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Hepatotoxicity in Patients Using Favipiravir for COVID-19: A Retrospective Study

COVID-19 Nedeniyle Favipiravir Kullanan Hastalarda Hepatotoksisite: Retrospektif Bir Çalışma

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ABSTRACT

Background: Antimalarial drugs (hydroxychloroquine sulfate), antiretroviral drugs (lopinavir/ritonavir), and antivirals (oseltamivir, remdesivir and favipiravir) are medications used for the treatment of Coronavirus disease-2019 (COVID-19). A detailed safety analysis of favipiravir, which is used extensively in the treatment of COVID-19 in our country under pandemic conditions, is important. Investigation of the hepatotoxicity risk of favipiravir in COVID-19 patients. Our study was designed retrospectively.

Materials and Methods: Demographic characteristics, comorbid diseases and liver function test (LFT) values of the patients were retrospectively scanned and recorded. The patients were divided into two groups as died and recovered according to their results. The changes in the mean values of the LFT results and patients with different results than the reference value was evaluated according to the treatment time.

Results: Mean age of the 175 patients included in the study was 60.9±16.4 years and 122 of them were male. In the total patient population, significant ($p<0.05$) differences were found between the mean values of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and albumin on day 1 and on the days 3 and 5. As for gamma glutamyl transferase (GGT), the difference between all three consecutive measurements was significant ($p<0.05$). The change in the number of patients with abnormal, international normalized ratio (INR), alkaline phosphatase (ALP), GGT, AST, ALT, and albumin values based on treatment days was statistically significant ($p<0.05$). Analysis of this difference according to groups showed a significant difference for GGT, AST, and ALT in the survivors and for total bilirubin, ALP, INR, and albumin in the deceased ($p<0.05$).

Conclusion: It was observed that GGT, AST and ALT increased after the drug loading dose. This condition was evaluated as drug-related hepatotoxicity. However, no serious height was found in any patient to require discontinuation of favipiravir. Therefore, close monitoring for hepatotoxicity is recommended in patients treated with favipiravir, especially after the loading dose.

Keywords: Favipiravir, hepatotoxicity, COVID-19

ÖZ

Amaç: Antimalaryal ilaçlar (hidroksiklorokin sülfat), antiretroviral ilaçlar (lopinavir/ritonavir) ve antiviraller (oseltamivir, remdesivir ve favipiravir), Koronavirüs hastalığı-2019 (COVID-19) tedavisinde kullanılan ilaçlardır. Pandemi koşullarında ülkemizde COVID-19 tedavisinde yoğun kullanılan favipiravirin detaylı güvenlik analizi önemlidir. Favipiravir kullanan COVID-19 hastalarında hepatotoksisite riskinin araştırılmasıdır. Çalışmamız retrospektif olarak tasarlanmıştır.

Gereç ve Yöntemler: Hastaların demografik özellikleri, komorbid hastalıkları ve karaciğer fonksiyon test (KCFT) değerleri geriye dönük olarak taranarak kaydedildi. Hastalar sonuçlarına göre ölen ve iyileşen olarak iki gruba ayrıldı. Tedavi süresine göre KCFT sonuçlarının ortalama değerlerindeki değişimler ve referans değerden farklı sonuç veren hastalar değerlendirildi.

Bulgular: Çalışmaya alınan 175 hastanın yaş ortalaması 60,9±16,4 yıl olup 122'si erkekti. Toplam hasta popülasyonunda 1. gün ile 3. ve 5. günlerdeki aspartat aminotransferaz (AST), alanin aminotransferaz (ALT) ve albümin ortalama değerleri arasındaki fark istatistiksel olarak anlamlı idi ($p<0,05$). Gama glutamil transferazın (GGT) ardışık üç ölçümü arasındaki fark da anlamlıydı ($p<0,05$). Uluslararası normalleştirilmiş oran (INR), alkalin fosfataz (ALP), GGT, AST, ALT ve albümin değerleri anormal olan hasta sayısındaki

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ÖZ

değişim, tedavi günlerine göre istatistiksel olarak anlamlıydı (p<0,05). Gruplara göre analiz yapıldığında; hayatta kalanlarda GGT, AST ve ALT, ölenlerde total bilirubin, ALP, INR ve albümin değerlerinde anlamlı farklılık tespit edildi (p<0,05).

