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Role of Favipiravir on the Hematologic parameters in patients with COVID-19 infection

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ABSTRACT

Objective: Favipiravir is a novel, orally bioavailable, purine nucleoside analogue drug. Recent studies showed that it was related to faster viral clearance time and a significant improvement rate in chest imaging in patients with COVID-19. While the mechanism of action of Favipiravir is well characterized, there is insufficient data about its effects on haematological inflammatory parameters during COVID 19 infection.

Material and Methods: This observational study included 92 patients with COVID-19 (50 of them were female) with mild to moderate disease who taken Favipiravir in the Pandemic Center at Giresun University School of Medicine from April 2020 to October 2020. Patients with severe COVID-19 infection were excluded from the study.

Results: After the five days of Favipiravir administration, compared to before the treatment, it was observed that the neutrophil counts of the patients (before the treatment mean 5.97 109/L (5.1 - 6.84) and after treatment 4.82 109/L (4.29 - 5.35) p=0.039) and Neutrophil/lymphocyte ratio (NLR) markedly decreased (before the treatment mean 6.88 (5.33 - 8.42) and after treatment 4.67 (3.23 - 6.10) p=0.002), while the lymphocyte count increased and these alternations were statistically significant. Platelet count and MCV levels were slightly increased after the treatment also statistically significant (p<0.001, p=0.001). Although there was a significant decrease in CRP levels, no significant change was observed in other inflammatory markers (Ferritin, Sedimentation, Fibrinogen, D-Dimer, and Troponin). The overall mortality rate was 4%, with no deaths in ICU.

Conclusion: In our study; in addition to previous knowledge from recent studies; increasing in the platelet count and decreasing in CRP and MPV levels are remarkable findings. These data may guide in the follow-up of Favipiravir treatment and in determining the prognosis.

Keywords: Favipiravir, COVID-19, Hematologic Parameters

INTRODUCTION

Coronavirus Disease 19 (COVID-19) is a severe acute infection that can lead to severe respiratory failure. Corona Virus (SARS)-CoV-2, coronavirus infection has affected the whole world since the world health organization declared it is a pandemic in March 2020 (1). COVID 19 infection is characterized by fever, shortness of breath, higher D dimer levels, lymphopenia and pulmonary infiltrates, including ground-glass opacities on computed tomography of the chest (2). Favipiravir is a novel, orally bioavailable, purine nucleoside analogue that competitively inhibits RNA-dependent RNA polymerase, and hence viral RNA is not produced in the infected cells (3). So it acts against a wide range of human viruses, including influenza A and B, viral haemorrhagic fever, and SARS-CoV-2. Treatment strategy with Favipiravir includes 6000 mg loading on the first day followed by maintenance therapy of 1200 mg orally twice daily for ten days (4).

Favipiravir is metabolized mainly by aldehyde oxidase and partially by xanthine oxidase to an inactive oxidative metabolite that is excreted in the hydroxylated form through the renal system.

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It also has complex nonlinear kinetics due to the self-inhibition of aldehyde oxidase, and its inhibition results in a reduced concentration of the drug during therapy (5). Favipiravir treatment in patients with mild to moderate renal impairment (GFR < 60 mL/min) results in a 1.5-fold increase in plasma levels of the drug than those with normal renal function; however, there is no evidence of its use among patients with GFR < 30 mL/min. Thus, renal functions play a major role in the metabolism of Favipiravir (6). Pharmacotherapy with Favipiravir is contraindicated for pregnant women due to its potential teratogenic and embryo toxic effects observed on animal studies (7). Although randomized, double-blinded, and placebo-controlled studies have not been conducted among patients on Favipiravir treatment, authors recently showed that it was related to faster viral clearance time and significant improvement rate in chest imaging in patients with COVID-19 (8). While the mechanism of action of Favipiravir is well characterized, there is insufficient data about its effects on haematological and inflammatory parameters during COVID 19 infection. The aim of this study was to determine if Favipiravir treatment affects the results of hematologic, biochemical and blood gas analysis parameters on the and fifth day of treatment during COVID 19 infection.

MATERIAL and METHODS

This observational study included 92 COVID-19 patients (50 of them were female) with mild to moderate disease who were given Favipiravir treatment in the Pandemic Center at Giresun University School of Medicine from April 2020 to October 2020. Mandatory permissions were obtained from the local ethics committee and the ministry of health. Patients with severe COVID-19 infection (patients with room air oxygen saturation < 90% or P/F ratio < 200 or need for ICU) were excluded from the study.

Demographic, laboratory and clinical data were retrospectively collected and analysed.

