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Correspondence

Use of protease inhibitors for the prevention of COVID-19

*Letter to the Editor:*

With the world facing the coronavirus disease 2019 (COVID-19) pandemic, intensive protection is critical for the vulnerable population, including older adults and those predisposed to cardiovascular/respiratory/renal diseases or diabetes. We recently proposed the prophylactic use of clinically proven protease inhibitors, such as camostat mesylate and nafamostat mesylate, for these populations until vaccines and/or drugs suitable for the prevention and/or treatment of COVID-19 are readily available worldwide (Sagawa et al. 2020). These protease inhibitors can serve as promising prophylactics to prevent the manifestation and progression of COVID-19, by blocking the entry of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) via angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) and inhibiting subsequent inflammation, coagulopathies, and multiple organ failure. We proposed that prophylactic use of clinically proven protease inhibitors could not only treat but also decrease the number of critically ill patients with COVID-19. Such measures are particularly important in countries with growing number of patients and/or limited health care resources. This letter discusses several protease inhibitors with varying routes of administration, lines of experimental and clinical evidence, and national insurance approval status in the context of COVID-19 prevention.

Recently, Ansarin et al. reported a randomized clinical trial in which early oral administration of bromhexine hydrochloride, a protease inhibitor, reduced the transfer to intensive care unit, intubation, and the mortality rate in patients with COVID-19 (Ansarin et al. 2020). Additionally, Maggio and Corsini suggested repurposing bromhexine hydrochloride either as a treatment for full-blown COVID-19 infections or as a prophylactic agent to prevent SARS-CoV-2 infection in high-risk subjects (Maggio and Corsini, 2020). Bromhexine hydrochloride is an inexpensive, affordable, safe, and over-the-counter medication used as a mucolytic agent in most countries. Although the suppression of viral entry itself has not been proven, bromhexine hydrochloride can inhibit TMPRSS2 and suppress subsequent inflammation (Ansarin et al. 2020), and can be used as a prophylactic option for the COVID-19 treatment.

Oral camostat mesylate, used to treat chronic pancreatitis mainly in Japan, is another potential prophylactic treatment option against COVID-19. Compared to bromhexine hydrochloride, it is relatively expensive, but it inhibits TMPRSS2 at lower concentrations (Hoffmann et al. 2020) (Lucas et al. 2014). Studies have demonstrated that it suppresses TMPRSS2 and inhibits the entry of SARS-CoV-2 into cells, thus suggesting its promising treatment efficacy (Hoffmann et al. 2020).

Intravenous nafamostat mesylate, an anticoagulant, has been widely used for extracorporeal circulation and in patients with disseminated intravascular coagulation mainly in Japan. In the autopsy series of patients with COVID-19, the presence of thrombosis and microangiopathy in the small vessels and capillaries of the lungs with associated hemorrhage has been reported to contribute significantly to death (Fox et al. 2020). The combination of nafamostat mesylate and fapiviravir has been reported to be potentially effective in critically ill patients, suggesting that inhibition of intravascular coagulopathy may be a contributing factor (Doi et al. 2020). In addition, *in vitro* studies have shown that nafamostat mesylate blocked SARS-CoV-2 infection of cells (Yamamoto et al. 2020). Thus, nafamostat mesylate should be considered as a promising prophylactic option for the clinical manifestations and disease progression of COVID-19, especially in cases with possible coagulopathies and in those in whom coagulopathies are predicted to be critical for their unfavorable prognosis.

Clinical trials of camostat mesylate or nafamostat mesylate, including in combination with other drugs, have been initiated in Japan. Results from these studies will provide important information, which will be useful in countries where these drugs are yet to be licensed.

Although effective treatment options for COVID-19 have not yet been determined, the protease inhibitors described in this letter can be considered as prophylactics to prevent the clinical manifestations and disease progression of COVID-19 in vulnerable populations – especially in those who interact with COVID-19 patients – depending on the situation and/or case.

Declaration of Competing Interest

None.

Acknowledgments

None.

Source of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Abbreviations: ACE-2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane protease serine 2

<https://doi.org/10.1016/j.ypmed.2020.106280>

Received 28 July 2020; Received in revised form 1 October 2020; Accepted 3 October 2020

Available online 06 October 2020

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