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Brief Report - Clinical

IBD Flare in the COVID-19 Pandemic: Therapy Discontinuation Is to Blame

Cristina Bezzio, MD, PhD,[*] Gionata Fiorino, MD, PhD,[†] Davide G. Ribaldone, MD, PhD,[‡] Alessandro Armuzzi, MD, PhD,[§,¶] Simone Saibeni, MD, PhD,[*] and the IG-IBD COVID-19 Study Group

From the *Gastroenterology Unit, Rho Hospital, ASST Rhodense, Rho, Italy;
[†]Gastroenterology and Endoscopy, IRCCS Ospedale San Raffaele, University Vita-Salute San Raffaele, Milan, Italy;
[‡]Division of Gastroenterology, Department of Medical Sciences, Università di Torino, Turin, Italy;
[§]IBD Unit, IRCCS Humanitas Research Hospital, Rozzano, Italy; and
[¶]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Italy.

*Address correspondence to: Cristina Bezzio, MD, PhD, Gastroenterology Unit, Rho Hospital, ASST Rhodense, Corso Europa 250, 20017 Rho, Milan, Italy (cribezzio03@yahoo.it).

Lay Summary

This prospective case-control study investigated the impact of severe acute respiratory syndrome coronavirus 2 infection on inflammatory bowel disease course and looked for risk factors associated with flares. In the severe acute respiratory syndrome coronavirus 2 pandemic era, inflammatory bowel disease course is not influenced by infection, while therapy discontinuation is a risk factor for disease flare.

INTRODUCTION

The relationship between viral infections and inflammatory bowel disease (IBD) is not fully understood. It is known that viral gastrointestinal infections trigger IBD development.[1] It is also known that patients with IBD are at increased risk of viral infection, especially if they are being treated with immunosuppressants, biologic agents, or small-molecule drugs.[2] Moreover, viral infections, not only of the gastrointestinal tract (eg, influenza), may induce an IBD flare.[3] Furthermore, temporary or prolonged withdrawal of therapy, as may happen during a viral infection, can lead to a flare-up of the disease.[4]

In the past 2 years, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has spread around the world. The outcome of this viral infection in patients with IBD has been widely evaluated considering patients' different clinical and demographic characteristics and different IBD therapies.[5] On the contrary, the impact of the viral infection on IBD course and treatment delivery has only been partially evaluated.[4,6-9] Therefore, this study investigated the impact of SARS-CoV-2 infection on IBD course and looked for risk factors associated with flares of disease.

METHODS

Study design

This was a prospective, multicenter, nationwide case-control study. The study protocol was approved by the Coordinating Ethical Committee and the ethics committees of participating centers.

Patients

Patients were enrolled from March 11, 2020, to June 31, 2020, and followed until death or at least 6 months. Patients were eligible for the study if they had (1) an established diagnosis of Crohn's disease (CD) or ulcerative colitis (UC) for at least 6 months and (2) a SARS-CoV-2 infection, defined as the polymerase chain reaction–confirmed presence of SARS-CoV-2 genome in a nasopharyngeal swab. Control subjects were patients with IBD without a SARS-CoV-2 infection; they were matched for sex, age, diagnosis (CD or UC), therapy, and disease activity.

For all enrolled patients, we collected the following data from medical charts: age, sex, current smoking habit (yes/no), comorbidities, IBD type (CD or UC), disease duration, and IBD treatments. Furthermore, we also registered IBD therapy delay or discontinuation and IBD activity.

Definitions

Disease activity was defined as remission, mild, moderate, or severe according to the partial Mayo score for UC and the Harvey-Bradshaw index for CD. Patients were considered in remission at enrollment if, in the previous 6 months, they were asymptomatic and did not require any change in therapy.

In order to attribute modification of IBD activity to a real flare, endoscopic and ultrasonographic assessments were performed. Disease flare was defined as the transition from remission to any degree of active disease. Disease worsening was defined as the transition from any degree of activity to a higher degree. Therapy delay was defined as a postponement of treatment by at least 14 days.

