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Uneventful course in IBD patients during SARS-CoV-2 outbreak in northern Italy

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LN: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript.

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NS: acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content.

PC: acquisition of data; analysis and interpretation of data.

SG: acquisition of data, critical revision of the manuscript for important intellectual content.

LD: study concept and design; critical revision of the manuscript for important intellectual content.

INTRODUCTION

From December 2019 the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) responsible for Coronavirus disease 2019 (COVID-19) has caused a pandemic, with over 350.000 cases and more than 15.000 fatalities reported worldwide so far (https://www.healthmap.org/covid-19/). The first case-series from the Wuhan population, describing the clinical characteristics of the SARS-CoV-2 infection in China, were recently published[1]. However, further evidences are required to predict who are the subjects at higher risk of developing clinical symptoms.

Following the outbreak in China, the Lombardy region in Italy has become one of the areas with the highest incidence of new cases, and the outbreak was estimated on February 18th. In particular, the province of Bergamo has reported to date 6471 positive nasopharyngeal swabs for SARS-CoV-2 in a population of 1.114.590 inhabitants, and is therefore the province with the highest rate of infection per 100.000 inhabitants worldwide[2] (http://www.salute.gov.it/portale/nuovocoronavirus/). A recent publication by the IBD Elite Union, which incorporates the seven largest Inflammatory Bowel Disease (IBD) referral centers in China, with more than 20.000 patients with IBD, reported no cases of COVID-19. This report included the three largest tertiary IBD centers in Wuhan (Tongji Hospital, Union Hospital, and Zhongnan Hospital) dating March 8th [3].

However, there is still uncertainty as to whether patients with IBD are more susceptible to COVID-19. To date, several strategies have been introduced in China to better manage IBD patients during the Chinese outbreak of SARS-CoV-2 (https://ecco-ibd.eu/images/6_Publication/6_8_Surveys/2nd_Interview_COVID-19_ECCO_Taskforce_published.pdf).

The aim of this communication is to report the experience of our IBD centre during the epidemic of SARS-CoV-2 in an area of high prevalence of the infection in Italy.

METHODS

This observational study includes all IBD patients (children and adults) regularly followed in our tertiary referral centre at "Papa Giovannni XXIII Hospital", Bergamo, Italy from February 19th to March 23rd 2020. As per our follow up policy, patients can communicate with our team through a dedicated email or a phone number reaching a case manager; thus any complication, including signs of SARS-CoV-2 infection, are promptly notified to our team. Moreover, all patients admitted to the hospital undergo a nasopharyngeal swab to identify carriers of SARS-CoV-2.

RESULTS

A total of 522 patients with IBD are currently followed in Bergamo. They include 59 (11%) pediatric patients (7- 18 years old). Patients' characteristics are described in table 1. Over the period analysed, all patients were recommended not to modify their treatment regimen (see Table 1). In our IBD cohort, we did not report any case of COVID-19, and in particular no patient was admitted to hospital with SARS-CoV-2 proven infection. More than a half of our patients (59%) were exclusively on salicylates treatment. Patients on immunosuppressive treatments such as thiopurines or methotrexate, steroids or other immunosuppressants (22% of our cohort) and patients on biologic treatment (Infliximab, Adalimumab, Vedolizumab and Ustekinumab, Golimumab) (16 %) continued their current dosage without noting any symptoms leading to diagnose COVID-19. Over the same period, 479 patients without history of IBD were admitted to the hospital because of severe COVID-19, after presenting to our emergency department with respiratory failure.

DISCUSSION

After more than one month from the SARS-CoV-2 outbreak in Bergamo and its surrounding area, no cases of COVID-19 have been reported in our IBD cohort. The recent onset of this pandemic outbreak, which is still ongoing, and the lack of epidemiologically robust data, preclude us from drawing certain conclusions regarding its incidence and its effects in specific populations of patients. However, if we base our calculation on a mathematical model applied to the Wuhan region, which estimated a 86% undocumented cases, we could speculate that in Bergamo province a total of 46.220 patients were infected by SARS-CoV-2, accounting for 4% of the total population[4]. From this model we could estimate that 21 cases among our IBD cohort should have been infected. Furthermore, biologic treatments, administered either in hospital setting (Infliximab, Vedolizumab) or at home (Adalimumab, Golimumab and Ustekinumab), were regularly continued without complications.

