Histamine receptors and COVID-19

Madeleine Ennis[1] · Katerina Tiligada[2]

Abstract

Objective Reports that the over-the-counter histamine H_2 receptor antagonist famotidine could help treat the novel coronavirus disease (COVID-19) appeared from April 2020. We, therefore, examined reports on interactions between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and histamine receptor antagonists.

Methods A systematic literature search was performed by 19 September 2020, and updated on 28 October 2020, in PubMed, Scopus, Cochrane Library and Google Scholar using (COVID-19 OR coronavirus OR SARS-CoV-2) AND (histamine antagonist OR famotidine OR cimetidine). ClinicalTrials.gov was searched for COVID-19 and (famotidine or histamine).

Results Famotidine may be a useful addition in COVID-19 treatment, but the results from prospective randomized trials are as yet awaited. Bioinformatics/drug repurposing studies indicated that, among several medicines, H_1 and H_2 receptor antagonists may interact with key viral enzymes. However, in vitro studies have to date failed to show a direct inhibition of famotidine on SARS-CoV-2 replication.

Conclusions Clinical research into the potential benefits of H_2 receptor antagonists in managing COVID-19 inflammation began from a simple observation and now is being tested in multi-centre clinical trials. The positive effects of famotidine may be due to H_2 receptor-mediated immunomodulatory actions on mast cell histamine–cytokine cross-talk, rather than a direct action on SARS-CoV-2.

Keywords COVID-19 · Histamine · Histamine receptor · Mast cells · Immunomodulation · SARS-CoV-2

Introduction

The novel coronavirus disease (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that emerged in the Chinese province of Hubei in December 2019 and rapidly spread worldwide [1]. COVID-19 is an ongoing major public health threat declared as pandemic by the World Health Organization (WHO) on 11 March 2020. The clinical manifestations of the disease range from mild to severe non-specific symptoms and signs with pneumonia and acute respiratory distress syndrome (ARDS) being common, frequently fatal, complications [2]. At present, there are no vaccines against SARS-CoV-2. Moreover, more than 20 therapeutic agents, mostly repurposed drug candidates, including the histamine H_2 receptor antagonist famotidine, are being evaluated in numerous clinical trials for the treatment of COVID-19 [3].

SARS-CoV-2

The SARS-CoV-2 is a zoonotic pathogen that belongs to the *Betacoronavirus* (*β*-CoV) genus of the *Orthocoronavirinae* subfamily of the *Coronaviridae* family [4]. Its genome is an enveloped, positive-sense, single-stranded genomic RNA (+ssRNA; gRNA) of approximately 30 kilobases (kb) that shows 88–96% sequence identity to the bat coronaviruses bat-Cov RaTG13, bat-SLCoVZXC21 and bat-SL-CoVZC45 and 80% homology to the human SARS-CoV [1, 5, 6].

The gRNA of the SARS-CoV-2 (Fig. 1), also functioning as messenger RNA (mRNA), comprises, at the 5′ end,

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✉ Katerina Tiligada
aityliga@med.uoa.gr

1 The Wellcome-Wolfson Institute for Experimental Medicine, School of Medicine, Dentistry and Biomedical Sciences, Queens University Belfast, 97 Lisburn Road, Belfast BT9 7BL, UK

