Journal of Gastroenterology and Hepatology

JGHF

doi:10.1111/jgh.15591

GASTROENTEROLOGY

Lower incidence of COVID-19 in patients with inflammatory bowel disease treated with non-gut selective biologic therapy

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Key words
Biologic therapy, COVID-19, Inflammatory bowel disease, SARS-CoV-2.

Accepted for publication 15 June 2021.

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Declaration of conflict of interest: C. B. received lecture fees from Takeda, AbbVie, and Janssen. S. S. received lecture fees and was an advisory board for Takeda and Janssen. L. P. received lecture fees from AbbVie, Takeda, Sandoz, and Janssen Pharmaceuticals and served as a member of the Advisory Board of Fresenius-Kabi. C. R. received lecture fees from AbbVie, Janssen Cilag, MSD, Recordati, and Takeda e Vifor. F. C. served as consultant to Mundipharma, AbbVie, MSD, Takeda, Janssen, Roche, and Celgene. F. C. received lecture fees from AbbVie, Ferring, Takeda, Allergy Therapeutics, and Janssen and unrestricted research grants from Giuliani, Sofar, MS&D, Takeda, and AbbVie. G. M. received lecture fees from Janssen-Cilag, Roche, Gilead, AbbVie, and Alfa-Sigma. S. A. served as a speaker, consultant, and/or advisory board member for the following organizations: AbbVie, MSD, Takeda, Janssen, Pfizer, Sandoz, and Enthera.

Abstract

Background and Aim: Since the outbreak of COVID-19, concerns have been raised as to whether inflammatory bowel disease (IBD) patients under biologic therapy may be more susceptible to the disease. This study aimed to determine the incidence and outcomes of COVID-19 in a large cohort of IBD patients on biologic therapy.

Methods: This observational retrospective multicenter study collected data about COVID-19 in IBD patients on biologic therapy in Italy, between February and May 2020. The main end-points were (i) to assess both the cumulative incidence and clinical outcome of COVID-19, according to different biologic agents and (ii) to compare them with the general population and a cohort IBD patients undergoing non-biologic therapies.

Results: Among 1816 IBD patients, the cumulative incidence of COVID-19 was 3.9 per 1000 (7/1816) with a 57% hospitalization rate and a 29% case-fatality rate. The class of biologic agents was the only risk factor of developing COVID-19 ($P = 0.01$). Non-gut selective agents were associated with a lower incidence of COVID-19 cases, related symptoms, and hospitalization ($P < 0.05$). Compared with the general population of Lombardy, an overall lower incidence of COVID-19 was observed (3.9 *vs* 8.5 per 1000, $P = 0.03$). Compared with 565 IBD patients on non-biologic therapies, a lower rate of COVID-19 symptoms was observed in our cohort (7.5% *vs* 18%, $P < 0.001$).

Conclusions: Compared with the general population, IBD patients on biologic therapy are not exposed to a higher risk of COVID-19. Non-gut selective agents are associated with a lower incidence of symptomatic disease, supporting the decision of maintaining the ongoing treatment.

Author contributions: S. A., F. F., and G. M. are responsible for the planning of the study, drafting of the article, statistical analysis, and interpretation of data. All other authors performed data collections and critical revision of article for important intellectual content. All authors approved the final version of the manuscript including authorship list.

Financial support: Nothing to disclose.

Guarantor of the article: Francesca Ferretti, MD.

Introduction

Since the outbreak of the pandemic caused by the novel severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), Italy was one of the earliest and most affected countries.[1] In particular, since its first case on February 20, 2020, Lombardy was the hardest hit Italian region with 85 775 confirmed cases and 15 662 deaths on the May 20, 2020.[2] Although in over 80% of cases COVID-19 (COronavirus DIsease 2019) may have an asymptomatic or mild clinical course, older age and pre-existing chronic diseases such as hypertension, diabetes, cardiovascular diseases, and obesity are risk factors for the development of severe forms and possible fatal outcome.[3,4]

