Manuscript Doi: 10.1093/ecco-jcc/jjaa061

Are patients with inflammatory bowel disease at increased risk for Covid-19 infection?

Giovanni Monteleone MD, PhD, 1, Sandro Ardizzone MD.

1Department of Systems Medicine, University of Rome "TOR VERGATA ", Rome, Italy

2 Gastrointestinal Unit, ASST-Fatebenefratelli Sacco - Department of Biochemical and Clinical Sciences "L. Sacco"- University of Milan, Italy.

Address for correspondence:

Giovanni Monteleone

Department of Systems Medicine

University of Rome "TOR VERGATA"

Via Montpellier, 1

00133 Rome, Italy

Phone: +39.06.72596158

Fax: +39.06.72596391

Email: Gi.Monteleone@Med.uniroma2.it

Manuscript Doi: 10.1093/ecco-jcc/jjaa061

Abstract

Crohn's disease (CD)] and ulcerative colitis (UC), the main inflammatory bowel diseases (IBD) in human beings, are chronic, immune-inflammatory diseases, whose pathogenesis implicates a complex interaction between environmental factors and genetic susceptibility. These disabling conditions affect millions of individuals and, together with the drugs used to treat them, can put patients at risk of developing complications and other conditions. This is particularly relevant nowadays, as coronavirus disease (Covid-19) has rapidly spread from China to countries where IBD are more prevalent and there is convincing evidence that Covid-19-mediated morbidity and mortality are higher in subjects with comorbidities. The primary objectives of this Viewpoint are to provide a focused overview of the factors and mechanisms by which the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects the cells and to illustrate the link between such determinants and the intestinal inflammation. We also provide clues about the reasons why the overall IBD population might have no increased risk to be infected with SARS-CoV-2 and highlight the potential of cytokine blockers, used to treat IBD patients, to prevent Covid-driven pneumonia.

Manuscript Doi: 10.1093/ecco-jcc/jjaa061

Although the cause of inflammatory bowel diseases (IBD) remains unknown, most experts agree that the IBD-associated tissue damage is driven by an excessive immune response against luminal bacteria arising in genetically-predisposed individuals as a result of the action of multiple environmental factors (1). These disabling conditions affect millions of individuals and have variable presentations and courses, which, together with the medications used to treat them, can put patients at risk of developing complications and other conditions (2). Nowadays there is an increasing concern about the risk that IBD patients have to be infected with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Indeed, after the initial cases diagnosed in Wuhan (China) in December 2019, coronavirus disease (Covid-19) has rapidly spread to countries where IBD are more prevalent and it is now clear that comorbidities are associated with poorer clinical outcome in patients with Covid-19 (3).

Why should IBD patients be at increased risk for SARS-CoV-2-induced infections? Coronaviruses bind to their target cells through angiotensin-converting enzyme 2 (ACE2), a monocarboxypeptidase best known for cleaving several peptides within the renin-angiotensin system and other substrates (4). ACE2 is constitutively expressed by epithelial cells of the lung, intestine, kidney, and blood vessels, and is present in the terminal ileum and colon in concentrations that are amongst the highest in the body (5). Analysis of the distribution of SARS-CoV-2 among different biological samples of patients with Covid-19 showed that up to 50% of the faecal samples were positive (6, 7). Moreover, more than one fifth of the patients remained positive in stools after showing negative in respiratory samples (7). These

findings could explain why some Covid-19 patients experience gastrointestinal symptoms and would imply that SARS-CoV-2 can spread through the faecal route. The expression of ACE2 is increased in inflamed gut of patients with IBD (8). Moreover, proteomic analysis of tissue samples of IBD patients revealed a significantly higher expression of ACE2 in Crohn's disease (CD) than in ulcerative colitis (UC) (9). Along with binding to ACE2, fusion of the coronavirus envelope with host cell membranes is critical for establishing a successful infection. This process is mediated by a specific fusion, or "spike" protein (10), which is activated though a proteolytic cleavage induced by host cell trypsin-like proteases, whose activity has been reported to be up-regulated in IBD (11). These observations suggest that the inflamed gut of IBD patients represents an optimal doorway through which the virus enters human tissues. However, based on a PubMed search on March 17, 2020, we found no evidence to suggest that Covid-19 occurs more frequently in IBD than in the general population. Moreover, so far, no IBD patient with SARS-CoV-2 infection has been reported from the tertiary IBD centres in Wuhan.

