been received the vaccine against COVID-19.

The main limitation of the study is the small sample. Therefore, further studies with larger populations are needed to confirm our observations.

CONCLUSION

We investigated both the SARS-CoV-2 IgG positivity in symptomatic and asymptomatic IBD patients and the relationship between IBD therapy and COVID-19 disease severity. The results are interesting and seem encouraging for the patients treated with biologic therapy, since they don't seem to carry a high risk of developing severe COVID-19. However, further and larger studies are needed to confirm these observations.

ARTICLE HIGHLIGHTS

Research background
Guidelines recommend to hold inflammatory bowel diseases (IBD) biologic therapy during coronavirus disease 2019 (COVID-19). It is still not clear if the IBD patients carry a high risk of developing severe COVID-19.

Research motivation
IBD patients could carry a high risk of relapse or worsening of the intestinal disease in holding the therapy.

Research objectives
To investigate the prevalence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies positivity and COVID-19 disease severity in IBD patients. Evaluate the correlation with clinical/therapeutic variables.

Research methods
Prospective cohort study. Patients with IBD were consecutively enrolled from April 22nd to May 31st 2020. Age, sex, BMI, IBD type, treatments and clinical activity and other comorbidities were anonymously collected in a Database. Charlson Comorbidity Index was calculated for each patient. A single blood test was performed to each patient to search for Immunoglobulin IgG anti SARS-Cov-2. The LIAISON® SARS-CoV-2 S1/S2 IgG test [DiasorinS.p.A, Saluggia (VC) – Italy] was used according to manufacturers' instructions. The analysis was performed using SARS-CoV-2 IgG value cut off of > 7 kAU/L. All patients who resulted positive to SARS-CoV-2 IgG were tested with SARS-CoV-2 swab throat test during the same week, using the Allplex 2019-nCoV assay (Arrow Diagnostics S.r.l., Genova,

Italy) a single-tube assay able to detect the three target genes (E gene, RdRP gene and N gene) as in the WHO recommended protocols. Categorical variables were described as count and percentage and compared between groups with chi square test; continuous variables were described as mean and standard deviation or median and inter-quartile range if not normally distributed (Shapiro-Wilks test) and compared with independent t- test or Mann-Whitney. Through univariate and multivariate logistic regression models were assessed: association between age, sex, BMI, IBD type, IBD treatments, IBD clinical activity, Charlson Comorbidity Index and SARS-CoV-2 IgG positivity or the presence of COVID-19 symptoms.

Research results

103 IBD consecutive patients were enrolled: 54 with Crohn's disease and 49 ulcerative colitis. 36 patients (35%) were treated with biologic treatment, 14 (13.6%) with azathioprine (AZA) and 53 (51.4%) with mesalazine. 19 out of 103 patients (18.4%) had SARS-CoV-2 IgG positivity, with value > 7. Among them: 10 were under biological treatment, 5 under AZA and 4 under mesalazine. 12 out of 19 (63%) reported symptoms related to COVID-19 disease. Among them, 2 were treated with mesalazine, 4 with AZA and 6 with biologic treatment. Among the 7 out 19 patients without history of COVID-19 related symptoms, but positive for antibodies, 2 were treated with mesalazine, one with AZA and 4 with biologic therapy. All but one patient, who had pneumonia and was under AZA treatment, did not require hospitalization. All the patients with IgG > 7 were tested for swab throat test. All of them resulted negative at the enrollment. SARS-CoV-2 IgG value ≥ 7 correlated at multivariate analysis only with IBD treatment. The relative risk of having SARS-COV-2 IgG ≥ 7 was higher for patients treated with AZA and lower with mesalazine: odds ratio (OR) 1.44 (95%CI: 0.27-7.56) and 0.16 (95%CI: 0.03-0.71), for AZA and mesalazine, respectively, *vs* biologic drug ($P = 0.0157$ between them). The relative risk for patients under mesalazine was lower than for those under biologic therapy, $P = 0.016$. The presence of COVID-19 related symptoms resulted correlated at multivariate analysis with Body Mass Index (BMI), $P = 0.05$ and with IBD therapy. The relative risk of having symptoms was strongly higher for patients treated with AZA and lower with mesalazine *vs* biologic drug: odds ratio (OR) 7.47 (95%CI: 1.22-45.73) and 0.52 (95%CI: 0.17-1.72, $P = 0.03$), for AZA and mesalazine, respectively ($P = 0.004$ between them).

Research conclusions

The patients treated with biologic therapy don't seem to carry a high risk of developing severe COVID-19.

Research perspectives

The patients treated with biologic therapy don't seem to carry a high risk of developing severe COVID-19. Therefore, further and larger studies are needed to confirm these observations and to understand if the strategy to hold the IBD treatment during COVID-19 disease could be modified.

