REVIEW ARTICLE

Anti-histamines and Covid-19: Hype or Hope

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Abstract

Histamine is a biogenic amine distributed extensively in the human cells. Histamine is linked with different inflammatory and allergic disorders through promoting of chemoatractant activity and endothelial changes. Antihistamine drugs are effective in the treatment and prevention of infection of influenza H7N9 through inhibition of viral entry to the host cells. A multiplicity of search strategies including experimental, preclinical and clinical studies were taken on and assumed to review the potential role of H1, H2 or their combination in the management of Coronavirus disease 2019 (Covid-19). Histamine release is associated with early and late pathology of Covid-19 and clinical presentation. Despite the potential effect of famotidine in attenuating the pathogenesis of Covid-19, famotidine has no direct effect on the replication of SARS-CoV-2. However, azelastine (H1receptor blocker) used for allergic rhinitis as nasal spray has potential anti-SARS-CoV-2 activity comparable to that of remdesivir, lopinavir and chloroquine. Azelastine is more effective than other agents that are used in the management of Covid-19 due to significant inhibition of endosomal acidification at respiratory epithelial cells. However, famotidine and cetirizine combination improve clinical outcome and reduce intubation and duration of hospitalization in Covid-19 patients. Taken together, hospitalised Covid-19 patients treated with famotidine only showed more complications as compared with those treated with combination of famotidine and cetirizine.

Conclusion: Both H1 and H2 blockade are effective in the management of Covid-19 patients through antiviral and anti-inflammatory properties, which together reduce the risk of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).

Keywords: Coronavirus disease 2019, Acute lung injury (ALI), Acute respiratory distress syndrome (ARDS).

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Introduction

Histamine is a biogenic amine distributed extensively in the human cells, and present in a high concentration in the brain, lung, gastrointestinal tract, and skin. Histamine has complex physiological effects and acts as a local mediator in the immune system.[1] It plays an important role in the chemotaxis and cytokine storm during acute and chronic inflammatory disorders. Histamine mediates its effect via G protein coupled receptors, which are H1, H2, H3 and H4 receptors. H1 receptor is mainly expressed in neurons, monocyte, B and T cells and are involved in the regulation of humoral immunity and T cells activation as well as production of pro-inflammatory cytokines such as IL-6. H2 receptor is expressed by gastric parietal cell, neuronal and endothelial cells as well as immune cells and is involved in local inflammatory response in the lung. H3 receptor is mainly expressed in the presynaptic neurons of central and peripheral nervous system and is involved in the regulation of histamine release. H4 receptors are expressed in various tissues including thymus, intestine, and bone marrow, adaptive and innate immune systems and are involved in the activation of mitogen-activated protein kinase (MAPK).[2]

Therefore, histamine is linked with different inflammatory and allergic disorders through promoting chemoatractant activity and endothelial changes, so H1 and H4 antagonists may be more effective in modulation of inflammatory reactions during acute lung inflammation and infection through reduction of cyclooxygenase 2(COX2), leukocyte infiltrations and production of transforming growth factor beta (TGF-β).[3]

Therefore, objective of the present study was to elucidate the potential of histamine antagonists in the management of Covid-19.

Method and search strategy

A multiplicity of search strategies including experimental, preclinical and clinical studies were taken on and assumed, including; electronic database searches of Medline, Pubmed, Scopus, Web of Science, and Cochrane Central Register of Control Trials by using MeSH terms, keywords and title words during the search. The terms used for these searches were as follow: [Antihistamines] AND [Covid-19 OR SARS-CoV-2 OR nCoV-19 OR, acute

lung injury, multi-organ failure]. [Antihistamines] AND [anti-inflammatory, OR hyperinflammation OR cytokine storm]. Reference lists of identified and notorious articles were reviewed. In addition, English and other language articles were considered and case reports were also included in this review. The key features of recognized applicable search studies were considered and the conclusions were summarized in a mini review.

