Should famotidine be used for treatment of COVID-19?

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RECOMMENDATION

We suggest against the use of famotidine in the treatment of COVID-19. *(Very low quality of evidence; Conditional recommendation)*

Consensus Issues

No issues were raised during the meeting.

Key Findings

Very low-quality evidence from seven retrospective cohort studies was found on the use of famotidine for the treatment of COVID-19. There was no significant reduction in the risk of mortality, mechanical ventilation, and composite outcome of mortality or mechanical ventilation. However, there was a significant increase in the risk of the composite outcome of mortality, mechanical ventilation, and intensive care unit admission. Adverse events were not examined in these retrospective cohort studies.

Introduction

Famotidine is a histamine H2 receptor antagonist and inverse agonist currently being used as alternative treatment for gastroesophageal reflux disease (GERD), hypersecretory disorders, non-ulcer dyspepsia, and benign gastric and duodenal ulceration. The H2 receptor, aside from its well-known role in gastric secretion, is also expressed by mast cells, which release pro-inflammatory cytokines that promote lung damage [1] and increase in number in the alveoli of severe acute coronavirus-2 (SARS-CoV-2)-infected patients. [2] It has recently become a drug of interest in the treatment of coronavirus disease 2019 (COVID-19). The mechanism of action for famotidine in this regard is currently unclear; however, it has been shown to inhibit neither (SARS-CoV-2) proteases nor SARS-CoV-2 infection and replication in cultured cells [1,3] and may instead act through direct H2 receptor inhibition [1]. This study investigated the effect of famotidine compared to placebo or standard-of-care treatment in influencing clinical outcomes of patients with confirmed COVID-19.

Methods

A database search of MEDLINE and Cochrane CENTRAL with a combination of free-text and MeSH terms including "COVID-19" and "famotidine" was done to search for randomized controlled trials, cohort studies, systematic reviews, and meta-analyses that report the effect of famotidine compared to placebo or standard of care in the management of COVID-19 patients. Preprints were obtained by searching the medRxiv, bioRxiv, and ChinaXiv databases, and ongoing clinical trials were searched in ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform, and the Chinese Clinical Trials Registry. These were supplemented by searches in the COVID-NMA living database and the COVID-19 Living

Evidence Database, the latter of which includes articles from Embase. The final search date was on May 2, 2021.

No restrictions on patient COVID-19 severity status, treatment outcome, country, or language were. Studies that were not original research, in-vitro studies, case-control studies and case series, studies combining famotidine with another drug, and those that compare famotidine to treatments that are not placebo or standard of care were excluded.

Included studies were appraised for risk of bias using the Newcastle-Ottawa Scale for cohort studies [4]. Data extracted included country, study design, patient profile, sample size (famotidine and non-famotidine groups), patient age and sex ratio, primary outcome, and reported hazard ratio (HR) or odds ratio (OR). Whenever possible, the review used HR and OR estimates reported after adjustment of study groups to minimize the risk of bias due to confounders [5]. All data were analyzed using Review Manager 5.4 (Cochrane Collaboration).

Results

Characteristics of included studies

Seven studies were obtained following the database search, with a total sample size of 42,459 (**Appendix 1**). All studies used data retrospectively obtained from either a single-center database [6,7] or a database spanning multiple centers [8-12]. A total of 4022 patients (median = 519, range 23-1623) were enrolled in the famotidine group, and 38437 (median = 1536, range 795-24404) in the non-famotidine group.

Methodological quality

Four studies (57%) had a Newcastle-Ottawa score of 9/9 [6,10-12], while three studies (43%) had a score of 8/9 [7-9], indicating low risk of bias across the included studies. Three studies [8-9,12] did not conclusively demonstrate that the specified treatment outcomes were not present at the start of the study, while one [7] did not specify the length of follow-up for recruited patients.

Efficacy and safety

Four categories of efficacy outcomes were reported by the included studies: 1) mortality, 2) need for mechanical ventilation (MV), 3) a composite of mortality or MV, and 4) a composite of mortality, MV, and ICU admission (**Appendix 1)**. Pooled estimates were not obtained for outcome categories with multiple studies as they reported both HR and OR. Four studies reported HR or OR for all-cause mortality [7,9-11]; of these, one study reported that famotidine significantly reduced the risk of mortality [7], while three reported no effect [9-11]. One study [9] reported data for MV only, with an aOR of 0.469 (95% CI 0.228-0.965). Three studies [6,9-10] reported HR or OR for a composite of death or MV; two studies reported a significant decrease in risk with famotidine [6,9], although their sample sizes were small compared with the third study, which reported no effect [10]. Two studies [8,12] reported HR for a composite of mortality, MV, and ICU admission; of these, one study reported no effect for famotidine [8], although the second study, which used the same database but with an expanded search date range, reported a significant decrease in risk [12]. Adverse events were not examined in these retrospective cohort studies.