2 Department of Pharmacology, Medical School, National and Kapodistrian University of Athens, M. Asias 75, 11527 Athens, Greece
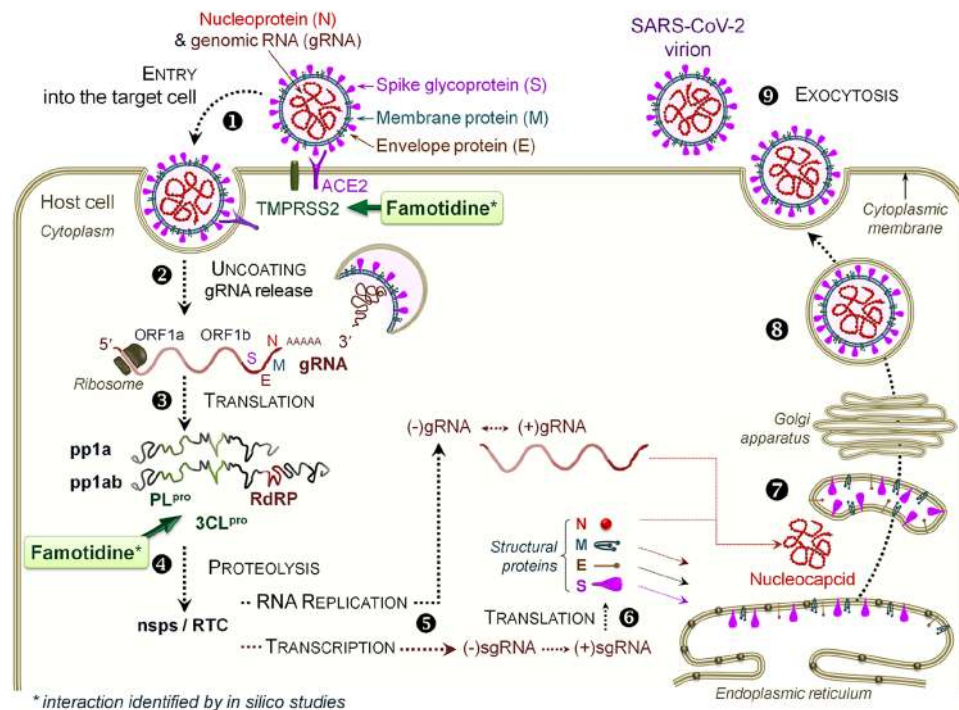
Fig. 1 Schematic presentation of the life cycle of SARS-CoV-2 in the host cell and proposed sites of famotidine action. The attachment and entry of the virus into the host cell (❶) require the interaction of angiotensin-converting enzyme 2 (ACE2) with the viral S glycoprotein, which is processed by the cellular transmembrane protease serine 2 (TMPRSS2). Following viral fusion with the target cell cytoplasmic membrane, the positive-sense single-stranded genomic RNA [(+)gRNA] of the virus is released into the host cytoplasm (❷) and the open reading frames (ORF) 1a and 1b are translated into the polyproteins pp1a and pp1ab (❸). These are cleaved by the viral papain-like (PL^pro) and 3C-like (3CL^pro) proteases to generate 16 non-structural proteins (nsps), including RNA-dependent RNA polymerase (RdRP), a core constituent of the replication–transcription complex (RTC) (❹). During replication (❺), the negative-sense genomic RNA [(−)gRNA] serves as template for the (+)gRNA, whereas the nested subgenomic RNAs [(+)sgRNA] produced by fragmented transcription through negative-strand intermediates [(−)sgRNA] (❺) are translated into the SARS-CoV-2 structural (❻) and accessory proteins. The nucleocapsids assembled from gRNA encapsidated by N protein and the structural proteins S, E and M inserted in the endoplasmic reticulum move along the secretory pathway (❼) and form mature virions that are transported to the cell surface in vesicles (❽) and released from the infected cell by exocytosis (❾) [7, 10, 11]. Bold arrows indicate the sites of action of the histamine H_2 receptor antagonist famotidine as proposed by computational studies [5, 36, 40], yet not experimentally confirmed [43, 51]

the large overlapping open reading frames (ORF) 1a and 1ab that encode the multifunctional polyproteins pp1a and pp1ab. At the 3′ end, the gRNA contains the genes for the structural proteins of the viral coat spike (S), envelope (E), and membrane (M) and for the nucleoprotein (N) involved in gRNA packaging, as well as for species-specific accessory proteins (ORF3a–ORF9b), all encoded by a nested set of subgenomic mRNAs (sgRNA) [7, 8].

