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RESEARCH ARTICLE

Eosinophilia Due To Famotidine Use In COVID-19 Patients

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Abstract

Introduction: Famotidine has been suggested as a potential treatment for coronavirus disease 2019 (COVID-19). We compared the incidence of COVID-19 outcomes (i.e. death and need for oxygen therapy or intensive service use) among hospitalized patients who received famotidine therapy and those who did not. **Methods:** We conducted a retrospective cohort study using data from COVID-19 Ankara Bilkent City Hospital electronic health records. The study population was COVID-19 hospitalized patients aged 18 years or older. **Results:** A total of 99 patients, 52 male and 47 female, aged between 20 and 93, were included in the study. All patients received standard of care (SOC) medications (favipiravir, hydroxychloroquine, low molecular weight heparin, acetylsalicylic acid or dipyridamole). 63 patients received famotidine treatment.36 patients did not receive famotidine.47 patients had decreased saturation and needed oxygen therapy. 38 patients who received famotidine needed anti-inflammatory treatment.There were 53 patients with fever, 49 with headache, 52 with dyspnea, 65 with cough, and 31 with decreased taste. Compared to the patients who were not treated with famotidine, the oxygen requirement was found to be lower in the patients treated with famotidine (p1: 0.001), but the eosinophil value increased after the treatment (p1: 0.025). While there were 10 patients who needed ICU (Intensive Care Unit), mortality developed in 8 patients. The mean hospital stay was 10.89±6.6 days. **Conclusıon:** According to our study, treatment with famotidine achieved a better clinical outcome compared to the control group in severe COVID-19 illness, although no significant survival benefit was found. The eosinophil level was found to be increased after treatment with famotidine.There are studies in the literature showing that eosinophilia increases thromboembolism. We do not recommend the use of famotidine treatment in patients with COVID-19 who have high eosinophil levels, as this may further aggravate the clinical picture in COVID-19 patients.

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Introduction

Coronavirus disease 2019 (COVID-19) is predominantly a respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) that first arose in December 2019 in Wuhan, China. Continued optimization of medical therapy remains essential in combating COVID-19 [1].

Famotidine is a competitive histamine H2-receptor antagonist. Its main pharmacodynamic effect is the inhibition of gastric acid secretion [2]. In February 2020, a study by Wu et al., used computational methods to predict structures of proteins encoded by the SARS-CoV-2 genome in order to identify available drugs that may be repurposed to treat COVID-19 [3]. Famotidine was found to be a potential candidate that may inhibit 3 chymotrypsin-like protease (3CLpro), a viral enzyme necessary for SARS-CoV-2 viral replication. Subsequently, several studies have reported on the use of famotidine in treating COVID-19 patients [4,5]. Specifically, Freedberg et al. and Mather et al. found that in patients hospitalized with COVID-19, famotidine use was associated with a reduced risk of clinical deterioration leading to intubation or death [6,7].

In light of a potential beneficial therapeutic effect, the purpose of the present study was to examine the impact of famotidine on clinical outcomes in a COVID-19 hospitalized patients. We hypothesized that famotidine would be associated with improved clinical outcomes among hospitalized patients with COVID-19. To explore this, we performed a retrospective cohort study at a single center located at the epicenter of the COVID-19 pandemic in Türkiye.

Material and Methods

Study population

The study group for this report was derived from an electronic database collected at Ankara Bilkent City Hospital encompassing consecutive patients screened for COVID-19 between January 20, 2020, and July 13, 2020. All patients who tested positive for severe acute respiratory syndrome (SARS-CoV-2) by nasopharyngeal polymerase chain reaction and who required inpatient admission were included in this study. Ethical approval for the study was granted by the Ethics Committee of Ankara City Hospital (Date: 15.03.2023, Number: E2-23-3598). red with an ADVIA 1800 device (Siemens Healthineers, Germany) and a commercially available kit (Rel Assay Diagnostics, Gaziantep, Turkey).

Famotidine use

All patients received standard of care (SOC) medications (favipiravir, hydroxychloroquine, low molecular weight heparin, acetylsalicylic acid or dipyridamole).Patients were classified as receiving famotidine if they were treated with oral drugs on hospital admission. Famotidine use was extracted directly from the electronic medical record.

Baseline data and covariates

COVID-19 was diagnosed by nasopharyngeal polymerase chain reaction. Severe COVID-19 infection was defined as SpO2 < 94% in room air, ratio of partial pressure of oxygen and inspired air fraction (PaO2/FiO2) < 300 mm Hg, more than 50% involvement of lungs, and respiratory rate > 30 breaths/min.

Statistical Analysis

Statistical analysis was made by Statistical Package for Social Sciences version 25. The conformity of the variables to the normal distribution was examined by histogram graphics and the Kolmogorov-Smirnov test. Mean, standard deviation, median, min-max values were used while presenting descriptive analyzes. Categorical variables were compared with the Chi-Square Test. The Mann Whitney U Test was used when evaluating non-normally distributed (nonparametric) variables between two groups. Repeated Measures Analysis was used to evaluate the change in measured values between groups. Cases with a P-value below 0.05 were considered as statistically significant results.