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Statistical analysis

Differences in quantitative variables at baseline were tested for significance using the Mann-Whitney *U* test. Associations among categorical variables were tested for significance using Fisher's exact test. A two-tailed $P < .05$ indicated statistical significance. Risk factors for worsening of disease activity were identified by logistic regression with univariate and multivariate analyses.

RESULTS

Patients

The study consecutively enrolled 219 patients with IBD (UC = 127, 58.0%) with a diagnosis of SARS-CoV-2 infection and 219 patients with IBD without viral infection (Table 1). Patients were followed for a mean period of 7.8 ± 1.2 months. During the follow-up, 7 patients with SARS-CoV-2 infection died; of these patients, 4 were in clinical remission and 3 had mild IBD activity.

Disease flare

The rate of disease flare among patients with IBD in remission at enrollment was not significantly different between those with SARS-CoV-2 infection (n = 28 of 118, 23.7%) and those without viral infection (n = 25 of 137, 18.3%) ($P = .35$). The rate of disease worsening among patients with IBD with mild-to-moderate disease activity at enrollment was not significantly different between those with SARS-CoV-2 infection (n = 16 of 85, 18.2%) and those without viral infection (n = 11 of 79, 13.9%) ($P = .53$). Overall, excluding the 7 patients who died and patients with severe disease at enrollment, the rate of disease flare or worsening was not significantly different between patients with IBD with SARS-CoV-2 infection (n = 44 of 203, 21.7%) and those without viral infection (n = 36 of 216, 16.7%) ($P = .19$).

TABLE 1. Baseline characteristics of patients with IBD and SARS-CoV-2 infection (cases) and matched patients with IBD but without SARS-CoV-2 infection (controls)

Characteristic	Cases (n = 219)	Controls (n = 219)
Age, y	45 (18-80)	46 (19-85)
Sex		
Male	119 (54.3)	119 (54.3)
Female	100 (45.7%)	100 (45.7%)
Current smoker	37 (16.9)	47 (21.4)
IBD diagnosis		
Ulcerative colitis	127 (58.0)	127 (58.0)
Crohn's disease	92 (42.0)	92 (42.0)
Disease duration, y	12 (1-43)	12 (1-49)
Disease activity		
Remission	122 (55.7)	137 (62.6)
Mild	53 (24.2)	54 (24.7)
Moderate	35 (16.0)	25 (11.4)
Severe	9 (4.1)	3 (1.4)
Therapy[a]		
None	17 (7.8)	15 (6.8)
Salicylates	111 (50.7)	110 (50.2)
Corticosteroids	22 (10.0)	16 (7.3)
Immunomodulators	22 (10.0)	21 (9.8)
TNF antagonists	76 (34.7)	69 (31.5)
Vedolizumab	33 (15.1)	35 (16.0)
Ustekinumab	10 (4.6)	13 (5.9)
Anti-IL-23	2 (0.9)	2 (0.9)
Other not biologics	2 (0.9)	2 (0.9)
Any comorbidity	107 (48.8)	99 (45.2)

Values are median (range) or n (%). No significant difference in any quantitative and categorical variable was found between cases and controls.
Abbreviations: IBD, inflammatory bowel disease; IL, interleukin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF, tumor necrosis factor.
[a]Some patients were receiving more than 1 therapy at de-enrollment.

Therapy discontinuation

Overall, 125 patients delayed or discontinued IBD therapy. The rate of delay or discontinuation was significantly higher in patients with IBD and SARS-CoV-2 infection (n = 95 of 202, 47.0%) than in those without viral infection (n = 30 of 204, 14.7%) ($P < .0001$). Among the 95 patients with IBD and SARS-CoV-2 infection, 56 postponed or stopped therapy on a physician's indication, with 39 by personal decision; among the 30 patients with IBD without infection, 2 delayed or discontinued therapy on a physician's indication, with 28 by personal decision.

