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REVIEW

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Famotidine for COVID-19

Anang Agung Chrisnanda[1], Anjar Hermadi Saputro[2*]

[1]Department of Pharmacy, Faculty of Health Sciences, Universitas Jenderal Soedirman, Purwokerto, Indonesia

[2]Department of Pharmacy, Faculty of Science, Institut Teknologi Sumatera, Lampung Selatan, Indonesia

[*]Corresponding author: anjar.saputro@fa.itera.ac.id

Abstract: Famotidine has emerged as a candidate for COVID-19 treatment, with various studies investigating its impact on the virus. These studies have reported encouraging results, suggesting that famotidine might contribute to fighting COVID-19 by potentially blocking histamine release, TMPRSS, and fortifying glycocalyx. Clinical trials aimed at assessing the effectiveness of famotidine in patients with COVID-19 have observed that it contributed to quicker alleviation of symptoms and reduction in inflammation, without compromising the body's immunity against SARS-CoV-2. However, in the case of patients with severe illness, famotidine's use did not significantly enhance survival rates. Although further investigation is necessary, famotidine has shown promise in alleviating symptoms and reducing inflammation in COVID-19 cases.

Keywords: famotidine, SARS-CoV-2, Covid-19, H_2-receptor blocker, histamine

Introduction

The emergence of COVID-19 has necessitated the rapid development of effective therapeutic interventions, resulting in a growing interest in the repurposing of existing medications. Famotidine, a histamine-2 receptor antagonist commonly used to treat gastrointestinal disorders, has attracted attention for its potential role in managing COVID-19. Several studies have suggested that famotidine may improve clinical outcomes in COVID-19 patients, indicating mechanisms of action that extend beyond its conventional use in acid suppression.

Research has proposed that famotidine may inhibit SARS-CoV-2 proteases, which are essential for viral replication and the inflammatory response associated with COVID-19 [1,2]. This novel mechanism underscores the significance of investigating existing medications for new therapeutic applications, particularly during a global pandemic where rapid solutions are critical.

Initial reports have observed a correlation between famotidine use and improved clinical outcomes in COVID-19 patients, including reductions in mortality and the need for mechanical ventilation [3]. These findings have spurred increased interest in evaluating famotidine's efficacy in both hospitalized and non-hospitalized patients with COVID-19.

Famotidine for COVID-19

Some research has reported that oral use of famotidine may improve recovery in COVID-19 patients, with one study noting that 10 patients who took famotidine for 5-21 days experienced symptomatic improvement [8]. Another study suggested that famotidine use could reduce the risk of death in COVID-19 patients [4].

Several studies have also investigated the potential of famotidine as a SARS-CoV-2 drug candidate through both in silico and in vitro analyses. In in silico studies, proteins such as the SARS-CoV-2 main protease (3CLpro) and Papain-like protease (PLpro) were predicted to interact with famotidine. However, molecular docking studies revealed only weak interactions between famotidine and the SARS-CoV-2 PLpro protein. Additionally, in silico assays indicated that famotidine had no significant effect on interferon signaling or NF-κB-dependent gene expression in the context of SARS-CoV-2 PLpro [5].

In vitro studies evaluating famotidine as a potential COVID-19 drug have focused on its ability to inhibit virus replication or eradicate the virus using various enzymatic assays. The results showed that famotidine did not bind to or inhibit the function of the 3CLpro and PLpro proteins, which are crucial for SARS-CoV-2 replication. Furthermore, famotidine at concentrations up to 200 μM did not exhibit antiviral activity in

lung cells, the primary target of the COVID-19 virus. Consequently, further research is required to understand the mechanisms by which famotidine may enhance recovery in COVID-19 patients [6].