How can we interpret these findings? There are two functional and distinct forms of ACE2. The full-length ACE2 contains an extracellular domain, which acts as a receptor for the spike protein of SARS-CoV-2, and a structural transmembrane domain, which anchors the extracellular domain to the plasma membrane (12) In contrast, the soluble form of ACE2 lacks the membrane anchor and circulates in small amounts in the blood (13). In vitro studies have shown that the latter form of ACE2 might act as a competitive interceptor of SARS-CoV-2 by preventing binding of the viral particle to the surface-bound, full-length ACE2 (14). Notably, the level of the soluble ACE2 is up-regulated in the peripheral blood of IBD patients (15), raising the possibility that this isoform could contribute to limit SARS-CoV-2 infection.

Although the live SARS-CoV-2 is detectable in faeces (7), there is no clear-cut evidence that the content of ACE2 in the ileum and colon influences entry and replication of the virus within the intestinal cells and, hence, facilitates its transmission by an extra-respiratory route. The SARS-CoV-2 could need of additional and yet unidentified cellular attachment-promoting factors to ensure robust infection of host cells. This is in line with the demonstration that SARS-CoV-2 spreads rapidly through the respiratory route despite the modest ACE2 expression in the upper respiratory tract (16).

Another aspect relevant for the Covid-19 infection in IBD relates to the current therapy, as many patients are taking immunesuppressors (e.g. azathioprine, methotrexate) for inducing and maintaining remission as well as preventing IBD-associated complications. The use of such compounds has been associated with increased risk of infections as they block intracellular signals needed for the host to fight pathogens (17). On the other hand, it is noteworthy that suppression of the effector cytokine driven-inflammatory response in IBD (e.g. using cytokine blockers) could be beneficial not only for dampening the ongoing mucosal inflammation but also for preventing Covid-19-driven pneumonia. Indeed, the profile of cytokines documented in patients with severe Covid-19 resembles that seen in inflamed intestine of IBD patients and during the “cytokine storm” syndrome, a life-threating condition characterized by hyper-activation of T cells and massive production of interleukin (IL)-2, IL-6, TNF, and interferon-γ (18–20). Consistently, blockers of IL-1 or IL-6 have been used with success in pathologies characterized by cytokine storm and preliminary evidence supports the use of IL-6 receptor antagonists in the treatment of Covid-19-driven pneumonia (21).

The overall available evidence suggests that IBD patients do not have increased risk to develop Covid-19 and should stay on IBD medications. Patients receiving

immunesuppressors should be carefully monitored for the occurrence of symptoms and/or signs suggestive for Covid-19. Moreover, those patients over 60 years and/or with comorbidities, which have been reported to have greater risk for Covid-19-induced pneumonia (e.g. coronary heart disease, hypertension, diabetes mellitus, lung disease, cerebrovascular diseases), should stay at home and avoid public gatherings.