The virions enter the target cells via the S surface glycoprotein, which mediates their interaction with angiotensin-converting enzyme (ACE) 2 at the host cell surface and their fusion with the host membrane, following processing by the cellular transmembrane protease serine 2 (TMPRSS2) (Fig. 1) [9]. The gRNA is released into the cytoplasm and translated by the ribosomes of the host cell into pp1a and pp1ab, which is composed of more than 7000 amino acids. The subsequent extensive proteolytic cleavage of pp1a and pp1ab by viral proteases yields 11 and 16 non-structural

proteins (nsps), respectively, that are involved in the replication and transcription of one of the largest known RNA genomes [10, 11]. These include the papain-like (PL^pro) and the 3C-like (3-chymotrypsin-like, 3CL^pro; or main, M^pro) proteases that correspond to nsp3 and nsp5, respectively, as well as the catalytic subunit nsp12 of the RNA-dependent RNA polymerase (RdRP) [12]. RdRP is a core component of the multisubunit replication-transcription complex (RTC) used by SARS-CoV-2 for the replication of its genome and for the gene transcription process (Fig. 1) [12].

Although studies on the structural and functional biology of SARS-CoV-2 are at early stages, the structural proteins, as well as the nsps are attractive therapeutic drug targets for COVID-19 and, consequently, they are being intensively investigated [5–8]. For instance, the RdRP has emerged as a promising druggable target used in repurposing strategies due to the structural similarities displayed in different RNA viruses. RdRP can be inhibited by the active metabolite of

the investigational nucleotide analog remdesivir that has shown broad antiviral activity and is under clinical evaluation for the treatment of COVID-19 [13, 14]. De novo drug development, drug repurposing and natural product screening are also directed at the essential proteases for viral replication [5], PL^{pro} [6, 15] and 3CL^{pro}, which cleaves itself and, by cleaving pp1ab at 11 canonical sites (between nsps), it generates nsp4-16 and mediates their maturation [16].

Histamine and histamine receptors

Histamine was the first inflammatory biogenic amine to be characterized and is one of the most studied biomedical substances [17]. Histamine is present in a wide range of immune and non-immune cells and tissues. However, it is primarily found in mast cells and basophils, where it is stored in cytoplasmic granules and released along with other inflammatory mediators upon activation in response to diverse immune and non-immune stimuli, including viruses and other pathogens [18–20].

Histamine exerts multiple (patho)physiological actions by activating four known types of histamine receptors that are designated as H_1–H_4, which belong to the G-protein-coupled receptor (GPCR) family and possess a multifaceted pharmacological and therapeutic profile [17]. Over the years, H_1, H_2, H_3 and H_4 receptors have been associated with allergic inflammation, stimulation of gastric acid secretion, neurotransmission and immune responses, respectively [17]. This led to the development and marketing of blockbuster drugs, such as H_1 antihistamines for the management of allergies and H_2 receptor antagonists for the treatment of gastrointestinal disorders, a first-in-class H_3 receptor antagonist for treating narcolepsy, as well as H_4 receptor-targeting compounds that are being evaluated in clinical trials for their potential exploitation in managing inflammatory disorders [17].

Histamine and COVID-19

In April 2020, reports appeared in the popular press as well as on several websites suggesting that the histamine H_2 receptor antagonist famotidine (approved for gastric acid-related diseases and marketed among others as Pepcid®, Amfamox®, Famocid®, Famodil®, Gaster®, Peptan®) [17] could relieve symptoms, speed up recovery and help fight COVID-19. The wide availability of this agent, taken together with its low cost made this seem like a wonderful idea. It has been difficult to find the original sources for some of the information presented. However, even before these reports, Johnson had suggested histamine as a potential therapeutic target to prevent COVID-19 from progressing

to ARDS, although he proposed the use of the H_1 receptor antagonist levocetirizine, which from the mode of action would also seem more likely to be successful [21]. Similarly, rupatadine, a second-generation H_1 receptor antagonist that possesses anti-platelet-activating factor (PAF) activity has been proposed to be a candidate repurposed medicine for COVID-19 prophylaxis [22].