The reasons for delaying or discontinuing therapy were the following: active SARS-CoV-2 infection (n = 69, 55.2%), anxiety about catching the viral infection (n = 21, 16.8%), concerns that IBD medications could increase the risk of having severe coronavirus disease 2019 (COVID-19) (n = 19, 15.2%), and difficulties accessing a hospital or pharmacy (n = 16, 12.8%).

The rate of delayed or discontinued biologic therapy for any reason was significantly higher in patients with IBD and SARS-CoV-2 infection (n = 67 of 121, 55.4%) than in those without viral infection (n = 15 of 119, 12.6%) ($P < .0001$). Overall, considering the 240 patients who were in treatment with biologics at enrollment, the rate of disease flare or worsening was significantly higher in those who delayed or discontinued therapy (n = 29 of 50, 58.0%) than in those who did not delay or discontinue therapy (n = 53 of 190, 27.9%) ($P < .001$).

At multivariate analysis (Table 2), a delay or discontinuation of therapy was the only factor that was significantly associated with a worsening of disease activity (odds ratio, 4.18; 95% confidence interval, 2.12-8.25; $P < .0001$).

TABLE 2. Multivariate analysis of factors possibly associated with a worsening of disease activity

Variable	Odds Ratio	95% CI	*P*
SARS-CoV-2 infection = 1	1.4755	0.9016-2.4149	.1217
Therapy discontinuation = 1	4.1820	2.1192-8.2529	<.0001
Male = 1	0.9336	0.5713-1.5256	.7840
Age >60 y = 1	1.0837	0.6090-1.9286	.7845
Smoking = 1	1.2783	0.6858-2.3829	.4396
CD = 1	0.9777	0.5921-1.6144	.9299
Disease duration	1.0226	0.9973-1.0485	.0801

Abbreviations: CD, Crohn's disease; CI, confidence interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

DISCUSSION

This study found that the rate of worsening of IBD activity was not different in patients with SARS-CoV-2 infection compared with patients without infection. On the other hand, the rates of IBD therapy delay or discontinuation were significantly higher in patients with SARS-CoV-2 infection than in patients without infection. Furthermore, a delay or discontinuation of biologic therapy was significantly associated with a worsening of disease activity regardless of SARS-CoV-2 infection.

A few studies investigated the impact of SARS-CoV-2 infection on IBD clinical course. One longitudinal observation study of 6 months showed no long-lasting impact of COVID-19 on IBD activity,[6] while a retrospective study demonstrated that patients with IBD and COVID-19 had a higher risk of IBD flare than patients with IBD without COVID-19 at the 3-month COVID-19 follow-up.[7] The rate of flare or worsening of IBD activity in our study is higher than previously reported[6-8]: this difference may be attributable to the longer follow-up in our study and to different definitions of IBD flare across the studies. Furthermore, two studies investigated IBD therapy delay or discontinuation during SARS-CoV-2 infection, and reported rates of 27% and 87%.[8,9] The differences may depend on definitions, length of observation, different pandemic situations, and different socioeconomic contexts.

The strengths of this study are its large sample size, prospective nature, and rigorous case-control study design. This study also has limitations, namely the relatively short follow-up period and a potential overlap between gastrointestinal symptoms due to SARS-CoV-2 infection and to actual IBD flare, although we used objective measures of inflammation to confirm all disease flares.

CONCLUSIONS

IBD course does not seem to be influenced by SARS-CoV-2 infection, while therapy discontinuation seems to be a risk factor for disease flare or worsening regardless of viral infection. Therefore, this study showed that discontinuation of therapy is associated with IBD flares and corroborates the recommendations of the ECCO-COVID Taskforce,[10] namely "Don't reduce the dose of immunomodulators or biologics to prevent SARS-CoV-2 infection" and "Do continue" immunomodulators, biologics, and JAK inhibitors.

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Conflicts of Interest

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