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Letter: intestinal inflammation, COVID-19 and gastrointestinal ACE2—exploring RAS inhibitors

EDITORS,

We read with interest the article by Taxonera et al outlining a high incidence of diarrhoea in patients with inflammatory bowel disease (IBD) diagnosed with coronavirus disease 19 (COVID-19).[1] The relationship between these symptoms and faecal calprotectin would be interesting to note. In patients without IBD and COVID-19, faecal calprotectin was noted to be higher in patients with continuing than resolved diarrhoea, suggesting intestinal inflammation due to COVID-19.[2]

As Taxonera et al suggest, angiotensin-converting enzyme 2 (ACE2) may be the link between intestinal inflammation and COVID-19. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), the virus that causes COVID-19, infects humans via the mucosal membrane ACE2 receptor, expressed in multiple tissues including the lung parenchyma and gastrointestinal tract.[3,4] The original transmission from animal to human may have occurred via the oral route, mediated by intestinal ACE2, and SARS-CoV2 RNA has been identified in faeces from infected patients.[5]

We have recently described the expression of all major components of the renin-angiotensin system (RAS), including ACE2, in terminal ileal and colonic mucosal tissue, with ACE2 activity differing between inflamed and non-inflamed biopsies in patients with inflammatory bowel disease (IBD).[4] We have recently postulated that intestinal inflammation may occur due to SARS-CoV2–mediated reduction of mucosal ACE2 following entry, resulting in elevated angiotensin II (Ang II, the effector peptide of the classical RAS pathway), reduced Ang 1-7 levels (the effector peptide of the alternative RAS pathway), increased tumour necrosis factor α (TNFα) and tryptophan deficiency.[6] Interestingly, mucosal ACE2 expression or activity were not associated with the use of conventional medications used to treat IBD, including steroids, 5 amino-salicylic agents, thiopurines or anti-TNFα therapies.[6]

Given that angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARBs) inhibit the classical RAS pathway and promote the alternative pathway via ACE2 and angiotensin (1-7), it was initially postulated that these may increase risk of COVID-19 infection. However, no such increased risk has been noted.[7,8]

Our additional data show no changes in ACE2 receptor mRNA expression, ACE2 activity or ACE2 immunohistochemical staining intensity with terminal ileal and colonic mucosa were not altered by pre-existing intake of ACEI or ARBs (Figure 1). Hence, it is unlikely that the use of these drugs would increase predisposition to gastrointestinal infection with SARS-CoV2. In previous studies, cardiac ACE2 expression, and plasma ACE2 activity were not influenced by these drugs.[9] The effect on respiratory epithelial ACE2 is uncertain.

Whether the underlying expression and activity of ACE2 in various tissues and plasma influences risk of COVID-19, or alters the chance of intestinal inflammation, remains unclear, but it is a fascinating avenue for further research. Mortality associated with COVID-19 rises sharply with age, and a trend towards higher mortality in males has been noted to date. Though multiple confounders may be present with this latter relationship, it may be worth noting that murine alveolar ACE2 expression declined with age, especially in males.[10]

Hence, investigation of the relationship between COVID-19 and tissue ACE2 may allow the development of management strategies for COVID-19 as well as intestinal inflammation.

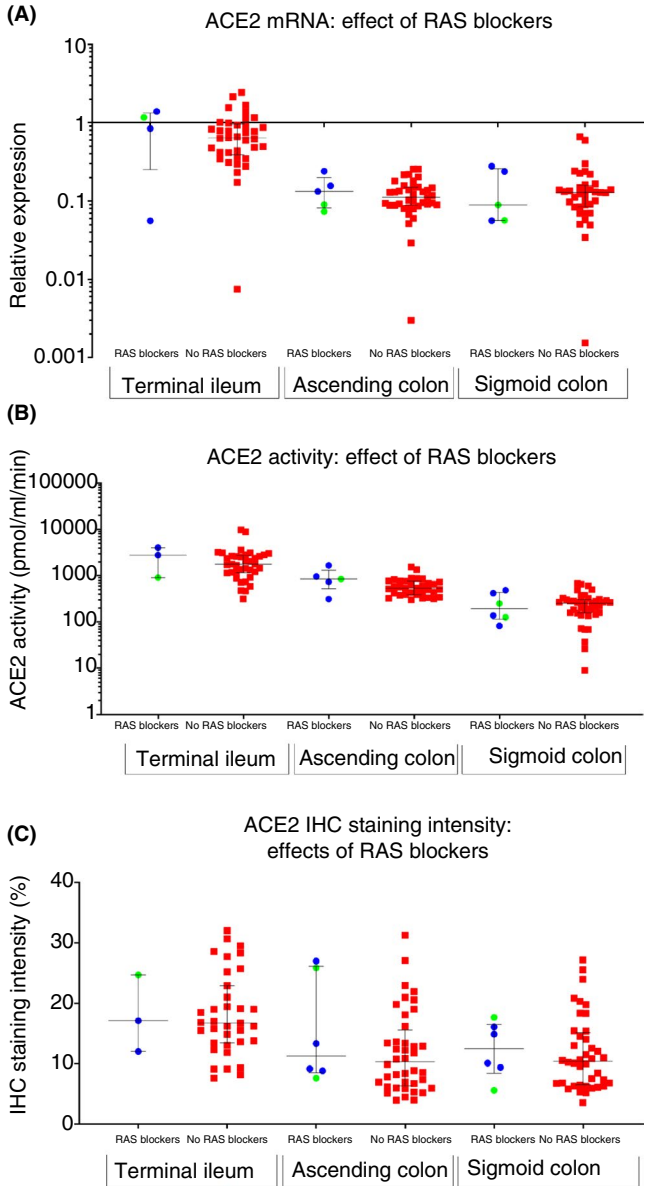

FIGURE 1 Effect of ACE inhibitors and angiotensin receptor blockers (ARBs) on (A) ACE2 mRNA expression, (B) activity and (C) immunohistochemical staining intensity in patients with and without IBD who underwent colonoscopic biopsies. No significant differences were noted. Blue circles represent ACE inhibitor use, green circles indicate ARB use

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LINKED CONTENT

This article is linked to Taxonera et al papers. To view these articles, visit https://doi.org/10.1111/apt.15804 and https://doi.org/10.1111/apt.15893.

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