Table 1. Effect measures of famotidine per outcome category.

STUDY ID	FAMOTIDINE	NO FAMOTIDINE	EFFECT MEASURES (95% CI)	ASSOCIATION
IN-HOSPITAL MORTALITY				
Mather 2020	83	795	aOR 0.366 (0.155-0.862)	No effect
Mura 2021	563	816	aOR 0.73 (0.57-0.94)	Decreased risk
Shoaibi 2020	1623	24404	aHR 1.03 (0.89-1.18)	No effect
Yeramaneni 2020	1127	6031	aOR 1.59 (0.94-2.71)	No effect
MECHANICAL VENTILATION				
Mather 2020	83	795	aOR 0.469 (0.228-0.965)	Decreased risk
COMPOSITE OF MORTALITY AND MECHANICAL VENTILATION				
Freedberg 2020	84	1536	aHR 0.43 (0.21-0.88)	Decreased risk
Mather 2020	83	795	aOR 0.469 (0.228-0.965)	Decreased risk
Shoaibi 2020	1623	24404	aHR 1.03 (0.95-1.15)	No effect
COMPOSITE OF MORTALITY, MECHANICAL VENTILATION, AND ICU ADMISSION				
Cheung 2021	23	929	aOR 1.34 (0.24-6.06)	No effect
Zhou 2020	519	3926	aHR 1.81 (1.28-2.58)	Increased risk

**aOR – adjusted odds ratio; aHR – adjusted hazards ratio*

Recommendations from other groups

The Infectious Disease Society of America released a guideline on famotidine for hospitalized patients dated June 2020. Based on one non-randomized study, the society recommends against famotidine use for the sole purpose of treating COVID-19 outside the context of a clinical trial [13].

Research gaps

Data from randomized controlled trials (RCTs) are needed to determine the efficacy of famotidine in treating COVID-19. To this end, 4 clinical trials, including 3 RCTs, are currently being run (**Appendix 3**).

References

[1] Malone RW, Tisdall P, Fremont-Smith P, Liu Y, Huang X-P, White KM, Miorin L, Moreno E, Alon A, Delaforge E, Hennecker CD, Wang G, Pottel J, Blair RV, Roy CJ, Smith N, Hall JM, Tomera KM, Shapiro G, Mittermaier A, Kruse AC, García-Sastre A, Roth BL, Glasspool-Malone J, Ricke DO. COVID-19: famotidine, histamine, mast cells, and mechanisms. Front. Pharmacol. 2021;12:633680.

[2] Motta Junior JDS, Miggiolaro AFRDS, Nagashima S, de Paula CBV, Baena CP, Scharfstein J, de Noronha L. Mast cells in alveolar septa of COVID-19 patients: a pathogenic pathway that may link interstitial edema to immunothrombosis. *Front Immunol.* 2020 Sep 18;11:574862.

[3] Loffredo M, Lucero H, Chen DY, O'Connell A, Bergqvist S, Munawar A, Bandara A, De Graef S, Weeks SD, Douam F, Saeed M, Munawar AH. The in-vitro effect of famotidine on SARS-CoV-2 proteases and virus replication. *Sci Rep*. 2021 Mar 8;11(1):5433.

[4] Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2013. Available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

[5] Reeves BC, Deeks JJ, Higgins JPT, Shea B, Tugwell P, Wells GA. Chapter 24: Including non-randomized studies on intervention effects. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions.* 2nd Edition. Chichester (UK): John Wiley & Sons, 2019: 595–620.

[6] Freedberg DE, Conigliaro J, Wang TC, Tracey KJ, Callahan MV, Abrams JA; Famotidine Research Group. Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 Patients: a propensity score matched retrospective cohort study. *Gastroenterology.* 2020 Sep;159(3):1129-1131.e3. doi: 10.1053/j.gastro.2020.05.053.