FOOTNOTES

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REFERENCES

1   **Rubin DT**, Feuerstein JD, Wang AY, Cohen RD. AGA Clinical Practice Update on Management of Inflammatory Bowel Disease During the COVID-19 Pandemic: Expert Commentary. *Gastroenterology* 2020; **159**: 350-357 [PMID: 32283100 DOI: 10.1053/j.gastro.2020.04.012]

2   **Cheung KS**, Hung IFN, Chan PPY, Lung KC, Tso E, Liu R, Ng YY, Chu MY, Chung TWH, Tam AR, Yip CCY, Leung KH, Fung AY, Zhang RR, Lin Y, Cheng HM, Zhang AJX, To KKW, Chan KH, Yuen KY, Leung WK. Gastrointestinal Manifestations of SARS-CoV-2 Infection and Virus Load in Fecal Samples From a Hong Kong Cohort: Systematic Review and Meta-analysis. *Gastroenterology* 2020; **159**: 81-95 [PMID: 32251668 DOI: 10.1053/j.gastro.2020.03.065]

3   **Ling Y**, Xu SB, Lin YX, Tian D, Zhu ZQ, Dai FH, Wu F, Song ZG, Huang W, Chen J, Hu BJ, Wang S, Mao EQ, Zhu L, Zhang WH, Lu HZ. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. *Chin Med J (Engl)* 2020; **133**: 1039-1043 [PMID: 32118639 DOI: 10.1097/CM9.0000000000000774]

4   **Zhang J**, Wang S, Xue Y. Fecal specimen diagnosis 2019 novel coronavirus-infected pneumonia. *J Med Virol* 2020; **92**: 680-682 [PMID: 32124995 DOI: 10.1002/jmv.25742]

5   **Wu Y**, Guo C, Tang L, Hong Z, Zhou J, Dong X, Yin H, Xiao Q, Tang Y, Qu X, Kuang L, Fang X, Mishra N, Lu J, Shan H, Jiang G, Huang X. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. *Lancet Gastroenterol Hepatol* 2020; **5**: 434-435 [PMID: 32199469 DOI: 10.1016/S2468-1253(20)30083-2]

6   **Ma C**, Cong Y, Zhang H. COVID-19 and the Digestive System. *Am J Gastroenterol* 2020; **115**: 1003-1006 [PMID: 32618648 DOI: 10.14309/ajg.0000000000000691]

7   **An P**, Ji M, Ren H, Su J, Ding NS, Kang J, Yin A, Zhou Q, Shen L, Zhao L, Jiang X, Xiao Y, Tan W, Lv X, Li J, Liu S, Zhou J, Chen H, Xu Y, Liu J, Chen M, Cao J, Zhou Z, Tan S, Yu H, Dong W, Ding Y. Prevention of COVID-19 in patients with inflammatory bowel disease in Wuhan, China. *Lancet Gastroenterol Hepatol* 2020; **5**: 525-527 [PMID: 32311321 DOI: 10.1016/S2468-1253(20)30121-7]

8   **Norsa L**, Indriolo A, Sansotta N, Cosimo P, Greco S, D'Antiga L. Uneventful Course in Patients With Inflammatory Bowel Disease During the Severe Acute Respiratory Syndrome Coronavirus 2 Outbreak in Northern Italy. *Gastroenterology* 2020; **159**: 371-372 [PMID: 32247695 DOI: 10.1053/j.gastro.2020.03.062]

9   **Bezzio C**, Saibeni S, Variola A, Allocca M, Massari A, Gerardi V, Casini V, Ricci C, Zingone F, Amato A, Caprioli F, Lenti MV, Viganò C, Ascolani M, Bossa F, Castiglione F, Cortelezzi C, Grossi L, Milla M, Morganti D, Pastorelli L, Ribaldone DG, Sartini A, Soriano A, Manes G, Danese S, Fantini MC, Armuzzi A, Daperno M, Fiorino G; Italian Group for the Study of Inflammatory Bowel Disease (IG-IBD). Outcomes of COVID-19 in 79 patients with IBD in Italy: an IG-IBD study. *Gut* 2020; **69**: 1213-1217 [PMID: 32354990 DOI: 10.1136/gutjnl-2020-321411]

10   **D'Amico F**, Danese S, Peyrin-Biroulet L. Systematic Review on Inflammatory Bowel Disease Patients With Coronavirus Disease 2019: It Is Time to Take Stock. *Clin Gastroenterol Hepatol* 2020; **18**: 2689-2700 [PMID: 32777550 DOI: 10.1016/j.cgh.2020.08.003]

11   **Neurath MF**. COVID-19 and immunomodulation in IBD. *Gut* 2020; **69**: 1335-1342 [PMID: 32303609 DOI: 10.1136/gutjnl-2020-321269]

12   **Buonaguro FM**, Puzanov I, Ascierto PA. Anti-IL6R role in treatment of COVID-19-related ARDS. *J Transl Med* 2020; **18**: 165 [PMID: 32290847 DOI: 10.1186/s12967-020-02333-9]

