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

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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. 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. Moreover, viral infections, not only of the gastrointestinal tract (eg, influenza), may induce an IBD flare. Furthermore, temporary or prolonged withdrawal of therapy, as may happen during a viral infection, can lead to a flare-up of the disease.

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. On the contrary, the impact of the viral infection on IBD course and treatment delivery has only been partially evaluated. 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

| 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)           |
| Therapya      |                |                   |
| 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.

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, 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. The rate of flare or worsening of IBD activity in our study is higher than previously reported; this difference may be attributable to the longer follow-up period and a potential overlap between gastrointestinal symptoms due to SARS-CoV-2 infection and actual IBD flare. Furthermore, two studies investigated IBD therapy delay or discontinuation during SARS-CoV-2 infection, and reported rates of 27% and 87%. 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 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, 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

C.B. has received lecture fees from Takeda, Gilead, and Janssen. G.F. has received consultancy fees from Ferring, MSD, AbbVie, Takeda, Janssen, Amgen, Sandoz, Samsung Bioepis, and Celltrion. D.G.R. has served as consultant and received lecture fees from Janssen, Ferring, and Errekappa. A.A. has served as a consultant for AbbVie, Allergan, Amgen, Biogen, Bristol Myers Squibb, Celgene, Celltrion, Ferring, Gilead, Janssen, Lilly, MSD, Mylan, Pfizer, Roche, Samsung Bioepis, Sandoz, and Takeda. S.S. has received lecture fees from and served as a consultant and advisory board member for AbbVie, Arena, Ferring, Gilead, Janssen, MSD, and Takeda.

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