Why then did famotidine hit the headlines? Borrell states that an American physician, Michael Callahan, and Chinese colleagues, noticed that, although the death rate in the over-80-year-old patients was high, many elderly survivors were poor [23]. A review of 6212 patient records from hospitalized COVID-19 patients was undertaken and in patients on famotidine, the death rate was 14%, whereas in patients not taking famotidine, the death rate reached 27% [23]. Despite the results not being statistically significant, Callahan contacted Robert Malone (Alchem Laboratories, FL, USA), who then partnered with the computational chemist Joshua Pottel (Molecular Forecaster, Montreal, Canada) to use computer modelling to assess the binding of candidate compounds to viral targets. Pottel examined ca. 2600 drug candidates, including famotidine, to see which of them could bind to the viral PL^{pro}, which is involved in the replication of the SARS-CoV-2 (Fig. 1). Famotidine was one of the top three candidates in the list of drug hits obtained. This led to Callahan contacting Kevin Tracey at Northwell Health, NYC about conducting a double-blind randomized trial for famotidine (further details are given below). The above information has been taken from a non-reviewed publication [23].

Clinical trials of H_2 receptor antagonist famotidine and COVID-19

The first published trial by Freedberg and colleagues (including M. Callahan) was published online in Gastroenterology on 21 May 2020 [24]. This was a retrospective cohort study on patients with COVID-19 from one institution in the USA. A total of 1620 patients met the inclusion criteria, including 84 patients (5.1%) who received famotidine within 24 h of admission to hospital. The group taking famotidine had a reduced risk of deterioration leading to intubation and a reduced risk of death [24]. In contrast, proton pump inhibitors (PPIs) did not provide any benefits. The authors acknowledged that the study was observational and highlighted the need for randomized clinical trials.

Shortly thereafter, on 4 June 2020, Janowitz and colleagues published a retrospective case study of 10 non-hospitalized COVID-19 patients self-medicated with famotidine at a dose range of 20–80 mg three times a day (t.i.d.) (ClinicalTrials.gov Identifier: NCT04389567) [25]. Famotidine was well tolerated and symptom improvement was seen within 2 days. However, the authors realised that although

the study seemed to indicate a benefit for the use of famotidine, limitations included enrolment and recall bias, and that the patients may have improved without the drug. Thus, they suggested that an outpatient study should be performed.

Another retrospective observational study that was conducted at Hartford Hospital, CT, USA, analysed the electronic records of 878 hospitalised patients with COVID-19, 83 of whom received famotidine. Despite the limitations of the study, famotidine was found to be associated with improved clinical outcomes, including lower in-hospital mortality, a lower composite of death and/or intubation, and lower levels of serum markers for serious disease [26]. On the contrary, a territory-wide retrospective cohort study in all COVID-19 patients from Hong Kong did not support any association between the use of famotidine and disease severity [27].

An interventional randomized comparative trial is currently underway (ClinicalTrials.gov Identifier: NCT04370262) [28]. This trial originally wanted to compare hydroxychloroquine plus intravenous (i.v.) administration of famotidine (360 mg/day) or placebo with 600 patients per group; plus a historical control of hospitalized patients who were not treated with hydroxychloroquine or famotidine during the early stages of the pandemic (1 February–26 March 2020). On 16 June 2020, an update was posted to reflect changes in treatment and the study was reduced to two arms: (1) standard of care (SOC) plus famotidine (360 mg/day) and (2) SOC plus placebo, with the aim of recruiting 471 patients per arm. This study is estimated to be completed in April 2021 and the results are eagerly awaited.

A further clinical trial started on 1 August 2020 (ClinicalTrials.gov Identifier: NCT04504240) which seeks to examine the role of famotidine in the symptomatic improvement of mild to moderately severe COVID-19 patients. Both hospitalized and outpatients will be recruited but not patients requiring ventilation. Subjects will receive 40–60 mg famotidine per os (p.o.) every 8 h along with other treatments [29]. In addition, a newly registered phase I trial (ClinicalTrials.gov Identifier: NCT04545008) will recruit outpatients with SARS-CoV-2 infection to assess the safety and toxicity profiles, as well as the possible efficacy of various dosages of the combination of famotidine with n-acetyl cysteine [30].