References

1. Macdonald TT, Monteleone G. Immunity, inflammation, and allergy in the gut. Science 2005; 307: 1920-1925.
2. Dulai PS, Thompson KD, Blunt HB, Dubinsky MC, Siegel CA. Risks of serious infection or lymphoma with anti-tumor necrosis factor therapy for pediatric inflammatory bowel disease: a systematic review. Clin Gastroenterol Hepatol 2014; 12: 1443-1451.
3. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W; China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020; 382:727-733.
4. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020 Mar 4. pii: S0092-8674(20)30229-4. doi: 10.1016/j.cell.2020.02.052.
5. Harmer, D, Gilbert, M, Borman, R. Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. FEBS Lett 2002; 532: 107–110.
6. Wang W, Xu Y, Gao R, Lu R, Han K, Wu G, Tan W. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA. 2020, Mar 11. doi: 10.1001/jama.2020.3786.
7. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2. Gastroenterology. 2020 Mar 3. pii: S0016-5085(20)30282-1. doi: 10.1053/j.gastro.2020.02.055.
8. Garg M, Royce SG, Tikellis C, Shallue C, Batu D, Velkoska E, Burrell LM, Patel SK, Beswick L, Jackson A, Britto K, Lukies M, Sluka P, Wardan H, Hirokawa Y, Tan CW, Faux M, Burgess AW, Hosking P, Monagle S, Thomas M, Gibson PR, Lubel J. Imbalance of the renin-angiotensin system may contribute to inflammation and fibrosis in IBD: a novel therapeutic target? Gut. 2019 Aug 13. pii: gutjnl-2019-318512. doi: 10.1136/gutjnl-2019-318512.
9. Ning L, Shan G, Sun Z, Zhang F, Xu C, Lou X, Li S, Du H, Chen H, Xu G. Quantitative Proteomic Analysis Reveals the Deregulation of Nicotinamide Adenine Dinucleotide Metabolism and CD38 in Inflammatory Bowel Disease. Biomed Res Int. 2019; 2019: 3950628.
10. Ibrahim IM, Abdelmalek DH, Elshahat ME, Elfiky AA. COVID-19 Spike-host cell receptor GRP78 binding site prediction. J Infect. 2020; S0163-445: 330107-33019.
11. Jablaoui A, Kriaa A, Mkaouar H, Akermi N, Soussou S, Wysocka M, Wołoszyn D, Amouri A, Gargouri A, Maguin E, Lesner A, Rhimi M. Fecal Serine Protease Profiling in Inflammatory Bowel Diseases. Front Cell Infect Microbiol. 2020; 10: 21.
12. Du L, He Y, Zhou Y, Liu S, Zheng BJ, Jiang S. The spike protein of sars-cov–a target for vaccine and therapeutic development. Nat. Rev. Microbiol. 2009; 7, 226-236.
13. Wysocki J1, Ye M, Rodriguez E, González-Pacheco FR, Barrios C, Evora K, Schuster M, Loibner H, Brosnihan KB, Ferrario CM, Penninger JM, Batlle D. Targeting the

degradation of angiotensin ii with recombinant angiotensin-converting enzyme 2: Prevention of angiotensin ii-dependent hypertension. Hypertension 2010; 55: 90-98.
14. Wysocki J, Satchell K. Soluble angiotensin-converting enzyme 2: a potential approach for coronavirus infection therapy? Clin Sci 2020; 134: 543-545.
15. Garg M, Burrell LM, Velkoska E, Griggs K, Angus PW, Gibson PR, Lubel JS. Upregulation of circulating components of the alternative renin-angiotensin system in inflammatory bowel disease: A pilot study. J Renin Angiotensin Aldosterone Syst. 2015; 16: 559-569.
16. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis J. Pathol 2004; 203: 631-637.
17. Govani SM, Higgins PD. Combination of thiopurines and allopurinol: adverse events and clinical benefit in IBD. J Crohns Colitis 2010; 4: 444-449.
18. Chen C, Zhang XR, Ju ZY, He WF. Advances in the research of cytokine storm mechanism induced by Corona Virus Disease 2019 and the corresponding immunotherapies. Zhonghua Shao Shang Za Zhi. 2020 Mar 1;36(0):E005.
19. Maude SL, Barrett D, Teachey DT, Grupp SA. Managing cytokine release syndrome associated with novel T cell-engaging therapies. Cancer J. (2014) 20:119–22.
20. Monteleone G, Pallone F, MacDonald TT. Emerging immunological targets in inflammatory bowel disease. Curr Opin Pharmacol. 2011; 11: 640-645.
21. Tanaka T, Narazaki M, Kishimoto T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. Immunotherapy. 2016 Jul;8(8):959-70.

Manuscript Doi: 10.1093/ecco-jcc/jjaa061

Conflict of Interest:

G Monteleone served as an advisory board member for AbbVie.

S Ardizzone served as a speaker, consultant, and/or advisory board member for AbbVie, MSD, Takeda, Janssen, Pfizer, Sandoz, Enthera.

Contribution:

GM: literature search, data collection and interpretation, and writing. SA: critical revision of the manuscript.

FUNDING:

No specific funding has been received for this work.