Antiviral activity of antihistamines: Xu et al., confirmed that antihistamine drugs are effective in the treatment and prevention of infection with influenza viruses mainly influenza H7N9 through inhibition of viral entry to the host cells.[4] Moreover, diverse studies illustrated that different antihistamines have potent antiviral activity as clemastine may block viral entry of Ebola virus.[5] As well, cyclizine was found to have potent antiviral activity against hepatitis C virus (HCV).[6] Besides, Desheva et al., found that mast cell stabilizers and antihistamines are effective in the management of influenza A/H5N1 as these drugs increased the survival up to 85-95%.[7]

Antihistamines and Covid-19: Coronavirus disease 2019 (Covid-19) is a pandemic global infectious disease caused by severe acute respiratory syndrome coronavirus 2(SARS-CoV-2). SARS-CoV-2 is a positive sense single-strand RNA sharing a genetic similarity with other betacoronaviruses like Middle East respiratory syndrome coronavirus1 (MERS-CoV-1) and severe acute respiratory syndrome coronavirus 1(SARS-CoV-1).[8] The entry-point of SARS-CoV-2 is through angiotensin converting enzyme 2

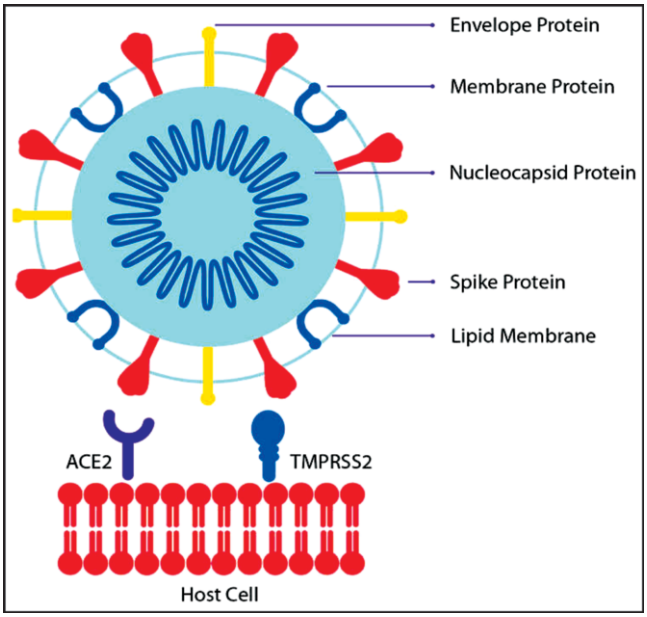

Figure-1: Interaction between SARS-CoV-2 and ACE2: Spike protein (SP) of SARS-CoV-2 binds ACE2, this interaction is facilitated by transmembrane protease serine protease 2 (TMPRSS2).

receptors (Figure-1), which are highly expressed in lung epithelial cells, proximal renal tubules, heart, and brain. SARS-CoV-2 infection triggers acute host immune response, inflammatory reactions and cytokine storm leading to acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).[9]

Covid-19 patients may present with a variety and range of clinical signs and symptoms from mild to severe within 2-14 days after exposure to SARS-CoV-2. The clinical presentations are dyspnoea, sweating, headache, fever, chill, sore throat, anosmia, and ageusia. Severe clinical presentations like cyanosis, persistent chest pain and complications like ARDS required hospitalization, since 20-40 of hospitalized patients require management and monitoring in the intensive care unit (ICU).[10] Various studies have looked into the use of antihistamines in the management of Covid-19.

H2 blockers and Covid-19: H2 blockers like cimetidine, ranitidine and famotidine are inverse agonists rather than receptor antagonists due to constitutive activity of these receptors. These drugs are used for the treatment of peptic ulcer, stress ulcer and prevention of aspiration pneumonia.[11]

Famotidine is currently being investigated for treating Covid-19 in different clinical trials alone or in combination with remdesivir or hydroxychloroquine. Freedberg et al's., retrospective study revealed that oral or intravenous famotidine in addition to the standard therapy in Covid-19 patient's reduced intubation and death risk in 84 infected patients compared to the standard therapy alone. However, famotidine produced an effective protection against Covid-19, which is not seen in other H2 blockers or proton pump inhibitors.[12]

Despite the potential effect of famotidine in attenuation the pathogenesis of Covid-19, famotidine has no direct effect on the replication of SARS-CoV-2 or other viral proteins in different cell lines.[13] Famotidine might not produce its anti-Covid-19 effect through H2-antagonist as cimetidine leads to blocking of H2 receptors without benefit in the management of Covid-19. Therefore, molecular pathways linked with famotidine may be the underlying mechanisms of the beneficial effect of famotidine. It has been reported that famotidine prevents vascular permeability and endothelial dysfunction mainly through blocking of bradykinin receptors, reduction of cAMP and cytosolic ca+2 concentrations.[14] Calabrese et al., demonstrated that famotidine may modulate the interaction between ACE2 and SARS-CoV-2 through inhibition of transmembrane protease serine protease 2(TMPRSS2) in pulmonary type II pneumocytes, mast cells,

