Pulm Ther (2023) 9:173–175
https://doi.org/10.1007/s41030-023-00220-4

COMMENTARY

Effect of Famotidine on COVID-19: Killing Virus or Opposing ARDS?

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Received: January 25, 2023 / Accepted: March 13, 2023 / Published online: April 1, 2023

ABSTRACT

Since the first detection of SARS-CoV-2 in China, COVID-19 (Corona Virus Disease 2019) has taken the lives of more than six million people. Although some antivirals seem proper for treatment, the investigation of finding the best therapeutic approach for COVID-19 is still continuing. Some observational research showed that famotidine has promising effects in addition to its acid-suppressing characteristics in the treatment of COVID-19. The definite viricidal effect of famotidine is not established. Opposing acute respiratory distress syndrome (ARDS) can be proposed as a probable mechanism for the action of famotidine, due to its inhibitory effect on histamine release, inhibition of transmembrane protease serine S (TMPRSS) and stabilizing glycocalyx. These hypotheses should be under investigation in the future.

Keywords: ARDS; COVID-19; Famotidine; TMPRSS; Histamine

Key Summary Points

It can be assumed that famotidine has some effects on COVID-19 beyond antiviral effect.

It can be proposed that immunomodulation and opposing ARDS are some actions of famotidine in treatment of COVID-19.

Inhibiting the transmembrane protease serine S protein, stabilization of glycocalyx and preventing histamine release are probable mechanisms that famotidine opposes acute respiratory syndrome that is induced by COVID-19.

COMMENTARY

Since the detection of the first cases of COVID-19 in Wuhan, China, the disease has caused more than six million deaths around the world. Besides the preventive, social, and economic aspects of the COVID-19 pandemic, finding the proper treatment for the disease is still a major concern [1]. Among antivirals and immunomodulators that were proposed, famotidine showed some promising effects beyond its action as an acid suppressor. Molecular

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studies on the virucide activity of famotidine are lacking and one study showed no antiviral activity [2]. Hence, one question rises that famotidine acts as an antiviral or immunomodulator?

Histamine is a biogenic amine that is widely found within all body tissues. Histamine is involved mainly in inflammation, and it is a mediator of early and late inflammatory responses and immune system diseases. Four types of histamine receptors exist. H2 receptor (histamine type 2 receptors) has action in the local inflammatory response in the lung [3]. That is why this receptor can be considered in the treatment of COVID-19.

An investigation has revealed that famotidine can reduce inflammatory biomarkers such as CRP (C-reactive protein), ferritin, TNF-α (tumor necrosis factor-α), and procalcitonin, the mediators that are important in the pathogenesis of COVID-19 [4]. These mediators have a role in the prognosis of acute respiratory distress syndrome (ARDS) and the act of famotidine in suppressing them may help in COVID-19-induced ARDS.

Transmembrane protease serine S (TMPRSS) is a protein expressed in the nasal mucosa, human trachea, distal airways, lungs, and airway epithelia. Inhibitors of TMPRSS have previously been proven to reduce the replication of the influenza virus [5]. Famotidine can act as a serine protease inhibitor on TMPRSS2 and may modulate the interaction between ACE2 (angiotensin-converting enzyme 2) and SARS-CoV-2 and reduces the replication of SARS-CoV-2 through the inhibition of key protease [6]. Besides, serine protease inhibitors also reduce IL-6 (interleukin-6) and TNF-α in human tracheal epithelial cells. These cytokines are of concern in the progression of ARDS. Hence, famotidine, as a serine protease inhibitor, may decrease IL-6 and TNF-α levels and prevents cytokine storms in ARDS [7].