Inflammatory bowel disease (IBD) is a disabling chronic relapsing condition that includes ulcerative colitis (UC) and Crohn's disease (CD). Along with other rheumatologic and dermatologic conditions, IBD belongs to the group of immune-mediated inflammatory diseases, affecting millions of individuals worldwide and sustained by an exaggerated cytokine response.[5] Indeed, cytokine blockers, such as anti-tumor necrosis (TNF) factors (infliximab, adalimumab, and golimumab) and anti-interleukin (IL)-12/23 (ustekinumab) as well as gut-selective integrin inhibitors (vedolizumab and etrolizumab) have been developed for inducing and/or maintaining remission.[6] Unfortunately, the use of biologic agents is notably associated with an increased risk of bacterial and viral infections.[7] Thus, although early studies have not reported an overall higher risk of SARS-CoV-2 infection in IBD patients,[8–10] the use of biologic agents in the COVID-19 era posed major challenges for clinicians in the management of these patients. Even if data regarding the incidence and clinical outcome of COVID-19 in patients with IBD on immunosuppressive and biologic therapies are included in recent studies,[11,12] a specific analysis focusing uniquely on patients undergoing different biologic agents is lacking.

Given these premises, the present study aimed at evaluating the incidence and outcome of COVID-19 in a large cohort of IBD patients on biologic therapy, coming from one of the earliest and most extensively hit regions in Europe.

Methods

This is an observational retrospective multicenter study collecting data about COVID-19 incidence and outcomes in IBD patients on biologic therapy, coming from 11 IBD referral units in Lombardy, one of the hardest hit Italian region, since the outbreak of the pandemic in Italy on February 20 until May 20, 2020.

Eligible patients were adults with a confirmed diagnosis of IBD who had been treated with any of the currently available biologic therapies for at least 2 months. All had undergone either a follow-up visit or were contacted by phone/email during the period of observation to check their clinical conditions.

The primary end-points of this study were (i) to assess both the cumulative incidence of COVID-19 and the main clinical outcome of infection (hospitalization/death) in this cohort of IBD patients and (ii) to identify differences among the available biologic agents. The secondary end-points were (i) to compare the incidence of COVID-19 with that of the general population of Lombardy and (ii) to compare the reported symptoms in our cohort of IBD patients on biologic therapy with a second cohort of IBD patients on non-biologic therapies, coming from the same geographic area.[2,13–16]

A definite diagnosis of COVID-19 was established either by a positive nucleic acid assay with real-time polymerase chain reaction on nasopharyngeal swab or positive SARS-CoV-2 serology assay and/or hospitalization for COVID-19-related pneumonia, the latter defined by typical computed tomography findings of COVID-19 infection. Patients were considered negative if they were not tested or had a negative swab and/or serological test. Suggestive symptoms of COVID-19 during the period of interest included fever, respiratory symptoms (cough and/or dyspnea), dysosmia, and/or dysgeusia.

Data for the general population of Lombardy were obtained from regional registries (data were not matched as individual data were not retrievable).[2,13] Data on the second cohort of IBD patients on non-biologic therapies were obtained from a larger study, recently published,[14] enquiring the onset of COVID-19-related symptoms by means of self-reported questionnaires during the same period.

Data were retrieved retrospectively from medical records, and anonymous data were entered in an electronic database accessible to the participating centers; thus, the need for consent was waived. The local Ethics Committee approved the study before starting (n. 2020/ST/062).

Statistical analysis. Demographic and clinical data were expressed as numbers or percentages for discrete variables and as median and interquartile range for continuous variables. Cumulative incidence of COVID-19 was calculated as "number of cases/overall population". The hospitalization rate was expressed as the ratio "number of hospitalized patients/number of cases" and the case-fatality rate (CFR) as "number of deaths/number of cases." The comparison between rates was expressed as relative risk and its 95% confidence interval (95% CI). Bivariate analysis was performed with χ^2 or Fisher's exact tests as required. Univariate analysis was performed with logistic regression and odds ratios (ORs) were calculated. For adjusted analysis, we performed multivariable regression models including age, gender, disease phenotype, pulmonary and cardiovascular comorbidities, and any other significant variable at univariate analysis. A $P < 0.05$ value was considered statistically significant. When variables were not available for some patients, these were excluded for percentage calculation. Statistical analyses were performed using GRAPHPAD PRISM (version 8.00 for Windows, GraphPad Software, La Jolla, California, USA) and IBM SPSS Statistics (release 23; IBM Corporation, USA).