Sonuç: İlaç yükleme dozundan sonra hastaların GGT, AST ve ALT'nin arttığı gözlendi. Bu durum ilaca bağlı hepatotoksisite olarak değerlendirildi. Ancak hiçbir hastada favipiravirin kesilmesini gerektirecek ciddi bir yükseklik bulunmamıştır. Özellikle yükleme dozundan sonra, favipiravir ile tedavi edilen hastalarda hepatotoksisite için yakın takip önerilir.

Anahtar Kelimeler: Favipiravir, hepatotoksisite, COVID-19

Introduction

Declared as a pandemic by the World Health Organization, Coronavirus disease-2019 (COVID-19) is a mostly asymptomatic or mild viral disease. Nevertheless, in 5-10% of cases, a severe clinical presentation is observed, even at times with a fatal outcome (1). For this reason, urgent treatment is required, albeit there is no definitive cure yet. Medications in use include antimalarial drugs (hydroxychloroquine sulfate), antiretroviral drugs (lopinavir/ritonavir), and antivirals (oseltamivir, remdesivir, and favipiravir) (2). Various combinations of these drugs are currently in experimental use worldwide in the treatment of COVID-19. Because of the pandemic status of COVID-19, detailed safety analyses of these drugs are of vital importance (2).

In Türkiye, Ministry of Health published a treatment guide for COVID-19, which is regularly updated online. One of the drugs recommended in this guide is favipiravir (3). Favipiravir, which was first used in the treatment of influenza, is produced through the chemical modification of a pyrosine analog. It is a selective and potent inhibitor of viral RNA polymerase. It is proven effective against Ebola and other RNA viruses, including resistant influenza strains (4).

In comparison to other treatments for COVID-19, favipiravir is an effective method and there are already studies investigating its safety and side effects (2). In Türkiye, favipiravir is administered for a total of 5 days first as a loading dose of 2x1,600 mg, followed by a maintenance dose of 2x600 mg. In our study, we aimed to investigate hepatotoxicity at these treatment doses.

Material and Methods

The study was approved by the University of Health Sciences Türkiye Hamidiye Scientific Research Ethics Committee on May 15, 2020 with the session no: 2020/5 and resolution no: 4/5. Furthermore, the study was approved by the Ministry of Health Scientific Research Platform.

Study Population and Design

The study was planned as a single-center retrospective cohort study in the University of Health Sciences Türkiye, Hamidiye Faculty of Medicine; İstanbul Sultan 2. Abdülhamid Han Training and Research Hospital, designated as a tertiary education and research hospital from the beginning of COVID-19 outbreak. Between March 11-May 30, 2020, 202 patients who began receiving treatment with favipiravir for COVID-19 were retrospectively analyzed and 175 patients over the age 18, whose treatment was completed in 5 days, were included in our study. Since our study was planned retrospectively, patient consent was not obtained.

Data Collection

Demographic characteristics of the patients, including age, gender, and comorbidity were recorded in Microsoft Office Excel Professional.

In the study, laboratory tests providing data on liver function and hepatotoxicity were examined (5). Total bilirubin, direct bilirubin, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), albumin, international normalized ratio (INR), aspartate aminotransferase (AST) and alanine aminotransferase (ALT) measured on days 1, 3, and 5 of the treatment with favipiravir were recorded. Mean values of the test results for day 1, 3, and 5 were calculated. Test results were interpreted using the reference intervals recommended by our laboratory. Values falling outside these reference ranges were defined as "abnormal."

Patients were divided into two groups as deceased and survived, according to clinical outcome.