One further trial has appeared in an internet source though is not yet listed in ClinicalTrials.gov [31]. This trial, which according to the source started on 9 June 2020 in Mississippi, USA, planned to randomise outpatients with COVID-19 to receive 10 mg of the H_1 antihistamine cetirizine plus famotidine 20 mg twice a day (b.i.d.) for up to 21 days or placebo [32]. In contrast to the information given in [32], the results that have now been published [33] have derived from a physician-sponsored cohort performed on 110 inpatients, without a placebo-controlled arm or randomisation. The authors compared their data with published results and felt that the drug combination reduced inpatient mortality and symptom progression. Yet, without the necessary controls, we believe that the data are not possible to interpret.

Histamine and COVID-19 bioinformatics/drug repurposing studies

The COVID-19 pandemic and the great many deaths throughout the world caused by the virus has prompted many investigations searching for currently available drugs, which could prevent or at least limit the severity of the disease. These bioinformatics/drug repurposing studies are available both as published/in press articles and also as unreviewed preprints. Some studies target the virus life cycle (Fig. 1) and others examine agents that would reduce disease severity. The topic is too large to be covered in its entirety in this review; therefore, we will concentrate on those which describe a potential use for H_1 and H_2 receptor antagonists.

Some authors did not perform in silico studies but rather looked at the properties of the agents. Glebov [34] suggested that the H_1 antihistamine terfenadine should be investigated as it may be able to inhibit SARS-CoV-2 endocytosis. Rogosnitzky et al. felt that both the H_2 receptor antagonists cimetidine and famotidine could be useful therapeutic agents in COVID-19 as they are known to have immunomodulatory activity [35].

Interestingly, recent computational studies have identified the histamine H_2 receptor antagonist famotidine as an inhibitor of 3CL^{pro} [5] and of PL^{pro} [36, 37] (Fig. 1), thus implying a direct antiviral effect on SARS-CoV-2. In contrast, a subsequent report argued for a weak, nonspecific binding of famotidine to these proteases [38]. In a preprint, Roomi et al. found that famotidine binds to key sites in the RdRP (Fig. 1), which would lead to the inhibition of virus replication [39]. Furthermore, another in silico molecular docking analysis indicated that the non-specific low-affinity binding of famotidine to the proteases involved in SARS-CoV-2 replication and its interaction with the human host TMPRSS2 (Fig. 1) could be related to the chemical structure of the compound [40]. On the other hand, considering the yet elusive implication of the H_2 receptor in histamine signalling in immunoregulation and inflammation [41, 42], the benefit of famotidine in managing the inflammatory and/or the immune response during the SARS-CoV-2 infection, including the likely automodulation of mast cell activation [43], cannot be excluded at the moment.

Studies have also reported that other potential mast cell mediator release and function-modifying drugs could interact with important pathways in viral replication. In silico docking studies have indicated that the cysteinyl leukotriene (cysLT) receptor antagonist montelukast that is indicated for

the treatment of asthma [5, 44], the 5-lipoxygenase (5-LOX) inhibitor setileuton [45] and the H_1 receptor antagonists fexofenadine [44], mizolastine and cetirizine [46] interact with M^{pro}, whereas the mast cell stabiliser cromolyn is a potential RdRP inhibitor [5]. Another work highlighted the interaction of montelukast with PL^{pro} [6].

Li and colleagues [47] studied the GPCR family named type 2 taste receptors (TAS2Rs), in particular TAS2R10, which they had found to be involved in controlling infectious diseases caused by bacteria, viruses, and parasites. They looked for agonists of TASR10 and other taste receptors. Three histamine receptor antagonists were listed as TASR10 agonists, namely chlorpheniramine, diphenhydramine and famotidine, which may target the most common symptoms of COVID-19.

Two further non-reviewed preprints suggested that the second-generation H_1 antihistamine astemizole inhibited the replication of SARS-CoV-2 with an EC_{50} of *ca.*1 μM [48]. Three H_1-receptor antagonists, clemizole hydrochloride, dimenhydrinate and tripelennamine hydrochloride, were also suggested to have antiviral activity [49]. In both studies, other drugs were better than the histamine receptor antagonists.