[7] Mura C, Preissner S, Nahles S, Heiland M, Bourne PE, Preissner R. Clinical evidence for improved outcomes with histamine antagonists and aspirin in 22,560 COVID-19 patients. *medRxiv.* 2021 Apr 5. doi: 10.1101/2021.03.29.21253914

[8] Cheung KS, Hung IFN, Leung WK. Association between famotidine use and COVID-19 severity in hong kong: a territory-wide study. *Gastroenterology.* 2021 Apr;160(5):1898-1899. doi: 10.1053/j.gastro.2020.05.098.

[9] Mather JF, Seip RL, McKay RG. Impact of famotidine use on clinical outcomes of hospitalized patients with COVID-19. *Am J Gastroenterol.* 2020 Oct;115(10):1617-1623. doi: 10.14309/ajg.0000000000000832.

[10] Shoaibi A, Fortin SP, Weinstein R, Berlin JA, Ryan P. Comparative effectiveness of famotidine in hospitalized COVID-19 patients. *Am J Gastroenterol.* 2021 Apr;116(4):692-699. doi: 10.14309/ajg.0000000000001153

[11] Yeramaneni S, Doshi P, Sands K, Cooper M, Kurbegov D, Fromell G. Famotidine use is not associated with 30-day mortality: a coarsened exact match study in 7158 hospitalized patients with coronavirus disease 2019 from a large healthcare system. *Gastroenterology*. 2021 Feb;160(3):919-921.e3. doi: 10.1053/j.gastro.2020.10.011.

[12] Zhou J, Wang X, Lee S, Wu WKK, Cheung BMY, Zhang Q, Tse G. Proton pump inhibitor or famotidine use and severe COVID-19 disease: a propensity score-matched territory-wide study. *Gut*. Epub ahead of print: 04 December 2020. doi: 10.1136/gutjnl-2020-323668.

[13] Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, Edwards KM, Gandhi R, Gallagher J, Muller WJ, O'Horo JC, Shoham S, Murad MH, Mustafa RA, Sultan S, Falck-Ytter Y. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America 2021; Version 4.2.0. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 12 May 2021.

Appendix 1. Characteristics of Included Studies

STUDY ID	COUNTRY	STUDY DESIGN	PATIENT PROFILE	SAMPLE SIZE		PATIENT AGE AND SEX RATIO	FAMOTIDINE INTERVENTION	CO-INTERVENTIONS	PRIMARY OUTCOME	NEWCASTLE-OTTAWA SCORE
				FAMOTIDINE	COMPARISON					
Cheung 2021	Hong Kong	Multi-center retrospective cohort study	Adult patients diagnosed with COVID-19 from January 1 to May 10, 2020	23	929	N/A	N/A	Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aspirin, statins, prednisolone	Severe disease, defined as: 1) Critical complication (respiratory failure, septic shock, and/or multiple organ dysfunction) 2) Ventilatory support 3) ICU admission 4) Mortality	8
Freedberg 2020	United States	Single-center retrospective cohort study	Patients testing positive for SARS-CoV-2 within 72 h after hospital admission	84	1536	Mean age 67 +/- 16 years 54.7% male, 45.3% female	PO (72%) IV (28% of total): 10 mg/d (17%), 20 mg/d (47%), 40 mg/d (35%) Median dose: 136 mg, 5.8 days	N/A	Death or intubation by hospital day 30	9
Mather 2020	United States	Multi-center retrospective cohort study	COVID-19-positive patients requiring hospital admission	83	795	55.7% female, 44.3% male	66.3% intake during admission only, 28.9% before and during admission, 4.8% before admission only PO (83% of total): 20 mg/d (95.2%), 40 mg/d (4.8%) IV (17% of total): 20 mg/2 mL solution Median inpatient dose: 80 mg, 4 d	Hydroxychloroquine, azithromycin, remdesivir, corticosteroids	In-hospital mortality, mechanical ventilation, intubation-free survival	8
Mura 2021	Multinational (30 countries)	Single-center retrospective cohort study	Patients with severe COVID-19 requiring ventilatory support	563	816	N/A	N/A	N/A	All-cause mortality	8
Shoaibi 2020	United States	Multi-center retrospective cohort study	Hospitalized adult patients with COVID-19	1623	24404	N/A	On the day of admission: 20 mg (73.29%), 40 mg (20.59%)	N/A	Mortality, or combination of mortality and intensive services	9