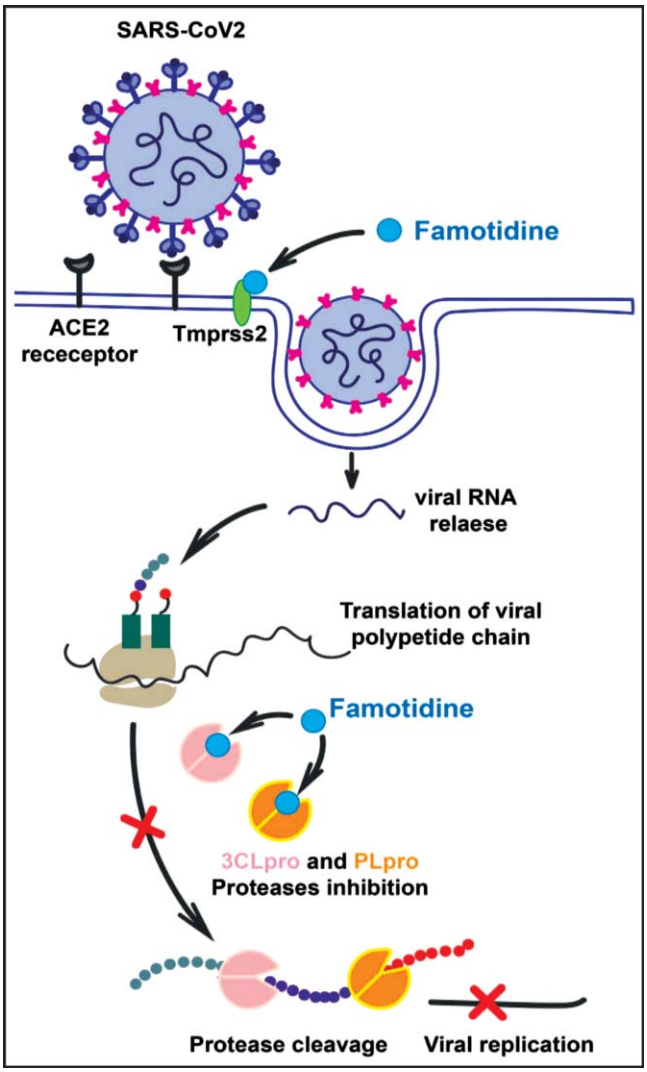

Figure-2: Role of famotidine in SARS-CoV-2 infection: Famotidine inhibits cellular transmembrane protease serine protease 2(TMPRSS2) and viral proteins.

eosinophils and smooth muscle cells leading to reduction in the progression of pulmonary injury and inflammations.[15] Besides, mast cell degranulation and histamine release are connected with development of pulmonary oedema in ALI and ARDS, which might be non-inflammatory oedema in early Covid-19 (Figure-2). Thus, histamine release is associated with early and late pathology of Covid-19 and clinical presentation.[16]

It has been reported that lung microthrombosis in Covid-19 is linked to the damage of endothelial glycocalyx which is caused by cytokine release, histamine, protease, and heparinase. Serum glycocalyx level is correlated with septic endothelial damage and Covid-19 severity.[17] Yamaoka-Yojo et al., found that dysfunction of endothelial glycocalyx in Covid-19 leads to micro-vascular leakage results in interstitial pulmonary oedema and development of ARDS as well as disseminated intravascular coagulation (DIC) and thromboembolism. Further, mast cells release heparin which activates production of plasmin and bradykinin that together lead to platelets activation, thromboembolism, and elevation of D-dimer.[18]

SARS-CoV-2 infection activates histamine release which per se provokes TNF-α; also histamine acts as an autocrine regulator of mast cell cytokine release through H2 receptors. Therefore, H2-blocker famotidine may prevent mast cell activation syndrome in Covid-19.[19]