13   **Cortegiani A**, Ippolito M, Greco M, Granone V, Protti A, Gregoretti C, Giarratano A, Einav S, Cecconi M. Rationale and evidence on the use of tocilizumab in COVID-19: a systematic review. *Pulmonology* 2021; **27**: 52-66 [PMID: 32713784 DOI: 10.1016/j.pulmoe.2020.07.003]

14   **Monteleone G**, Ardizzone S. Are Patients with Inflammatory Bowel Disease at Increased Risk for Covid-19 Infection? *J Crohns Colitis* 2020; **14**: 1334-1336 [PMID: 32215548 DOI: 10.1093/ecco-jcc/jjaa061]

15   **Perkmann T**, Perkmann-Nagele N, Breyer MK, Breyer-Kohansal R, Burghuber OC, Hartl S, Aletaha D, Sieghart D, Quehenberger P, Marculescu R, Mucher P, Strassl R, Wagner OF, Binder CJ, Haslacher H. Side-by-Side Comparison of Three Fully Automated SARS-CoV-2 Antibody Assays with a Focus on Specificity. *Clin Chem* 2020; **66**: 1405-1413 [PMID: 32777031 DOI: 10.1093/clinchem/hvaa198]

16   **Plebani M**, Padoan A, Negrini D, Carpinteri B, Sciacovelli L. Diagnostic performances and thresholds: The key to harmonization in serological SARS-CoV-2 assays? *Clin Chim Acta* 2020; **509**: 1-7 [PMID: 32485157 DOI: 10.1016/j.cca.2020.05.050]

17   **Gaebler C**, Wang Z, Lorenzi JCC, Muecksch F, Finkin S, Tokuyama M, Cho A, Jankovic M, Schaefer-Babajew D, Oliveira TY, Cipolla M, Viant C, Barnes CO, Bram Y, Breton G, Hägglöf T, Mendoza P, Hurley A, Turroja M, Gordon K, Millard KG, Ramos V, Schmidt F, Weisblum Y, Jha D, Tankelevich M, Martinez-Delgado G, Yee J, Patel R, Dizon J, Unson-O'Brien C, Shimeliovich I, Robbiani DF, Zhao Z, Gazumyan A, Schwartz RE, Hatziioannou T, Bjorkman PJ,

Mehandru S, Bieniasz PD, Caskey M, Nussenzweig MC. Evolution of antibody immunity to SARS-CoV-2. *Nature* 2021; **591**: 639-644 [PMID: 33461210 DOI: 10.1038/s41586-021-03207-w]

18   **Grassia R**, Testa S, De Silvestri A, Drago A, Cereatti F, Conti CB. Lights and shadows of SARS-CoV-2 infection risk assessment in endoscopy. *Dig Liver Dis* 2020; **52**: 816-818 [PMID: 32601027 DOI: 10.1016/j.dld.2020.06.013]

19   **Melgaço JG**, Azamor T, Ano Bom APD. Protective immunity after COVID-19 has been questioned: What can we do without SARS-CoV-2-IgG detection? *Cell Immunol* 2020; **353**: 104114 [PMID: 32361409 DOI: 10.1016/j.cellimm.2020.104114]

20   **Long QX**, Liu BZ, Deng HJ, Wu GC, Deng K, Chen YK, Liao P, Qiu JF, Lin Y, Cai XF, Wang DQ, Hu Y, Ren JH, Tang N, Xu YY, Yu LH, Mo Z, Gong F, Zhang XL, Tian WG, Hu L, Zhang XX, Xiang JL, Du HX, Liu HW, Lang CH, Luo XH, Wu SB, Cui XP, Zhou Z, Zhu MM, Wang J, Xue CJ, Li XF, Wang L, Li ZJ, Wang K, Niu CC, Yang QJ, Tang XJ, Zhang Y, Liu XM, Li JJ, Zhang DC, Zhang F, Liu P, Yuan J, Li Q, Hu JL, Chen J, Huang AL. Antibody responses to SARS-CoV-2 in patients with COVID-19. *Nat Med* 2020; **26**: 845-848 [PMID: 32350462 DOI: 10.1038/s41591-020-0897-1]

21   **Zou L**, Ruan F, Huang M, Liang L, Huang H, Hong Z, Yu J, Kang M, Song Y, Xia J, Guo Q, Song T, He J, Yen HL, Peiris M, Wu J. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *N Engl J Med* 2020; **382**: 1177-1179 [PMID: 32074444 DOI: 10.1056/NEJMc2001737]

22   **Kassir R**. Risk of COVID-19 for patients with obesity. *Obes Rev* 2020; **21**: e13034 [PMID: 32281287 DOI: 10.1111/obr.13034]

23   **Yu C**, Lei Q, Li W, Wang X, Liu W. Epidemiological and clinical characteristics of 1663 hospitalized patients infected with COVID-19 in Wuhan, China: a single-center experience. *J Infect Public Health* 2020; **13**: 1202-1209 [PMID: 32718894 DOI: 10.1016/j.jiph.2020.07.002]