Results

There were 1816 IBD patients included for analyses. Mean age was 45 years, and 998 were male patients. Of them, 1177 were CD, 626 UC, and 13 IBD-U, with a median duration of disease of 10 years. They were all on biologic therapy, including 481 on intravenous anti-TNF, 782 on subcutaneous anti-TNF, 398 on Vedolizumab, 144 on Ustekinumab, and 11 on others (etrolizumab, mirikizumab, and risankizumab).

Of them, seven patients had a definite COVID-19 diagnosis made by nasopharyngeal swab in five cases and SARS-CoV-2

serology assay in two, with an incidence of 3.9 per 1000. Among them, four patients were hospitalized for COVID-19 pneumonia documented by radiological exams (X-ray and chest computed tomography-scan). Of these, two patients died from complications, one survived after non-invasive ventilation therapy, and one had a milder course. Thus, the hospitalization rate was 57% (4/7) and the CFR was 29% (2/7). Globally, nasopharyngeal swab and/or serological tests for SARS-CoV-2 identification were available in 52 and 5 patients, respectively. Clinical details of COVID-19 cases are reported in Table 1. Only one patient (#4) had a concomitant active IBD and ongoing steroid treatment at the onset of COVID-19. Moreover, we collected also data about referred symptoms during the same period of observation in roughly two-thirds of the IBD patients on biologic therapy (1120/1816 patients). Of them, 84/1120 (7.5%), including the seven patients with a confirmed diagnosis, reported at least one of the following symptoms: fever (60%), respiratory symptoms (59%), and/or dysosmia/dysgeusia (23%).

As reported in Table 2, the univariate analysis demonstrated that in our cohort of IBD patients, only the type of ongoing biologic therapy affected the risk of developing COVID-19. In particular, the treatment with non-gut-selective agents (anti-TNF, ustekinumab, mirikizumab, and risankizumab) was associated with a lower risk of COVID-19 (OR 0.1, 95% CI 0.1–0.6, $P = 0.01$). No differences were observed among patients on anti-TNF and on ustekinumab.

Table 1 Demographic characteristics, clinical data, and outcome of IBD patients who developed COVID-19 on biologic therapy

Patient	IBD type	IBD duration (years)	Therapy	Comorbidities	Diagnosis	Symptoms	Hospitalization	Clinical course	Outcome
#1 78, F	CD	12	Vedolizumab	COPD, AF, arterial hypertension, obesity	Swab	Fever, respiratory symptoms	Yes	Interstitial pneumonia	Dead
#2 26, M	CD	11	Adalimumab	None	Swab	Fever, respiratory symptoms	Yes	Interstitial pneumonia, acute kidney injury	Recovered
#3 65, F	UC	1	Vedolizumab, 5-ASA, steroids	None	Swab	Fever, respiratory symptoms	Yes	Interstitial pneumonia, NIV therapy	Recovered
#4 68, F	UC	15	Vedolizumab	None	Serology	Mild respiratory symptoms	No	—	Recovered
#5 39, M	UC	14	Vedolizumab	None	Swab	Fever, respiratory symptoms	No	—	Recovered
#6 56, M	UC	26	Vedolizumab	None	Swab	Fever, respiratory symptoms	Yes	Interstitial pneumonia, ICU admission, tracheal intubation	Dead
#7 47, F	CD	6	Ustekinumab	Arterial hypertension	Serology	Mild respiratory symptoms	No	—	Recovered

5-ASA, 5-aminosalicylic acid; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; CD, Crohn's disease; F, female; IBD, inflammatory bowel disease; M, male; UC, ulcerative colitis.