Statistical Analysis

Because of compatibility with the central limit theorem, parametric tests were used without testing normality (6). However, higher degree of deviations in the mean values measured on day 5 of the treatment required the use of the non-parametric test for ALT. In the analysis of data, especially in the statistical work of the continuous data in the scales, the mean value, standard deviation, median, quartiles, and minimum and maximum values of the characteristics were used. Frequency and percentage values were used to define

categorical variables. The means of two independent groups were evaluated with "Student's t-test" and "Mann-Whitney U test." "Repeated ANOVA test" and "Cochran's Q test" were used to compare the means for more than two dependent groups. In evaluating the relationship between categorical variables, "chi-square test" was used. Statistical significance of data was defined at $p<0.05$. In the evaluation of data, www.e-picos.com New York software and MedCalc statistics software package were used.

Results

A total of 202 patients receiving favipiravir treatment in the University of Health Sciences Türkiye Hamidiye Faculty of Medicine; İstanbul Sultan 2. Abdülhamid Han Training and Research Hospital, were identified. Thirteen patients who had not yet completed the 5-day favipiravir treatment as the study was beginning were excluded, 9 patients who died during the favipiravir treatment, and 5 patients who were discontinued upon the decision of a physician during their follow-up. Favipiravir treatment was not discontinued due to side effects or drug interactions in any patient.

Mean age of the 175 patients included in the study was 60.9±16.4 (minimum=21 and maximum=96) years and 122 of them (69.7%) were male. In the investigation of comorbid diseases, hypertension appeared as the most frequent (75, 42.9%). No comorbidity was found in 74 (42.28%) of the patients. As for the clinical outcomes, the number of patients who died was 53 (30.3%) and the number of those who recovered was 122 (69.7%).

When other drugs used for COVID-19 treatment were examined, hydroxychloroquine sulfate use was detected in all patients. The most common choice of antibiotics for the treatment of a possible bacterial superinfection was the beta-lactam group. Among these ceftriaxone ranked the first (Table 1).

An examination of the mean values of the laboratory tests performed on study patients on day 1, 3, and 5 of the favipiravir treatment, the difference between GGT mean values on days 1, 2, and 3 was found statistically significant ($p<0.05$).

The difference between the mean values of AST, ALT, and albumin on day 1 and the mean values on days 3 and 5 were statistically significant ($p<0.05$). However, the difference between the mean values of the days 3 and 5 was not found to be statistically significant (Figure 1, Table 2).

The change in the mean values for GGT, AST, ALT, and albumin based on treatment days was significant in the recovered group of patients ($p<0.05$). For GGT, ALT, and albumin, a statistically significant difference was found between the mean values of day 1 and day 3, while there was no significant difference between the mean values of day 3 and day 5. For AST, there was a significant difference between the mean values of day 3 and day 1 and the mean values of day 3 and day 5, while no difference was found between the mean values of days 1 and 5 (Table 2).

In the group of deceased patients, significant differences ($p<0.05$) were found between the mean values of day 5 and other days for GGT and the mean values of day 1 and other days for albumin (Table 2).

Changes in the number of patients with abnormal test values were examined on the basis of treatment days. There was a statistically significant difference in the total

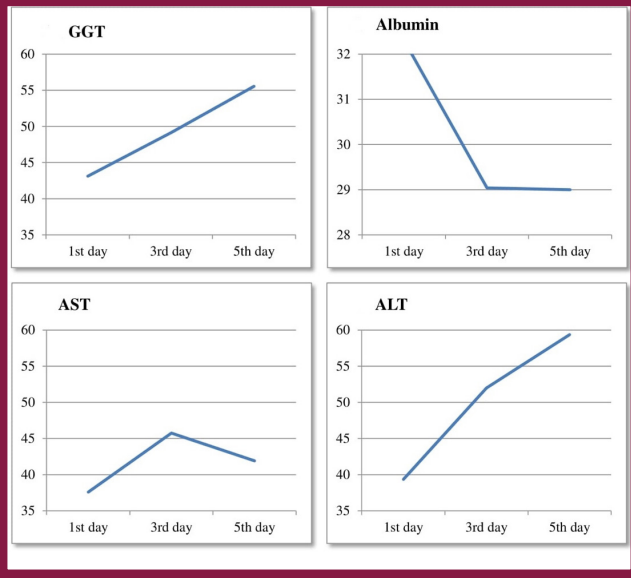

Figure 1. Change of test measurement mean values of patients using favipiravir according to treatment days. GGT: Gamma glutamyl transferase ($p<0.0001$), albumin ($p<0.0001$), AST: Aspartate aminotransferase ($p=0.03$), ALT: Alanine aminotransferase ($p=0.006$)