The treatment protocol was as follows: 6000 mg loading on the first day followed by maintenance therapy of 1200 mg orally twice daily for five days as recommended by the ministry of health. We assessed the key baseline demographics and laboratory parameters at the first and fifth days of the treatment. Significant factors were assessed on univariate analysis. Exclusion criteria were prior to chronic renal failure, known malignancy, or using antibiotics or steroids for other reasons

RESULTS

Total 92 patients included the study Female %54.3 (n=50) Male %47.7 (n=42).

Alternations of hematological parameters: The alternation before and after the Favipiravir treatment was summarized in **Table 1**. Compared to before the treatment it was observed that the neutrophil counts of the patients and Neutrophile/lymphocyte ratio (NLR) markedly decreased, while the lymphocyte count increased and these alternations were statistically significant. The total count of leukocytes decreased but not statistically significant. Platelet count and MCV levels were slightly increased after the treatment also statistically significant. Hgb was not changed.

Inflammatory parameters: Although there was a significant decrease in CRP levels, no significant change was observed in other inflammatory markers (summarized in **Table 2**).

There was a significant increase in uric acid level parallel to MCV. Significant increase in uric acid levels compared to before treatment (before the treatment mean 4.9 mg/dl (4.43 - 5.36) and after treatment 5.46 mg/dl (4.95 - 5.97, p=0.013). The overall mortality rate was 4%, with no deaths in ICU.

Table 1: Hematological parameters

	n	Before Treatment	After Treatment	Before - After	p
WBC (10^9/L)	92	7.82 (6.93 - 8.71)	7.05 (6.48 - 7.62)	0.77 (-0.03 - 1.58)	0.293
NEU(10^9/L)	92	5.97 (5.1 - 6.84)	4.82 (4.29 - 5.35)	1.15 (0.32 - 1.97)	**0.039**
LYMP(10^9/L)	92	1.44 (1.00 - 1.89)	1.50 (1.35 - 1.64)	-0.05 (-0.5 - 0.39)	**0.001**
MPV (fL)	92	9.3 (9.1 - 9.5)	9.1 (8.9 - 9.3)	0.20 (0.05 - 0.35)	**0.010**
PLT(10^9/l)	92	246 (224 - 268)	328 (300 - 356)	-81.5 (-106.1 - -56.9)	**<0.001**
NLR	92	6.88 (5.33 - 8.42)	4.67 (3.23 - 6.10)	2.21 (0.39 - 4.03)	**0.002**
HGB (g/dL)	92	12.4 (12 - 12.8)	12.2 (11.8 - 12.6)	0.19 (-0.03 - 0.42)	0.097
MCV(fL)	92	88 (87 - 89)	88 (87 - 89)	-0.15 (-0.65 - 0.34)	**0.019**

Table 2: Inflammatory markers

	n	Before Treatment	After Treatment	Before - After	p
CRP (mg/L)	92	73.1 (59.3 - 86.8)	27.2 (20.2 - 34.2)	45.86 (31.42 - 60.31)	**<0.001**
FERRITIN (µg/L)	54	320 (222 - 417)	433 (278 - 587)	-109.6 (-276.4 - 57.3)	0.650
SEDIMANTATION (mm/s)	62	48.26 (41.61 - 54.9)	45.92 (38.71 - 53.13)	1.19 (-7.02 - 9.4)	0.814
FIBRINOGEN (mg/dL)	73	504 (466 - 543)	477 (441 - 512)	32.6 (-11.6 - 76.9)	0.316
D-DIMER (ng/mL)	84	1163 (821 - 1504)	1069 (773 - 1364)	-5 (-460.5 - 450.5)	0.722
TROPONİN (µg/L)	79	0.026 (0.005 - 0.048)	0.03 (0.01 - 0.05)	-0.010 (-0.034 - 0.013)	0.629

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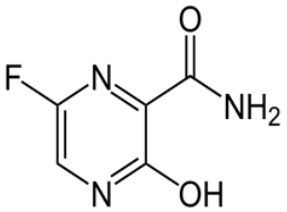
DISCUSSION

Favipiravir (6-fluoro-3-hydroxy-2-pyrazinecarboxamide), originally named as T-705, and the related pyrazine carboxamide compounds T-1105 and T-1106 were evolved and synthesized by Toyama Chemical Co., Ltd. Japan, during the last decade (**9**). During the COVID-19 pandemic, the Turkish Health Ministry ordered and recommended five days Favipiravir treatment for all patients with COVID-19 infection even in an asymptomatic state (**10**).