Table 2 Univariate analysis of clinical variables predicting the risk of COVID-19 in our cohort of IBD patients on biologic therapy

	Cases of COVID-19	Controls	Univariate analysis		
			OR	95% CI	*P*
N	7	1809	—	—	—
Age, mean ± standard deviation	55 ± 18	45 ± 14	1.0	1.0–1.1	0.09
Male pts, *n* (%)	3 (43)	994 (55)	0.6	0.1–2.8	0.52
CD, *n* (%)	3 (43)	1174 (62)	0.4	0.1–1.8	0.23
Smokers, *n* (%)[†]	3 (43)	338 (31)	3.3	0.6–20	0.19
Disease duration, mean ± standard deviation	12 ± 8	12 ± 9	1.0	0.9–1.1	0.99
Non-gut-selective therapy, *n* (%)	2 (29)	1414 (78)	0.1	0.1–0.6	0.01
Comorbidities[†]					
Pulmonary	1 (14)	45 (3)	5.6	0.6–48.9	0.12
Cardiovascular	2 (29)	159 (12)	3.6	0.6–19.7	0.14

[†]When variables were not available for some patients, these were excluded for percentage calculation.
CI, confidence interval; IBD, inflammatory bowel disease; OR, odds ratio.

Thus, we analyzed the two groups of patients on gut-selective and non-gut-selective therapy, separately. Clinical and demographic parameters are reported in Table 3. Compared with gut-selective drugs, non-gut selective anti-cytokine therapies were statistically associated with a lower rate of COVID-19 cases (1.4% *vs* 12.5%, $P = 0.01$), COVID-19 symptoms (6% *vs* 10%, $P = 0.01$), and hospitalization (0.1% *vs* 0.7%, $P = 0.04$). Although an older age and a higher rate of cardiopulmonary comorbidities were observed in patients on gut-selective treatment, the association with the lower incidence of COVID-19 and referred symptoms was maintained even after adjustment with the multivariate model (Table 4). Notably, no deaths were reported in the non-gut selective group, while two in the gut-selective group.

When compared with data of the general population in Lombardy (Table 3), the same geographic area of provenance of our cohort, a significant lower cumulative incidence of COVID-19 was observed among IBD patients (3.9 *vs* 8.5 per 1000, $P = 0.03$). Conversely, the outcome of COVID-19 was comparable in terms of both hospitalization rate (57% *vs* 50%, $P = 0.71$) and CFR (29% *vs* 18%, $P = 0.56$).

The data about COVID-19-related referred symptoms were compared with a second cohort of 565 IBD patients treated with non-biologic conventional therapies (Table 4). A significantly lower rate of symptoms was observed in patients on biologic therapy (7.5% *vs* 18%, $P < 0.001$), even when considering any symptom individually ($P < 0.001$).

Discussion

In this multicenter study assessing the incidence of COVID-19 in a large cohort of IBD patients on biologic therapy during the first 2 months of the pandemic, we found an overall incidence of 3.9 cases per 1000 patients. Notably, 5 of the 7 (71%) COVID-19 cases were diagnosed in patients undergoing vedolizumab therapy. Indeed, gut-selective agents were associated with an increased risk of COVID-19 compared with non-gut selective therapies. It could be speculated that the suppression of the cytokine driven-inflammatory response by systemic cytokine blockers could be effective, not only for dampening mucosal inflammation in IBD but also in preventing COVID-19 inflammatory complications associated with the hyper-activation of T cells and the massive production of IL-2, IL-6, TNF, and interferon-γ during the "cytokine storm."[17,18] Consistently, with these findings, cytokine blockers and JAK inhibitors have been evaluated as potential therapies in COVID-19 cases with hyperinflammation and acute respiratory distress syndrome.[19] Moreover, a case report recently described the efficacy of Infliximab during an IBD flare with concomitant COVID-19 pneumonia.[20] Our study further strengthens these hypotheses by evaluating and comparing the effect of all biologic agents currently available on COVID-19. In fact, differently from vedolizumab and etrolizumab, which are known for their gut-selective effect,[21,22] a protective role of other anti-cytokine drugs in the development of symptomatic COVID-19 was

Table 3 Main clinical and demographic characteristics of IBD patients and the general population of Lombardy and COVID-19 incidence and outcomes