Table 1. Other drugs used due to COVID-19 and their distribution (n=175)

Drug	n (%)
Hydroxychloroquine sulfate	175 (100)
Lopinavir/ritonavir	28 (16)
Oseltamivir	89 (51)
Azithromycin	161 (92)
Ceftriaxone	91 (52)
Piperacillin-tazobactam	50 (29)
Moxifloxacin	10 (6)
Levofloxacin	22 (13)
Clarithromycin	16 (9)

COVID-19: Coronavirus disease-2019

patient population for ALP, GGT, INR, AST, ALT, and albumin ($p<0.05$). While there was a significant difference for GGT, AST, and ALT in the group of recovered patients, significant differences were found in the of deceased patients for total bilirubin, ALP, INR, and albumin ($p<0.05$) (Table 3).

Discussion

Research is ongoing for the specific treatment of COVID-19, a respiratory viral disease. Existing drugs, used for treating other diseases, now provide a treatment alternative (7). The side effects of these commonly used drugs gained

Table 2. Change of laboratory test measurement averages according to treatment days of patients using favipiravir

Variant (for reference, unit)		1st day MV (SD)	3rd day MV (SD)	5th day MV (SD)	p
Total bilirubin (0.1-1.2 mg/dL)	Total (n=100)	0.82 (0.95)	0.94 (1.3)	0.87 (0.82)	0.54
	Recovered (n=63)	0.76 (0.84)	0.96 (1.6)	0.72 (0.58)	0.18
	Deceased (n=37)	0.92 (1.27)	0.9 (0.74)	1.13 (1)	0.30
Direct bilirubin (0.01-0.3 mg/dL)	Total (n=102)	0.41 (0.55)	0.45 (0.74)	0.46 (0.59)	0.64
	Recovered (n=64)	0.37 (0.4)	0.42 (0.86)	0.33 (0.37	0.47
	Deceased (n=38)	0.479 (0.67	0.51 (0.5)	0.68 (0.81)	0.14
ALP (35-125 U/L)	Total (n=105)	73.45 (34.59	75.04 (46.1)	79.15 (42.15)	0.16
	Recovered (n=73)	74.09 (38.97)	77.79 (52.81)	78.67 (44.67)	0.44
	Deceased (n=32)	72 (22)	68.78 (24.36)	80.25 (36.39)	0.06
GGT (7-32 U/L)	Total (n=106)	43.11 (44.4)	49.12 (49.24)	55.55 (53.48)	**<0.0001**
	Recovered (n=74)	42.27 (46.84)	50.54 (52)	52.08 (48.59)	**0.002**
	Deceased (n=32)	45.06 (39.05)	45.84 (39.72)	63.59 (63)	**0.009**
Albumin (35-50 g/L)	Total (n:91)	32.31 (5.56)	29.04 (4.84)	29 (5.26)	**<0.0001**
	Recovered (n=55)	33.56 (5.83)	30.78 (5.11)	31.41 (4.63)	**<0.0001**
	Deceased (n=36)	30.38 (4.56)	26.38 (2.83)	25.3 (86)	**<0.0001**
INR (0.8-1.2)	Total (n=81)	1.64 (2.54)	1.6 (2)	1.52 (2)	0.53
	Recovered (n=45)	1.67 (3.1)	1.65 (2.6)	1.65 (2)	0.98
	Deceased (n=36)	1.62 (1.6)	1.52 (0.88)	1.36 (0.33)	0.48
AST (5-40 U/L)	Total (n=173)	37.58 (27.8)	45.75 (39.6)	41.91 (39.7)	**0.03**
	Recovered (n=122)	35.97 (26.35)	43.08 (34.49)	37.5 (23.94)	**0.01**
	Deceased (n=51)	41.54 (31.24)	52.32 (49.93)	52.7 (62.9)	0.33
ALT (5-40 U/L)	Total (n=172)	39.35 (31.16)	52 (49)	59.36 (70.03)	**0.006**
	Recovered (n=122)	40.16 (32.38)	55.29 (53.73)	55.49 (40.71)	**<0.0001**
	Deceased (n=50)	38.4 (28.15)	43.96 (34.39)	52.74 (77.04)	0.2