Results

A total of 99 patients, 52 male and 47 female, aged between 20 and 93, were included in the study. Of these, 63 received famotidine. 47 patients needed O2.There are 53 patients with fever, 49 patients with headache, 52 patients with dyspnea, 65 patients with cough, 31 patients with decreased taste. While there were 10 patients who needed ICU, mortality developed in 8 patients. The mean hospital stay was 10.89±6.6 days. Evaluation of symptoms, mortality and need for intensive care unit admission according to famotidine treatment is shown in Table 1-2.

Table 1: Symptoms,mortality,clinical and demographic characteristics according to famotidine treatment

		n	%
Gender	Male	52	(52,53)
	Female	47	(47,47)
Famotidine		36	(36,36)
Oxygen supplementation		47	(47,47)
Fever		53	(53,54)
Headache		49	(49,49)
Dyspnea		52	(52,53)
Cough		65	(65,66)
Taste disorders		31	(31,31)
Mortality		8	(8,08)
Intensive care unit admission		10	(10,10)

n: Number of patients

Urea, NLR, Eosinophil, WBC values are given in Table 2.

Table 2:

	n	%
Age	59,8±18,24	61 (20-93)
Urea 1 (mg/dL)	46,94±29,2	38,73 (13-167)
Urea 2 (mg/dL)	54,99±43,67	41 (17-338,12)
NLR 1	7,19±7,74	4,42 (0,96-51,5)
NLR 2	6,86±7,41	4,3 (0,89-45)
Eosinophil 1 (x10^9/L)	0,05±0,07	0,02 (0-0,35)
Eosinophil 2 (x10^9/L)	0,09±0,13	0,04 (0-0,8)
WBC 1 (x10^9/L)	7,39±3,58	7,16 (0,03-19,34)
WBC 2 (x10^9/L)	9,03±4,34	8,42 (0,09-24,1)
Hospital admission	10,89±6,6	9 (1-33)

n is replaced by mean±s.d,% is replaced by median (min-max).

WBC:White Blood Cell Count (x10^9/L)
NLR:Neutrophil to Lymphocyte Ratio
Urea1:Urea Value Before Treatment (mg/dL)
Urea2:Urea Value After Treatment (mg/dL)
NLR1: NLR Before Treatment
NLR 2:NLR After Treatment
Eos1:Eosinophil Value Before Treatment (x10^9/L)
Eos2: Eosinophil Value After Treatment (x10^9/L)
WBC1:WBC Before Treatment (x10^9/L)
WBC2:WBC After Treatment (x10^9/L)

Table 3: Evaluation of symptoms, mortality and need for intensive care unit admission according to famotidine treatment

		Famotidine				
		No		Yes		p[1]
		n	%	n	%	
Age		67±15,58	69,5 (25-93)	55,68±18,48	54 (20-91)	**0,002**
Gender	Male	22	(61,11)	30	(47,62)	0,196
	Female	14	(38,89)	33	(52,38)	
Oxygen supplementation		25	(69,44)	22	(34,92)	**0,001**
Fever		16	(44,44)	37	(58,73)	0,170
Headache		15	(41,67)	34	(53,97)	0,239
Dyspnea		20	(55,56)	32	(50,79)	0,648
Cough		28	(77,78)	37	(58,73)	0,055
Taste disorders		9	(25,00)	22	(34,92)	0,306
Mortality		5	(13,89)	3	(4,76)	0,109
Hospital admission		12,11±7,34	10 (4-32)	10,19±6,09	9 (1-33)	0,238
Intensive care unit admission		5	(13,89)	5	(7,94)	0,344

n: Number of patients

Pre-treatment Urea, Post-treatment Urea, Pre-treatment NLR values are lower in those taking famotidine, while Eosinophil level is higher after treatment. There was no significant difference between those who took famotidine and those who did not in terms of changes in Urea, NLR, Eosinophil, WBC values. Those who took famotidine were younger than those who did not. O2 need was found to be less in those taking famotidine. Evaluation of laboratory values before and after famotidine treatment is shown in Table 4.

Compared to the patients who were not treated with famotidine, the oxygen requirement was found to be lower in the patients treated with famotidine (p^1:0.001), but the eosinophil value increased after the treatment (p^1:0.025).

