



Repurposed GI Drugs in the Treatment of COVID-19

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We read with great interest the review article authored by Dr. Kopel and colleagues. Their study discussed on different therapies that are being investigated for the treatment of COVID-19 [1]. Recently, there have been studies regarding antisecretory agents as repurposed drugs. We would like to highlight the evidence of these common GI drugs and their potentials in the treatment of COVID-19.

The COVID-19 pandemic caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been continuously affecting different populations and territories since it was first reported in China in December 2019. Since the pandemic has begun, it has been an unprecedented challenge to identify effective drugs for the prevention and treatment of COVID-19. Several drugs with antiviral activity against SARS-CoV-2 have been tested and with several more ongoing in a race against time. Vaccines are being developed in different centers all around the world, but experts predict it would not be available soon. Just recently, famotidine and omeprazole have been added on the fast-growing list of possible COVID-19 treatments due to their potential therapeutic effects. As gastroenterologists, this could have great implications to our practice, hence worth knowing.

Famotidine is a histamine-2 receptor antagonist (H2RA) that suppresses the production of gastric acid. Early data show that H2RAs had antiviral properties inhibiting HIV replication in vitro [2]. Famotidine's role in SARS-CoV-2 was elucidated in a study by Wu et al. [3] where they conducted molecular modeling to predict structures of proteins encoded by the virus. After screening the ZINC US Food and Drug Administration-approved drug database for potential pharmacological agents that could target predicted proteins, they found out that famotidine could act as a potential inhibitor to the 3CL pro (3-chymotrypsin-like

protease), a key enzyme in the life cycle of the SARS-CoV-2 directly mediating the maturation of nonstructural proteins. This knowledge has spurred interest to the potential of the drug, and the results of the recent cohort study in New York were promising. The study showed that famotidine use was associated with reduced risk for intubation or death among hospitalized COVID-19 patients (adjusted hazard ratio 0.42, 95% CI 0.21–0.85) [4].

Omeprazole is a proton pump inhibitor (PPI) that is also used to suppress gastric acid production. Previous studies have shown that omeprazole may inhibit viral replication by interfering with the acidification of the lysosomes [5]. A recent drug research in Germany has shown that omeprazole interfered viral formation of SARS-CoV-2 beyond therapeutic plasma concentrations at 8 μM [6]. However, at therapeutic concentrations, it enhanced the anti-SARS-CoV-2 effects of aprotinin, an approved protease inhibitor and remdesivir by 2.7-fold and tenfold, respectively. Therefore, aprotinin or remdesivir with omeprazole may represent as candidates for therapy for the treatment of COVID-19.

To date, there is still little knowledge on the potential of famotidine and omeprazole as repurposed drugs to treat COVID-19. The associations drawn in the pioneering studies should be interpreted carefully as the evidence needs further validations. For famotidine, findings are observational and could not conclude any possible protective effect of the drug. For omeprazole, clinical studies have yet to be done. Prospective randomized controlled trials (RCT) are recommended to be able to determine the efficacy and safety of these 'repurposed drugs' as adjuncts to standard antiviral treatment. Specifically, it is important to determine the appropriate route, dosages and timing of these medications. As for famotidine, a multicenter RCT (NCT04370262) is already ongoing [4].

The future of these common GI drugs in the context of the pandemic is still unclear and there is much to be learned. The knowledge of the 3CL pro molecular target has triggered further studies on famotidine. Evidence of omeprazole enhancing therapeutic concentrations of different antivirals should also not be ignored. With their attractive drug

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profile, famotidine and omeprazole are definitely favorable candidates for drug repurposing strategies. Nevertheless, it is still a long process until we discover the results of more studies proving their efficacy and safety in the context of this pandemic.

Reply

We thank Aguila et al. for their interest in our article [7]. In their letter, Aguila and colleagues provide an insight into commonly used acid suppressants such as famotidine and omeprazole as the potential agents for drug repurposing against COVID-19.

Recently, in a retrospective study involving hospitalized COVID-19 patients, famotidine use was associated with a twofold reduction in clinical deterioration leading to intubation or death [4]. However, this effect was not observed in PPI users for unclear reasons [4]. The role of famotidine in interfering maturation of SARS-CoV-2 by inhibiting 2-chymotrypsin-like protein and reduction in inflammation needs to be studied. We all are eagerly waiting for the results of a multicenter randomized controlled trial (RCT) (NCT04370262) of famotidine in COVID-19.

The authors also note that omeprazole at therapeutic concentration increased the anti-SARS-CoV-2 effects of remdesivir and aprotinin. Antiviral properties of PPI have been noted in the past on herpes virus, major and minor-type rhinoviruses [8]. However, high concentrations in vivo might be needed to achieve such a protective effect. For example, in famotidine RCT (NCT04370262), the proposed daily dosing of famotidine is nine times the manufacturer-recommended adult dosage. Furthermore, anti-inflammatory and antioxidative properties have been established with PPIs, probably by inhibiting the production of proinflammatory cytokines. It remains to be studied if such effects can mitigate the cytokine storm caused by SARS-CoV-2.

Many viruses are sensitive to low gastric pH, and hence theoretically, hypochlorhydria induced by these agents can increase the risk of viral infections [9]. Therefore, there is a theoretical concern that the use of H2-blockers and PPIs could diminish or abolish the neutralizing effects of gastric acid on SARS-CoV-2, which could potentially increase the risk of GI manifestations and severity in COVID-19. Furthermore, PPIs have been implicated in diarrhea by altering the composition of gut microbiota and small intestinal bacterial overgrowth. It is increasingly recognized that these mechanisms, at least in part, play a role in diarrhea noticed in COVID-19 patients. It is unclear if these changes in pH by H2-blockers and PPI could interfere with the protective effect of gastric acid from SARS-CoV-2 [10].

Nevertheless, we are cautiously optimistic about these medications given their wide availability, low cost, higher bioavailability, and overall better tolerance. The novel use of H2-blockers and PPI in COVID-19 is still at its nascent stage without any confirmatory research. Further, high-quality RCTs are urgently needed to define the role of these anti-acid drugs in the treatment of COVID-19.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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