There is lack of evidence regarding Coronaviridiae infection in IBD patients, especially those under immunosuppressive treatment. An extensive nationwide population based study performed in France, and including nearly 191.000 adult patients with IBD, showed a total of 262 opportunistic infections, with an apparent decreased risk in patients on anti-TNF monotherapy compared with those on thiopurines monotherapy (HR, 0.57; 95% CI, 0.38–0.87) [5].

If we look back to recent history, we can find two outbreaks of Coronaviruses with high lethality, sharing with SARS-CoV-2 the same family of viruses and the characteristics of zoonoses: the severe acute respiratory syndrome (SARS) and the MERS-CoV infection. Immunosuppression was not found to be a risk factor neither for SARS nor MERS, and no patient with IBD as the only risk factor was reported to develop severe SARS or MERS-related disease.

Systemic inflammation is a crucial target for the treatment of COVID-19 pneumonia[6], even though salicylates haven't been tested as a modifying agent. However, a recent report seems to suggest an important role of a cytokine cascade in the development of COVID-19 acute respiratory distress[7]. This speculation supports the theory that patients on immunosuppressive treatment could be at lower risk of developing complicated SARS-CoV-2 complications.

Our data cannot definitely ascertain what can be the rate of SARS-CoV-2 infected patients in our cohort of IBD patients. In fact, only patients with severe symptoms and/or with established contact with infected patients received a nasopharyngeal swab, leaving the asymptomatic subjects out of the count. However we believe our estimated rate of infection should be reliable, since it has been calculated according to well-established criteria (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/index.html).

Based on our evaluation, as of March 23nd, we conclude that none of our patients with IBD was affected by a complicated SARS-CoV-2 related pneumonia. All our patients were advised to continue their current immunosuppressive regimen,.
These findings warrant further investigation, to confirm our preliminary findings and allow implementing guidelines on the management of these patients during the SARS-CoV-2 global pandemic.

Table 1: Characteristic of the IBD population of Bergamo

*Results are expressed in median (minimum-maximum)

References:

1. Guan W-J, Ni Z-Y, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020.
2. Nacoti M, Ciocca A, Giupponi A, et al. At the Epicenter of the Covid-19 Pandemic and Humanitarian Crises in Italy: Changing Perspectives on Preparation and Mitigation. NEJM Catalyst Innovations in Care Delivery 2020.
3. Mao R, Liang J, Shen J, et al. Implications of COVID-19 for patients with pre-existing digestive diseases. Lancet Gastroenterol Hepatol 2020.
4. Li R, Pei S, Chen B, et al. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV2). Science 2020.
5. Kirchgesner J, Lemaitre M, Carrat F, et al. Risk of Serious and Opportunistic Infections Associated With Treatment of Inflammatory Bowel Diseases. Gastroenterology 2018;155:337-346.e10.
6. Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis 2020.
7. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020.
8. D'Antiga L. Coronaviruses and immunosuppressed patients. The facts during the third epidemic. Liver Transpl 2020.

Number of patients	**522**
Female (%)	219 (42%)
Age*	46 (7-86)
Disease phenotype:	
• **Crohn's Disease (%)**	186 (36%)
• **Ulcerative Colitis (%)**	336 (64%)
Previous IBD related surgery (%)	69 (13%)
Treatments:	
• **Anti-inflammatory (Salicylates) (%) - Age***	304 (58%) - 49 (9-86)
• **Thiopurines or Methotrexate (%) - Age***	89 (17%) - 44 (7-78)
• **Biologics (Infliximab, Adalimumab, Ustekinumab and Vedolizumab, Golimumab) (%) - Age***	82 (16%) - 37 (13-72)
• **Steroids - Age***	16 (3%) - 45 (13-80)
• **Other immunosuppressants (Tacrolimus, Cyclosporin, Mofetil Micofenolate) - Age***	11 (2%) - 41 (21-65)
• **Off therapy - Age***	20 (4%) – 59 (19-79)