The most observed adverse events were mildly elevated liver transaminases, psychiatric symptom reactions, digestive tract reactions, and hyperuricemia (**11**).

It has been a well-known fact that pharmacotherapy with Favipiravir has been associated with hyperuricemia due to Favipiravir's purine analogue effect, which is mostly presented in erythrocytes. Thus, there are also established mechanistic links between macrocytosis and the use of Favipiravir. At the end of the fifth day of therapy with Favipiravir, we observed increased serum uric acid levels. Those identified changes in serum uric acid levels and main corpuscular volume (MCV) warrants further investigation of their prognostic significances in the treatment of COVID-19 infection. Although in our study it was observed that MCV increased statistically with five days of Favipiravir treatment, a clinically significant increase could not be shown. This was thought to be due to the short duration of the treatment. In many studies in the literature, use of Favipiravir has been scheduled for ten days. In some studies, it was used for five days. Turkey's Health Ministry has recommended 5-day treatment in the COVID-19 treatment guidelines; however, the health ministry last updates are permitted to extend the treatment up to 10 days.

Lymphopenia (defined as an absolute lymphocyte count <1.0 × 10^9/L) is one of the most important keys of laboratory parameter of COVID-19 infection, as recent reports pointed out that (**10, 12**). Preliminary reports also indicate that severe lymphopenia is a common hematologic finding in COVID-19 patients and is associated with worse outcomes (**13**). Other hand, there have been geographical differences between Asian countries and the European Union in terms of the prevalence of lymphopenia. While authors of Western countries have been reported much higher lymphopenia rates than that Far East (**14**).

In our study, we found that the mean lymphocyte level was 1.44 × 10^9/L and statistically significant reduced levels were observed at the end of the fifth day compared to the day of initiating therapy. Lack of lymphopenia may have been due to viral mutations during the pandemic or may have been linked to the presence of the Chinese variant of the virus rather than the European type in Turkey. Other hand, increased lymphocyte levels by therapy mean that Favipiravir had a good performance for treating the disease and could be used safely.

In addition, we also observed increased platelet levels by the therapy even in normal ranges. Recent reports involving COVID 19 patients showed that coronavirus disease has related to platelet hyperactivity and thrombocytopenia as well as higher D-dimer levels, prolonged prothrombin time, which were totally related to hyper coagulopathy with disease severity during this pandemic (**15, 16**). In this context, our finding supports the success of Favipiravir treatment in mild to moderate COVID- 19 patients.

Recent studies have shown that platelets have important functions not only in haemostasis, but also in inflammatory processes. In physiological platelet count controlled by feedback mechanism between Thrombopoietin which releasing from liver and Thrombopoietin receptors on thrombocytes and megakaryocytes which are to maintain constant platelet mass. However, in inflammation, the increasing concentration of proinflammatory cytokines, mainly IL-6, via stimulation of Thrombopoietin generation causes increasing platelet count. It is also associated with the increased percentage of large platelets. This is thought to be due to proinflammatory and procoagulant processes. However, it is known that these large platelets are more active, rapidly migrate to the inflammatory area, and are consumed faster. This may explain the alternations in MPV in inflammatory processes. Thrombocytopenia has been shown to be associated with mortality in COVID-19 infection. These thrombocytopenic patients were also found to have higher MPV levels (**17, 18**). In our study, a significant decrease was found in MPV values after Favipiravir treatment. This may be an indicator that the treatment is successful.

It has been shown that CRP, which is widely used in the clinical follow-up of inflammatory processes, is an important marker associated with mortality and treatment success in COVID-19 pneumonia. CRP was also found to be directly related to the severity of tomography findings (**19**). In our study, a significant decrease in CRP levels was observed with treatment. This situation shows the importance of CRP follow-up in Favipiravir treatment follow-up.

The increase in ferritin levels has been shown to be associated with COVID-19 infection but may continue to increase throughout the duration of the hospital stay, although treatment can still be high even at 16 days (**20**). In our study, the fact that it was still high in the 5th-day values was thought to be related to this situation.

Although the relation of COVID-19 infection with coagulopathy and thrombosis is known, knowledge on this subject is still insufficient. Similarly, although the relationship of fibrinogen and d-dimer levels to disease severity has been reported but data from recent studies still conflicting. In our study, no significant change was observed in the first 5 days.

CONCLUSION

In our study, observed data that demonstrate increasing in the platelet count and decreasing in CRP and MPV levels are remarkable findings. These data may guide in the follow-up of Favipiravir treatment and in determining the prognosis. Studies with more patients are needed to support our data.

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