	IBD patients on biologics	General population of Lombardy	*P*	IBD patients on non-gut selective drugs (IV anti-TNF, SC anti-TNF, ustekinumab, mirikizumab, risankizumab)	IBD patients on gut-selective drugs (vedolizumab, etrolizumab)	*P*
Overall, *n*	1816	10 103 969	—	1416	400	—
IBD classification, *n* (%)						<0.01
CD	1177 (65)	—	—	1009 (71)	169 (42)	
UC	626 (34)	—	—	398 (28)	228 (57)	
IBD-U	13 (1)	—	—	9 (1)	3 (1)	
Male, *n* (%)	998 (55)	4 950 945 (49)	<0.01	778 (55)	220 (55)	0.7
Age, median (IQR), years	45 ± 15	44.7 ± NA	NA	43 (31–53)	50 (37–62)	<0.01
Duration of disease, median (IQR), years	10 (5–18)	—	—	10 (5–18)	10 (5–17)	0.45
Smokers, *n* (%)[†]	201 (15)	1 747 675 (17)	0.03	171 (16)	30 (10)	0.02
Comorbidities, *n* (%)[†]						
Pulmonary	46 (3.5)	NA	—	27 (3)	19 (7)	<0.01
Cardiovascular	161 (12.3)	—	—	120 (11)	41 (16)	0.04
COVID-19 cases, *n* (%)	7 (0.4)	85 481 (0.8)	0.03	2 (0.1)	5 (1.3)	0.01 (0.04)[‡]
COVID-19 symptoms, *n* (%)[†]	—	—	—	58 (6)	26 (10)	0.01 (0.01)[‡]
COVID-19 hospitalization, *n* (%)	4 (57)	42 942 (50)	0.71	1 (0.1)	3 (0.7)	0.04 (0.09)[‡]
COVID-19 death, *n* (%)	2 (29)	15 597 (18)	0.56	0 (0)	2 (0.5)	NA

COVID-19 symptoms included fever, respiratory symptoms (cough and/or dyspnea), and dysosmia and/or dysgeusia.

[†]When variables were not available for some patients, these were excluded for percentage calculation.

[‡]After adjustment in the multivariate model including age, gender, IBD type, and comorbidities.

CD, Crohn's disease; IBD, inflammatory bowel disease; IBD-U, unclassified inflammatory disease; IQR, interquartile range; IV, intravenous; NA, not available; ns, not significant; SC, subcutaneous; TNF, tumor necrosis factor; UC, ulcerative colitis.

Table 4 Comparison between referred COVID-19-related symptoms among IBD patients on biologic and non-biologic therapies

	IBD patients on biologic therapy	IBD patients on non-biologic therapy	*P*
Subjects, *n*	1816	565	
Male, *n* (%)	998 (55)	276 (49)	0.01
Age, mean ± standard deviation, years	45 ± 15	51 ± 15	<0.01
IBD classification, *n* (%)			
CD	1177 (65)	281 (50)	<0.01
UC	626 (34)	284 (50)	
IBD-U	13 (1)		
Duration of disease, median (IQR), years	10 (5–18)	16 (6–26)	<0.01
Comorbidities, *n* (%)[†]			
Pulmonary	46 (3.5)	34 (6)	0.02
Cardiovascular	161 (12.3)	118 (21)	<0.01
COVID-19-related symptoms, *n* (%)	84 (7.5)	104 (18)	<0.001
Fever, *n* (%)	51 (4.6)	101 (17.9)	<0.001
Respiratory symptoms, *n* (%)	49 (4.4)	61 (10.8)	<0.001
Dysosmia and/or dysgeusia, *n* (%)	19 (1.7)	25 (4.4)	<0.001

[†]When variables were not available for some patients, these were excluded for percentage calculation.

CD, Crohn's disease; IBD, inflammatory bowel disease; IBD-U, unclassified inflammatory disease; IQR, interquartile range; UC, ulcerative colitis.

observed, considering the lower incidence of SARS-CoV-2 infection and reported symptoms in this subset of patients, even after adjustment in a multivariate model. However, it is correct to presume that the difference could also be partially influenced by older age and cardiopulmonary comorbidities, which are more frequently observed in patients treated with vedolizumab as reported in Table 3, thus requiring validation in future studies.