The glycocalyx is a layer of carbohydrates located on the inner face of blood vessels. When the structure is damaged, it causes increased vascular permeability, adhesion, and neutrophil uptake. In ARDS, the glycocalyx of vasculature in the lung is damaged by the release of cytokines, histamine, protease, and heparinase. Destruction in glycocalyx causes micro-vascular leakage results in interstitial pulmonary edema and the development of ARDS, disseminated intravascular coagulation (DIC), and thromboembolism. Famotidine reduces neutrophil migration and blocks the release of histamine from mast cells and prevents pulmonary edema, so it may help in the treatment of ALI (acute lung injury) and ARDS [8]. Many clinical studies have shown that famotidine also reduces vascular permeability and prevents protein leakage from blood vessels and endothelial dysfunction through molecular pathways such as blocking bradykinin receptors, and reduction of cAMP and cytosolic ca^{+2} concentrations [9]. Stabilization of glycocalyx and helping in the improvement of ARDS may be the probable actions of famotidine in the treatment of COVID-19.

Because of the joint effect of histamine on the pathology of COVID-19 and ARDS, it can be suggested that famotidine is effective in ARDS. Confirmation of this suggestion demands several clinical trials in patients with Covid-induced ARDS.

ACKNOWLEDGEMENTS

The authors appreciate Dr. Elahe Karimpour-Razkenari for her assistance in forming the hypothesis for this article.

Funding. No funding or sponsorship was received for this study or publication of this article.

Data availability. This study was not a human or animal study. However, the data that are used in present investigation is accessible in case of reasonable request.

Authorship. All authors have the criteria for the International Committee of Medical Journal Editors (ICMJE) for authorship have approved the final version of this article.

Author Contributions. Mahnaz Sadat Hosseini and Effat Davoudi-Monfared wrote the main body of manuscript and Farhad Najmeddin and Mojtaba Mojtahedzadeh proposed the main idea and edited the manuscript.

Disclosures. Mahnaz Sadat Hosseini, Effat Davoudi-Monfared, Farhad Najmeddin, and Mojtaba Mojtahedzadeh state that they have nothing to disclose.

Compliance with Ethics Guidelines. The authors state that the present article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

REFERENCES

1. Hu B, Guo H, Zhou P, Shi Z-L. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol. 2021;19(3):141–54.

2. Loffredo M, Lucero H, Chen DY, O'Connell A, Bergqvist S, Munawar A, Bandara A, De Graef S, Weeks SD, Douam F, Saeed M. The in-vitro effect of famotidine on SARS-CoV-2 proteases and virus replication. Sci Rep. 2021;11(1):1–9.

3. Eldanasory OA, Eljaaly K, Memish ZA, Al-Tawfiq JA. Histamine release theory and roles of antihistamine in the treatment of cytokines storm of COVID-19. Travel Med Infect Dis. 2020;37: 101874.

4. Mather JF, Seip RL, McKay RG. Impact of famotidine use on clinical outcomes of hospitalized patients with COVID-19. Am J Gastroenterol. 2020;115(10):1617–23.

5. Yamaya M, Shimotai Y, Hatachi Y, Kalonji NL, Tando Y, Kitajima Y, et al. The serine protease inhibitor camostat inhibits influenza virus replication and cytokine production in primary cultures of human tracheal epithelial cells. Pulm Pharmacol Ther. 2015;33:66–74.

6. Ortega JT, Serrano ML, Jastrzebska B. Class AG protein-coupled receptor antagonist famotidine as a therapeutic alternative against SARS-CoV2: an in silico analysis. Biomolecules. 2020;10(6):954.

7. Calabrese F, Pezzuto F, Fortarezza F, Hofman P, Kern I, Panizo A, et al. Pulmonary pathology and COVID-19: lessons from autopsy. The experience of European Pulmonary Pathologists. Virchows Arch. 2020;477(3):359–72.

8. Yamaoka-Tojo M. Endothelial glycocalyx damage as a systemic inflammatory microvascular endotheliopathy in COVID-19. Biomed J. 2020;43(5):399–413.

9. Leurs R, Smit MJ, Timmerman H. Molecular pharmacological aspects of histamine receptors. Pharmacol Ther. 1995;66:413–63.