Table 4: Evaluation of laboratory values before and after treatment

	Famotidine					
	No		Yes			
	n	%	n	%	p¹	p²
Urea 1 (mg/dL)	63,99±36,43	53 (23-167)	37,19±18,27	32,1 (13-98)	0,001	0,216
Urea 2 (mg/dL)	78,43±61,68	59,46 (24-338,12)	41,59±19,11	34,4 (17-96)	<0,001	
NLR 1	7,24±4,51	6,22 (1,5-18,19)	7,17±9,13	3,37 (0,96-51,5)	0,022	0,058
NLR 2	9,35±10,24	5,46 (1,1-45)	5,44±4,67	3,5 (0,89-20,45)	0,062	
Eosinophil 1 (x10^9/L)	0,05±0,06	0,03 (0-0,2)	0,05±0,07	0,02 (0-0,35)	0,915	0,055
Eosinophil 2 (x10^9/L)	0,06±0,09	0,02 (0-0,46)	0,11±0,14	0,07 (0-0,8)	0,025	
WBC 1 (x10^9/L)	7,19±3,5	7,29 (0,03-15)	7,49±3,64	7,07 (0,8-19,34)	0,907	0,436
WBC 2 (x10^9/L)	8,37±4,64	7,78 (0,09-22,28)	9,41±4,14	8,53 (1,5-24,1)	0,234	

n is replaced by mean±s.d, % is replaced by median (min-max).
p¹:Difference between pre- and post-treatment laboratory values with famodin
p²:The value showing the relationship between famodin and the parameters before and after treatment
Urea 1:Urea Value Before Treatment (mg/dL)
Urea 2:Urea Value After Treatment (mg/dL)
NLR1:Neutrophil to Lymphocyte Ratio Before Treatment
NLR 2:Neutrophil to Lymphocyte Ratio (After Treatment
Eos1:Eosinophil Value Before Treatment (x10^9/L)
Eos2: Eosinophil Value After Treatment (x10^9/L)
WBC1:White Blood Cell Count Before Treatment (x10^9/L)
WBC2:White Blood Cell Count After Treatment (x10^9/L)

Discussion

The treatment of famotidine has been shown to reduce the need for oxygen in some studies.[6] In our study, the oxygen requirement was also found to be lower in patients who received famotidine. However, the lower mean age of the patients receiving famotidine was the limitation of our study. Also, the low number of patients and the evaluation of patients who were suitable for service follow-up at the time of diagnosis were the limitations of our study.We recommend that similar studies be conducted in patients with intensive care hospitalization.

In the study of Mather et al[7] and Pahwani et al[8] famotidine was shown to shorten the length of stay, but in our study, no significant difference was found between the length of stay. Again, in the study of Mather et al,[7] famotidine was shown to reduce mortality, but in our study, no significant difference was found between the effect of famotidine on mortality in COVID-19 patients and the length of stay of the patients.According to our study, there was no significant survival benefit among patients who received famotidine therapy and those who did not. Also no significant difference was observed between those who used famotidine and those who did not, in terms of the need for intensive care admission, but in the meta-analysis of Chiu et al. it was observed that the need for intensive care hospitalization was less among famotidine users.[9]

Although the neutrophil-lymphocyte ratio was shown as a critical determinant for the assessment of disease severity in COVID-19 patients,[10] we did not find a significant difference between the neutrophil-lymphocyte ratio in both groups in our study.However we thought that generalization would be wrong and further studies were needed on this subject.

There are several studies showing that the use of histamine H2 blockers causes hypersensitivity. It has been reported that ranitidine may be associated with eosinophilic myocarditis,[10] famotidine causes erythema together with eosinophilia.[11] However, more studies are needed on famotidine and other histamine H2 blockers. In addition, the link between hypereosinophilic syndrome and ischemic stroke has been shown, and there are studies in the literature indicating that secondary eosinophilia also causes thromboembolism[12-13] In our study, there was no significant difference between the groups that received and did not receive famotidine for the number of eosinophils before treatment, but a significant increase was observed in the number of eosinophils after famotidine treatment. The relationship between eosinophilia and thromboembolism secondary to famotidine use has been reported in previous studies.[11-12] In the literature review published by Zerangian et al., it was stated that there were many embolism cases in patients hospitalized due to covid and similar viral infections, although the reason is not clear.[14] Eventually, hospitalized patients infected with the viral diseases could mainly suffer from an anomalous risk of coagulation activation with enhanced venous

thrombosis events and poor quality clinical course. Since this situation may aggravate the clinical picture in hospitalized patients with viral infections, we suggest that the risk of thromboembolism should be taken into account when using famotidine as a treatment option in COVID-19 patients with high pre-treatment eosinophil values and other thromboembolism-related viral diseases. Although no thromboembolic event was observed in our study, we thought that an increase in eosinophilia would predispose to hypercoagulability. From this, we suggest that the relationship between eosinophil levels and thromboembolism in patients hospitalized for COVID-19 patients and viral infections and who had a thromboembolic event should be retrospectively examined. In our study, we did not observe an increase in mortality secondary to a thromboembolic event related to COVID-19. However, the limitation of our study was that we did not observe an increase in mortality due to the small number of patients.

As a result, it was observed that the use of famotidine could increase the number of eosinophils. Therefore, we recommend paying attention to the use of famotidine to reduce the risk of thromboembolic events secondary to eosinophilia in patients with high eosinophil count before treatment.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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