The main strength of our study consists in the fact that we report data regarding a large series of IBD patients treated with biologic agents and coming from the earliest and most affected region in Europe, including provinces with the highest fatality rates, such as Bergamo, Brescia, and Milan. The large number of patients allowed a comparison among the different classes of biologic agents currently in use. Of course, the major limitation of the study is that IBD patients have not been systematically tested for COVID-19. Hence, COVID-19 might have been underdiagnosed, especially in patients who presented typical symptoms but were not tested with swab and/or serology. However, the same bias can be applied to the general population, especially in the first months of pandemic, making them comparable. Moreover, all patients treated with biological drugs are closely and regularly monitored and should follow a specific hospital triage protocol, including a COVID-19 questionnaire, body temperature scan, and a "clean" route of access to the ward.[23] Finally, these preventive measures, as well as the awareness of "frailty" in IBD patients and the possibility of subcutaneous administration at home of some biologics, could have affected the exposure to the virus and minimized the risk of contagion.

Bearing in mind the abovementioned limitations, the overall cumulative incidence of COVID-19 in our cohort of IBD patients under biologic therapy was significantly lower than that of the general population of Lombardy. It is not possible to exclude that demographic or environmental factors such as age, smoking status, or comorbidity rate could partially influence this difference. Unfortunately, the exact percentage of the general population of Lombardy undergoing biologic therapy was not available. Nonetheless, it is reasonable to assume the number to be exiguous and, therefore, not affect the comparison obtained in our study. Moreover, this result is consistent with Taxonera *et al*.,[24] who reported a lower standardized risk of COVID-19 in IBD patients (12/1912, of whom only 36.6% on immunosuppressants and/or biologics). Similarly, in a nationwide cohort of IBD patients in the Veterans' Affairs Healthcare System, Khan *et al*.[25] found that only 2/2391 (0.84 × 1000) IBD patients under thiopurines and 3/4920 (0.61 × 1000) on anti-TNF therapy developed COVID-19 without observing an association between treatment and increased risk of infection.

Nevertheless, despite a lower incidence of infection, IBD patients on biologic therapies who developed COVID-19 showed a hospitalization rate and a CFR comparable with that of the general population. Likewise, the prospective observational study of Bezzio *et al*. demonstrated that only active IBD, old age, and comorbidities, but not IBD treatments, were associated with a worse prognosis and clinical course of COVID-19.[26] In addition, a study by Brenner *et al*., based on a large international registry, demonstrated no correlation between TNF antagonist therapy and severe forms of COVID-19.[27]

Lastly, the comparison between patients undergoing non-biologic conventional therapy and those under biologic treatment demonstrated a lower incidence of typical symptoms associated with COVID-19 in the latter group. Thus, even if these data are presumably weakened by the limitation of the self-report and affected by the demographic differences among the two cohorts of patients (Table 4), our result confirm the recent post-hoc analysis of SECURE-IBD demonstrating that the use of thiopurine monotherapy and mesalamine/sulfasalazine are associated with an increased risk of severe COVID-19.[12] Analogously, the same association has been observed in IBD patients on corticosteroids[18]; however, their effect on COVID-19 is still debatable, as dexamethasone showed a protective effect on mortality in the RECOVERY trial and corticosteroids are currently recommended by the more recent WHO guidelines in the management of severe COVID-19.[28,29] It could be hypothesized that the use of corticosteroids in IBD patients implies an underlying active disease, which would affect the outcome of the patient.[26] Unfortunately, even if a state of remission is presumable in most of our patients, the lack of specific information about disease activity in our dataset limited the analysis, and future studies are warranted.

In conclusion, the results of this large case series confirm that IBD patients on biologic therapy are not exposed to an overall higher risk of COVID-19. Moreover, compared with gut-selective agents, non-gut selective therapies are associated with a lower incidence of symptomatic SARS-CoV-2 infection and a lower rate of COVID-19 typical symptoms, supporting clinicians in advising patients with IBD about the necessity to maintain

and adhere to their treatment plan in order to prevent acute flares. Further research is warranted to evaluate the potential therapeutic role of anti-cytokines agents in COVID-19.

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