Experimental data examining histamine receptor antagonists and SARS-CoV-2 or other viruses

There is little published information about the direct effects of histamine receptor antagonists on SARS-CoV-2. Thus, famotidine (up to 2.5 mM) did not inhibit viral replication in human intestinal organoids derived from pluripotent stem cells or Caco-2 cells [50]. Malone and colleagues demonstrated that famotidine did not inhibit SARS-CoV-2 infection in Vero E6 cells nor did it inhibit PL^{pro} [43]. Loffredo et al. failed to show, any significant effect of famotidine on protease function and SARS-CoV-2 replication when tested in A549 and Vero E6 cell lines [51].

There is slightly more information about H_1 receptor antagonists, though much in preprints. Gordon and coworkers found that cloperastine and clemastine inhibited viral infectivity [8]. Both ebastine and mequitazine showed antiviral activity in infected Vero cells with IC_{50} values of 6.92 and 7.28 μM, respectively [52]. The antiviral activity of some compounds was found to be dependent on the cell type used. Thus, the H_1 receptor antagonist ebastine was tenfold less active against the virus grown in Vero cells than in Calu-3 or Huh7.5 cells [53]. Loratadine, in a preprint, was reported to have an IC_{50} of 15.13 μM in Caco-2 cells [54]. Incubation for 25 min with the nasal spray formulation of chlorpheniramine maleate of SARS-CoV-2, USA-WA1/2020

strain in Vero 76-infected cells reduced the levels of the virus [55].

Regarding the effect of histamine receptor-targeting compounds against viruses other than SARS-CoV-2, Bourinbaiar and Fruhstorfer found that the H_2 receptor antagonists cimetidine, ranitidine and famotidine suppressed the replication of human immunodeficiency virus (HIV), whereas the H_1 receptor antagonists cyproheptadine and diphenhydramine were without effect [56]. On the other hand, diphenhydramine and chlorcyclizine inhibited infectious Kikwit Ebola virus strain in human foreskin fibroblast cells with IC_{50} 2.2 μM and 3.2 μM, respectively. However, the authors found that the newer H_1 receptor antagonists cetirizine and fexofenadine, as well as the H_2 receptor antagonist tiotidine, lacked anti-filovirus activity [57].

Where else could histamine antagonists act to modify COVID-19?

The emerging role for mast cell-derived histamine in combination with interleukin (IL)-1 in COVID-19 lung inflammation has been proposed [58]. There are numerous studies showing that mast cells and basophils can respond to viruses by releasing mediators such as histamine and cytokines [20]. For example, HMC-1 cells release cytokines in response to Zika virus [59]. Ng et al. found that the responses of both LAD2 mast cells and the epithelial Calu-3 cells depended on which influenza A strain was used in the experiments [60]. Cord blood-derived mast cells release a range of cytokines on infection with Reovirus [61]. In addition, human mast cells have been reported to express neuropilins (NRP), the transmembrane co-receptors for angiogenic and lymphangiogenic members of the vascular endothelial growth factor (VEGF) family, thus contributing to the recruitment of immune cells in chronic inflammation [62]. Interestingly, NRP1 has been suggested to play a role in the increased infectivity of SARS-CoV-2, by promoting viral entry in physiologically relevant cells [63, 64].

Both H_1 and H_2 receptor antagonists have been demonstrated to inhibit both histamine and cytokine secretion. The H_1 antihistamines cetirizine and desloratadine, as well as the H_2 receptor antagonist ranitidine inhibited cytokine secretion from HMC-1 cells but the inhibition varied depending on which cytokine was examined [65]. Early work demonstrated that the negative feedback effect of histamine on basophil activation was mediated via the H_2 receptor [66] and the inhibitory effect of dimaprit on histamine release from human basophils was reversed by cimetidine [67].