ALP: Alkaline phosphatase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyl transferase, INR: International normalized ratio, MV: Mean value, SD: Standard deviation

new importance in the circumstances of the pandemic (1,2). In our study, one of these alternative drugs used in the treatment of COVID-19, favipiravir, was investigated in terms of hepatotoxicity.

The liver has its biochemical markers that indicate its metabolic and cholestatic functions and that can be detected in the blood. Transaminases are the most important of these markers and they move outside cell as a result of increased cell membrane permeability of the hepatocyte and their levels in the blood increase (5). In our study, biochemical markers showing hepatotoxicity were examined.

The COVID-19 treatment guide published by the Turkish Ministry of Health recommends favipiravir for the treatment of patients with a need for oxygen and reimburses the costs (3). Moreover, owing to the fact that our hospital is a pandemic center and its intensive care unit bed capacity is increased, risky and poorly patients are referred to our hospital since the outbreak. For these reasons, our study includes a high number of male patients over the age of 65 and with comorbidities, all characteristics associated with the risk of a severe picture (1,8,9).

The changes in the mean laboratory values of the study patients based on treatment days were found significant for GGT, ALT, AST, and albumin. Half-lives of GGT, ALT, AST, and albumin are 26 days, 47 hours, 17 hours, and 20 days, respectively (5). The mean value of GGT, which has a long half-life, continued to increase on days 3 and 5. However, the increase in the mean values of AST and ALT, with shorter half-lives, was statistically significant on day 3, but not on day 5. In this case, it is possible to suppose that hepatotoxicity depends on the loading dose administered on day 1 of the treatment. Thus, it can be concluded that hepatotoxicity is dose-dependent for favipiravir. Low albumin levels were more common in the group of deceased patients. The rate of patients with low albumin value higher in the deceased patient group, despite its longer half-life (20 days), but the decrease in the mean value of albumin on day 3 did not continue on day 5. This was interpreted that the change in

Table 3. Change of patients with abnormal test values by treatment days

Variant		1st day n (%)	3rd day n (%)	5th day n (%)	p
Total bilurubin >1.2 mg/dL	Total (n=100)	12 (12)	16 (16)	17 (17)	0.23
	Recovered (n=63)	5 (7.9)	8 (12.7)	4 (6.3)	0.44
	Deceased (n=37)	7 (18.9)	8 (21.6)	13 (35.1)	**0.02**
Direct bilurubin >0.3 mg/dL	Total (n=102)	40 (39.2)	41 (40.2)	42 (41.2)	0.74
	Recovered (n=64)	24 (37.5)	24 (37.5)	20 (31.3)	0.58
	Deceased (n=38)	16 (42.1)	17 (44.7)	22 (57.9)	0.06
ALP >125 U/L	Total (n=105)	6 (5.7)	9 (8.6)	13 (12.4)	**0.04**
	Recovered (n=73)	3 (4.1)	5 (6.8)	7 (9.6)	0.32
	Deceased (n=32)	3 (9.3)	4 (12.5)	6 (18.7)	**0.02**
GGT >32 U/L	Total (n=106)	47 (44.3)	53 (50)	50 (47.2)	**0.009**
	Recovered (n=74)	22 (29.8)	23 (31.1)	30 (40.5)	**0.004**
	Deceased (n=32)	25 (78.1)	30 (93.7)	20 (62.5)	0.65
Albumin <32 gr/L	Total (n=91)	65 (78)	76 (87.9)	75 (85.4)	**0.04**
	Recovered (n=55)	31 (56.4)	41 (74.5)	40 (72.7)	0.35
	Deceased (n=36)	34 (94)	35 (97)	35 (97.2)	**0.02**
INR >1.2	Total (n=81)	24 (29.7)	39 (48.1)	40 (49.4)	**0.003**
	Recovered (n=45)	13 (28.9)	17 (37.8)	17 (37.8)	0.79
	Deceased (n=36)	9 (25)	12 (33.3)	23 (63.9)	**<0.0001**
AST >40 U/L	Total (n=173)	50 (28.9)	67 (38.7)	58 (33.5)	**0.03**
	Recovered (n=122)	31 (25.4)	45 (36.9)	38 (31.1)	**0.02**
	Deceased (n=51)	19 (37.3)	22 (43.1)	20 (39.2)	0.57
ALT >40 U/L	Total (n=172)	56 (32.5)	79 (45.9)	85 (49.5)	**<0.0001**
	Recovered (n=122)	41 (33.6)	59 (48.4)	66 (54.1)	**<0.0001**
	Deceased (n=50)	15 (30)	20 (40)	19 (38)	0.59

