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Famotidine Research Progress

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ABSTRACT

There has been an increasing interest in famotidine research within the scientific medical community because of the emerging preliminary evidence suggesting its possible beneficial role in patients with COVID-19. The aim of this paper to provide an overview of famotidine research progress relevant to COVID-19.

INTRODUCTION

Covid-19 is a viral disease associated with Severe Acute Respiratory Syndrome and caused by Coronavirus 2 (SARS-CoV-2). The disease emerged and spread during December, 2019, in Wuhan, Hubei in China. The disease has rapidly became a worldwide pandemic, and according to the live online update available at https://www.worldometers.info/coronavirus/, on the 6th of October, 2020, The disease affected more than 35.5 million person throughout the world, and was associated with more than 1.04 million deaths.

SARS-CoV-2 has already overcome the international efforts to prevent its spread and caused probably the most worldwide pandemic in history. The virus relentlessly continued to infect people and continued to take lives without the emergence of a treatment that is confirmed to have clinically a significant effectiveness. The logical scientific approach to face a potentially fatal viral pandemic with no known effective specific therapies dictate the early use of all the available preliminary research evidence with prioritizing emphasis on safety to avoid making more harm than good in such situation [1-8].

The recent use of famotidine, a class A G protein-coupled receptor antagonist in SARS-CoV2 has been associated with a good outcome. It is worth mentioning that the successful treatment of the USA president, Donald Trump included famotidine [7,9,10].

The combined use of famotidine and hydroxychloroquine has been suggested and is currently being tested in an ongoing clinical trial in the United States. In the 1990s, the use of famotidine as an antiviral agent against Human Immunodeficiency Virus (HIV) has been suggested. The antiviral effect of famotidine has been attributed to the inhibition of proteases involved in the virus replication because it can interact within the catalytic site of the three proteases associated with SARS-CoV2 replication. However, weak binding affinity of famotidine to the three proteases makes successful famotidine therapy more likely when combined with other antiviral drugs and when given intravenously [9,10].

Histamine type 2 receptor antagonists have been reported to have antiviral activities during the 1980s [11]. Kapińska-Mrowiecka, et al. [12] reported the successful treatment of 221 patients with Herpes zoster with cimetidine (200 mg three times daily, and 400 mg once daily at night).

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Bourinbaiar and Fruhstorfer [13] studied the suppressive effect of Histamine Type 2 (H2) receptor antagonists (Cimetidine, ranitidine, and famotidine) on human immunodeficiency virus replication. They found 50% reduction (IC50) in p24 antigen expression caused by the anti-ulcer agent, cimetidine. In contrast to azidothymidine which is a reverse transcriptase inhibitor, cimetidine blocked HIV infection and didn't affect cell growth, and was not associated with cytotoxicity even at high dose. Famotidine and ranitidine had the same effect, but were less potent than cimetidine.

Harcourt, Worley, and Leighton [14] used cimetidine (40 mg/kg for 4 months) as an adjuvant treatment in addition to alpha-interferon in the treatment of a patient with very advanced recurrent papillomatosis who had tracheo-bronchial-pulmonary. The patient experienced a significant improvement in her clinical condition.

Malone, et al. [15] thought that the chief mechanism of action of famotidine for Covid-19 involves on-target histamine receptor H_2 activity, and they emphasized the possibility of the occurrence of dysfunctional mast cell activation and histamine release in association with Covid-19.

Hogan, et al. [16] reported a physician-sponsored cohort study of the use of cetirizine (10 mg b.i.d.) and famotidine (20 mg b.i.d,) in 110 covid-19 hospitalized patients with severe to critical respiratory symptoms. Patients also received standard-of-care. Treatment was associated with a 16.4% rate of intubation, a 7.3% rate of intubation after a minimum of 48 hours of treatment, a 15.5% rate of inpatient mortality, and 11.0 days duration of hospitalization. Treatment was also associated with beneficial lowering of inpatient mortality and progression of symptoms when compared to previously reported cases of COVID-19 inpatients. Concomitant use of hydroxychloroquine was associated with worse outcomes. Hogan, et al. [16] suggested that the use of cetirizine and famotidine can be a safe and effective strategy to reduce the progression in symptom severity, possibly by minimizing the histamine-mediated cytokine storm.

Mather, Seip, and McKay [17] reported a retrospective, propensity-matched observational study which included 878 consecutive COVID-19 patients observed during the period from February 24, 2020, and May 13, 2020. The study aimed at comparing the outcomes in hospitalized covid-19 patients receiving famotidine therapy (83 patients, 9.5%) with patients not receiving famotidine. Famotidine treated patients were younger (63.5 ± 15.0 vs 67.5 ± 15.8 years, p = 0.021), but the two groups did not differ with in baseline demographics and preexisting co-morbidities. Famotidine treatment was associated with a lower risk of in-hospital mortality (odds ratio 0.37, 95% confidence interval 0.16-0.86, p = 0.021) and combined death or intubation (odds ratio 0.47, 95% confidence interval 0.23-0.96, p = 0.040). Patients treated with received famotidine also had lower levels of serum markers for severe disease including lower median peak C-reactive protein levels (9.4 *vs* 12.7 mg/dL, p = 0.002), and lower median procalcitonin levels (0.16 *vs* 0.30 ng/mL, p = 0.004).

Janowitz, et al. [18] reported a study using oral famotidine in 10 covid-19 non- hospitalized patients. Most frequently, famotidine was given in a dose of 80 mg three times daily (n = 6) for a median of 11 days (range: 5-21 days). Treatment was well tolerated, and the ten patients reported marked improvements of symptoms after starting famotidine. The combined symptom score markedly improved within 24 hours of starting famotidine and peripheral oxygen saturation (n = 2) and device recorded activity (n = 1) also increased.

Freedberg, et al. [19] reported a retrospective study which included 1620 covid-19 hospitalized patients with, 84 patients (5.1%) received famotidine within 24 hours of hospital admission. The use of famotidine was associated with a reduced risk of clinical deterioration leading to intubation or death.

A recent evidence-based recommendation which was published in 9 languages [5,6,20-27] emphasized that until now, there is no single drug can result in a virological cure. Therefore, the early use of a combination of safe well-known therapeutic agents having the potential to control the virus has been recommended. Drug combinations may include Azithromycin+ teicoplanin + famotidine, remdesivir + azithromycin, + teicoplanin. The addition of low dose chloroquine can also be considered in patients with healthy hearts [5-7,20-27].

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