Mechanism of famotidine for COVID-19

Research suggests that famotidine may exert therapeutic effects in COVID-19 through multiple mechanisms. One proposed mechanism is the inhibition of histamine release from mast cells, which are integral to the inflammatory responses observed during viral infections [7]. By blocking histamine, famotidine may help mitigate the cytokine storm that is often associated with severe cases of COVID-19 [8]. Furthermore, famotidine has been reported to inhibit toll-like receptor 3 (TLR3)-mediated inflammatory signaling, a pathway implicated in the pathogenesis of SARS-CoV-2 infection [2]. These findings indicate that famotidine may not only alleviate gastrointestinal symptoms but also play a critical role in modulating the immune response in COVID-19 patients.

Clinical studies on famotidine in COVID-19 treatment

A comprehensive analysis of the existing literature reveals mixed but promising results regarding the efficacy of famotidine in the treatment of COVID-19. Observational studies have reported a significant reduction in the risk of intubation and mortality among hospitalized patients treated with famotidine compared to those who did not receive the drug [9, 10]. For instance, famotidine use has been associated with a twofold reduction in the risk of death or intubation among hospitalized COVID-19 patients [11]. Additionally, a meta-analysis suggested that famotidine could potentially reduce symptom severity and improve overall outcomes in both inpatient and outpatient settings [12, 13]. However, the optimal dosage and timing of administration remain critical factors influencing these outcomes, with higher doses than those typically used for gastrointestinal conditions being proposed to yield better results [14].

Several clinical studies have aimed to clarify the efficacy of famotidine in COVID-19 treatment. A phase III randomized clinical trial, for example, demonstrated that famotidine could improve outcomes in hospitalized COVID-19 patients, underscoring its potential as a therapeutic agent [7]. Moreover, a systematic review and meta-analysis found that famotidine use was associated with a statistically significant reduction in the risk of death or intubation among hospitalized patients [12]. Despite these encouraging findings, the results across various studies have been inconsistent, with some research indicating no significant protective effect of famotidine compared to standard treatments [15]. This inconsistency highlights the need for further rigorous clinical trials to establish definitive conclusions regarding famotidine's role in COVID-19 management.

Concerns related to side effects and diseases

Although rare, severe adverse effects, including life-threatening conditions, may occur in some individuals. Immediate medical attention should be sought if symptoms indicative of severe side effects arise, such as dizziness, syncope, tachycardia, arrhythmias, or signs of an allergic reaction, including rash and swelling.

Cardiac effects (ECG): Prolongation of the QT interval has been observed in patients with moderate to severe renal impairment, raising concerns about potential cardiac risks.

Vitamin B12 deficiency: Prolonged use of this treatment, especially beyond two years, can impair vitamin B12 absorption, leading to deficiency. This deficiency is dose-dependent and more commonly observed in women and individuals under 30 years of age [16].

Gastrointestinal conditions: The resolution of symptoms does not necessarily indicate the resolution of the underlying gastric disorder.

Renal impairment: Caution is advised due to an increased risk of central nervous system (CNS) adverse effects and QT interval prolongation. Dose adjustments may be required.

Geriatric considerations: Older adults are at increased risk for CNS-related adverse reactions, such as confusion, delirium, hallucinations, disorientation, agitation, seizures, and lethargy.

Pediatric considerations: The use of gastric acid suppressants, including proton pump inhibitors and H2 blockers, may elevate the risk of acute gastroenteritis and pneumonia in children.

Conclusion

Famotidine, a potent H2 receptor antagonist, offers significant promise in peptic ulcer therapy due to its high selectivity and minimal side effects

compared to alternatives. Beyond its traditional use, emerging studies suggest potential benefits in COVID-19 treatment, indicating symptomatic improvement and reduced mortality risk in some cases. However, its efficacy against the virus directly remains unproven, necessitating further research. Despite its benefits, caution is advised due to rare but serious side effects and considerations for specific patient populations.

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Conflict of interest

None.

Author contributions

AAC and AHS took the lead in conducting the literature review, compiling and synthesizing relevant research findings, and drafting the initial manuscript. AHS provided critical guidance on the direction of the review, contributed to refining the research scope, and offered revisions to the manuscript. Both AAC and AHS reviewed the final manuscript, and approved the submission of the final version for publication.

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