Furthermore, the immunomodulatory activity of the H_2 receptor has been shown in a variety of models. In a study where nonallergic beekeepers were exposed to high doses of bee venom antigens, Meiler and colleagues reported that the

H_2 receptor plays a role in tolerance by inducing IL-10 and reducing the proliferation of allergen-specific T cells [68]. Using human immature dendritic cells, Mazzoni et al. found that activation of the H_2 receptor resulted in elevated IL-10 production and reduced IL-12 secretion [69]. Histamine, again via the H_2 receptor, enhances the suppressive activity of transforming growth factor (TGF)-β1 and the responsiveness of CD4 + T cells [70] and inhibits the production of IL-12 from human monocytes [71]. Histamine suppresses Toll-like receptor (TLR)-induced cytokine responses from peripheral blood mononuclear cells and this is reversed by famotidine [72]. Also, a recent review discusses the immunomodulatory properties of cimetidine [73].

Potential problems with the use of famotidine

Famotidine is usually regarded as an extremely safe drug in normal use and indeed is available over-the-counter in many countries. However, as highlighted in a recent review, there are instances where its use and indeed that of other H_2 receptor antagonists have been associated with increased delirium [74]. This was reviewed in 1991 where central nervous system reactions including delirium were attributed to H_2 receptor antagonists [75]. Discontinuing H_2 antagonist treatment in patients who have developed delirium alleviates the symptoms in a number of clinical settings [76, 77].

Further publications since the time of submission

As may be appreciated this is a rapidly moving field. In the time since submission of this article, there have been several new papers, which will be briefly discussed. One further clinical trial has been listed in ClinicalTrials.gov, which is not yet recruiting, and, in an estimated 216 participants, will compare the use of one and two daily doses of 20 mg famotidine plus 2000 IU vitamin D3 daily and 1 g vitamin C b.i.d. in both arms [78]. A study protocol for a further trial has been published [79]. This trial examined the effect of standard treatment alone or standard treatment plus p.o. 160 mg famotidine 4 times daily (q.i.d.) on the recovery of 20 hospitalized patients in total. This trial has already been completed but the results are not yet published. In a nationwide survey of 53,130 participants, Almario and colleagues reported that the use of PPIs increased the odds for reporting a positive COVID-19 test, whereas the use of H_2 receptor antagonists was not associated with an elevated risk [80]. Severity of symptoms was not investigated in this study.

In contrast to previously reported studies [24, 26], Yeramaneni et al., did not find that use of famotidine within 24 h

of admission provided any benefit to 30-day mortality [81]. Indeed, those who only received famotidine in hospital had a 77% higher risk of 30-day mortality. An unreviewed preprint reported in a consecutive series of 25 patients that p.o. administration of 80 mg q.i.d. famotidine plus the selective cyclooxygenase-2 (COX-2) inhibitor celecoxib (p.o. loading dose of 400 mg, followed by 200 mg b.i.d. administered p.o. within 24 h of admission) led to 100% survival and improvements in a number of clinical and biomarker measurements [82]. The authors suggested that a randomized trial of the combination of high-dose famotidine with celecoxib as adjuvant therapy to SOC should be performed [82].

In a detailed study, Yuan and co-workers found that ranitidine bismuth citrate inhibited the replication of SARS-CoV-2 in Vero E6 and Caco-2 cells, as well as the activity of SARS-CoV-2 helicase (nsp13) [83]. In a golden Syrian hamster model, ranitidine bismuth citrate also suppressed replication of the virus, leading to decreased viral loads in the upper and lower respiratory tracts and reduced virus-associated pneumonia [83]. Given the safety profile associated with the clinical use of ranitidine bismuth citrate, this makes it a very interesting potential therapeutic agent for the treatment of COVID-19.

Conclusion

Clinical research into the potential benefits of H_2 receptor antagonists in treating patients with COVID-19 began from a simple observation and now is being tested in a multi-centre clinical trial. Drug repurposing/computational biology studies have suggested that H_2 receptor antagonists may be beneficial, among MANY other drugs. However, the evidence so far does not suggest a direct effect of these compounds on the SARS-CoV-2. From previous studies, the immunomodulatory effects of H_2 receptor antagonists are well characterized, but further investigations are required to explore their potential implication in managing the immune response in COVID-19.

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