							63.6% PO, 39.04% IV, 1.4% both		(mechanical ventilation, tracheostomy or ECMO)	
Yeramaneni 2020	United States	Multi-center retrospective cohort study	Hospitalized patients with COVID-19	1127	6031	Mean age 57.9 +/- 19.3 years 50.9% female, 49.1% male 44.6% white, 25.2% black	PO or IV within 24 h of admission	Azithromycin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, remdesivir, tocilizumab, corticosteroids	All-cause mortality by hospital day 30	9
Zhou 2020	Hong Kong	Multi-center retrospective cohort study	Adult patients diagnosed with COVID-19 from January 1 to August 22, 2020	519	3926	Median age 44.8 years 50% male, 50% female	Famotidine group = median age 60.4, 46.62% male Non-famotidine group = median age 42.3, 50.61% male		Need for ICU admission, intubation, or death	8

Appendix 2. GRADE Summary of Evidence

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	famotidine	no famotidine	Relative (95% CI)	Absolute (95% CI)		
In-hospital mortality												
4	observational studies	not serious	serious [a]	not serious	serious [b]	none	Two studies (Mather et al, Mura et al) reported decreased odds, while two studies (Shoaibi et al, Yeramaneni et al) reported no change in risk or odds.				⨁◯◯◯ VERY LOW	
Mechanical ventilation												
1	observational studies	not serious	not serious	not serious	not serious	none	18/83 (21.7%)	221/795 (27.8%)	**OR 0.469** (0.228 to 0.965)	**125 fewer per 1,000** (from 197 fewer to 7 fewer)	⨁⨁◯◯ LOW	
In-hospital mortality and mechanical ventilation												
3	observational studies	not serious	not serious	not serious	serious [b]	none	Two studies (Freedberg et al, Mather et al) reported decreased odds or risk, while one study (Shoaibi et al) reported no change in odds.				⨁◯◯◯ VERY LOW	
In-hospital mortality, mechanical ventilation, and ICU admission												
2	observational studies	not serious	not serious	not serious	serious [b]	none	One study (Zhou et al) reported increased risk, while the other (Cheung et al) reported no change in odds.				⨁◯◯◯ VERY LOW	

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. One study (Mura 2020) included only patients with severe disease requiring ventilatory support, while the others included hospitalized patients only.

b. Narrative synthesis conducted, estimates not precise.

Appendix 3. Characteristics of ongoing trials

Clinical Trial Identifier (Location)	Official Title	Methodology	Outcome Measures	Population	Estimated Date of Completion
NCT04724720 United States	A Randomized, Double-Blind, Comparative Trial of the Safety and Efficacy of Famotidine vs Placebo for the Treatment of Non-Hospitalized Symptomatic Adults With COVID-19	Randomized, Double-Blind Comparative Placebo Controlled Trial	**Primary outcome:** Cumulative incidence of symptom resolution [Time Frame: Day 28] **Secondary outcomes:** Cumulative incidence of symptom resolution [Time Frame: Day 60] Relative change of symptoms Assessment of serious adverse events Clinical improvement Improvement in peripheral oxygen saturation Mortality Comparative proportions of hospitalized patients Change in systemic inflammation (CRP, procalcitonin, ferritin	56 non-hospitalized symptomatic adults with COVID-19	December 2021
NCT04565392 United States	Proof-of-concept Randomized Placebo-controlled Trial of Famotidine for Outpatients With COVID-19	Parallel double-blind placebo-controlled interventional trial	**Primary outcomes:** Clinical course binary outcome Serious adverse events **Secondary outcomes:** 30- and 60-day follow-up of: Time to symptomatic recovery Self-check list of 18 COVID-19 symptoms Patient's global impression of change Adverse events	150 adult patients with COVID-19 symptoms	January 31, 2022
NCT04834752 South Korea	Effect of Histamine 2 Receptor Antagonist (H2RA) and Proton Pump Inhibitor (PPI) on the Positivity Rates and Clinical Outcomes of Coronavirus Disease-19 (COVID-19).	Multi-center retrospective cohort study	**Primary outcomes:** COVID-19 test positivity Mortality at 60 days **Secondary outcomes**: ICU admission rate Mechanical ventilator application rate Oxygen support application rate Rates of vasopressor and inotrope use	400000 adult patients testing for COVID-19	December 31, 2021
IRCT20200509047364N2 Iran	The effect of Famotidine on the improvement of patients with COVID-19	Randomized single-blind comparative placebo clinical trial	Respiratory rate Oxygen saturation state Lung infiltration status LDH, CRP levels Lymphocyte, platelet counts Patient temperature Length of hospitalization Length of ICU admission	20 confirmed COVID-19 patients	N/A