Currently, there are limited number of studies regarding the probable benefit from using famotidine in the management of Covid-19 patients as most patients use proton pump inhibitors for peptic ulcer and gastro-esophageal reflex disorders. However, Aguila et al's., cohort study in New York found that famotidine therapy reduces hospitalisation and complications in Covid-19 patients as famotidine has potent anti-SARS-CoV-2 effect through inhibition of 3-chymotrypsin-like protease (3CL-pro), which is involved in in its life cycle.[20] Similarly, a retrospective cohort study illustrated that famotidine user patients with Covid-19 are at lower risk for intubation as compared with non-famotidine user patients.[12]

Moreover, famotidine therapy in Covid-19 patients leads to significant reduction of inflammatory biomarkers including CRP, ferritin, TNF-α and procalcitonin.[21] Thus, famotidine improves the clinical and pathological outcomes in Covid-19 patients due to several mechanisms which are;

1- Famotidine has antiviral effects against HIV but its direct effect on SARS-CoV-2 has not been proved. 2- Computational study observed that famotidine may inhibit the replication of SARS-CoV-2. 3- Famotidine prevents mast cells activation and cytokine storm during SARS-CoV-2 infection as well famotidine prevents up-regulation of ACE2 receptor at mast cells.[22]

However, Malone et al's., molecular study confirms that famotidine does not affect the replication and functional proteins of SARS-CoV-2.[23] Recently, Ortega et al., found that a combination of famotidine and hydroxychloroquine illustrates a synergistic effect against SARS-CoV-2 replication.[22] Therefore, famotidine ameliorates the clinical outcomes of Covid-19 patients through H2-dependent pathway, which attenuate Covid-19 induced-cytokine storm, and H2-indepndent pathway through inhibition of SARS-CoV-2 replications.

H1 blockers and Covid-19: Different H1 blockers such as levocetirizine and cetirizine have potent antiviral effects

against rhino virus through inhibition of viral replication and suppression of associated cytokine storm through inhibition of IL-6.[24] Geurdes et al., confirmed that levocetirizine and cetirizine are effective against Covid-19 through suppression the replication of SARS-CoV-2.[25]

Recently, azelastine which is a H1receptor blocker used for allergic rhinitis as nasal spray is investigated for its potential anti-SARS-CoV-2 activity. Azelastine inhibits SARS-CoV-2 replication significantly and comparable to that of remdesivir, lopinavir and chloroquine. Besides, Azelastine is more effective than other agents that are used in the management of Covid-19 due to significant inhibition of endosomal acidification in respiratory epithelial cells.[26]

In addition to its antiviral effects against SARS-CoV-2, azelastine has potent anti-inflammatory effect through stabilization of mast cells and inhibiting the release of pro-inflammatory mediators and development of cytokine storm. Therefore, azelastine may prevent and attenuate ALI and ARDS induced by hyperinflammation in Covid-19. Thus, azelastine nasal spray may inhibit the colonization of SARS-CoV-2 and limit viral transmission.[27]

In a similar way, Westover et al., found that chlorpheniramine maleate nasal spray has viricidal effects against influenza virus and SARS-CoV-2. Chlorpheniramine maleate reduces the titer of SARS-CoV-2 concentration by 99.7% following single nasal spray.[28]

Furthermore, Covid-19 is associated with allergic skin manifestations such as urticarial skin eruptions, which are present in 55% of Covid-19, thus H1 receptor blockers are mandatory to treat these allergic manifestations.[29]

Dual H1 and H2 blockers in Covid-19: It has been reported that dual H1-H2 blockades (cimetidine plus diphenhydramine) are effective in the management of ALI, ARDS and allergy in animal model studies. Combination of cimetidine plus diphenhydramine in this model reduced pulmonary micro-vascular injury, pulmonary hypertension and hypoxaemia.[30] Therefore, dual H1-H2 blockades may reduce and mitigate Covid-19 induced-ALI and ARDS through attenuating the development of cytokine storm. Famotidine and cetirizine combination improve clinical outcome and reduce intubation and duration of hospitalization in Covid-19 patients.[31] Also hospitalized Covid-19 patients treated with famotidine only showed more complications as compared to those treated with combination of famotidine and cetirizine.[30]

Therefore, dual H1-H2 blockade is more effective than either H1 receptor or H2 receptor blockades in the management of Covid-19 patients.

Conclusion

Both H1 and H2 blockade are effective in the management of Covid-19 patients through antiviral and anti-inflammatory properties which together may reduce risk of ALI and ARDS. However, this review cannot provide a final conclusion. Therefore, clinical trials and prospective studies are required to find the robust association between uses of anti-histamines in the management of Covid-19.

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