ALP: Alkaline phosphatase, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyl transferase, INR: International normalized ratio

albumin value was related to the progression of the disease rather than hepatotoxicity. Chronic exposure is required for a decrease in albumin in a drug-induced hepatotoxicity (6).

The change of the number of patients with abnormal values by the day of treatment was significant for ALP, GGT, INR, AST, ALT, and albumin. This change was found significant for GGT, AST, and ALT in the group of recovered patients, whereas in the deceased group total bilirubin, ALP, INR, and albumin were also found significant. Based on these findings, it was thought that changes in AST, ALT, and GGT could be linked to drug toxicity. Total bilirubin, ALP, INR, and albumin exchange were interpreted as associated with the progression.

Being a drug long in use for influenza and gaining widespread use during the COVID-19 pandemic, favipiravir is the subject of many studies with regard to its side effects (10,11). Chen et al. (10) examined 116 patients receiving favipiravir in their comparative study on arbidol and favipiravir. In this study, liver function elevated test values were found 6 times the upper limit and elevation of transaminase was detected in 10 (8.62%) of the patients (10). In another study examining 501 cases that were given a dose lower than what our patients received, 100 patients suffered side effects. The most common side effects were elevated levels of uric acid (4.79%) and diarrhea (4.79%), while others side effects included a low neutrophil count (1.8%) and an increase in AST (1.8%) and ALT (1.6%) (12). In our study, the rates of patients with transaminase elevation were 28.9%, 38.7%, 33.5% for AST on days 1, 3, and 5, respectively; as for ALT, 32.5%, 45.9%, and 49.5%, respectively. These values are higher compared to the existing literature (10,12). In a study comparing hydroxychloroquine and favipiravir in our country, 32 patients using favipiravir were examined. As a result of the study, no statistically significant increase was found in AST, total bilirubin, direct bilirubin and ALP values in this group, while there was a statistically significant increase in ALT, LDH and GGT values (13). The fact that the drug was administered in higher doses in our study and that the reference values were accepted as limit values for the liver function test elevation criteria could account for this situation. Furthermore, our study population comprised patients with a severe clinic presentation and higher needs for oxygen. Consequently, the use of drugs that may impair liver function tests in addition to favipiravir in these patients could be considered as other factors.

There are many meta-analyses examining the efficacy and safety of favipiravir in the treatment of COVID-19 in our country and in the world. In a meta-analysis that included nine studies involving 827 patients, between the favipiravir group and the control group showed lesser odds for adverse effects in the favipiravir group but of no statistical significance ($p<0.001$) (14). Another meta-analysis showed lesser odds for adverse effect in the treatment group but of no statistical significance (odds ratio 0.69; participants=376; studie=3; I^2=88%) (15). In a meta-analysis comparing drugs used in the treatment of COVID-19, it was emphasized that the side effects caused by favipiravir, similar to our study, were mild and manageable (16).

In our study, patients had high rates of comorbidity. For this reason, patients used several different drugs for the treatment of chronic diseases. However, as our study examined the change as compared to the values on day 1, no information was included on the drugs the patients used chronically. In all patients, hydroxychloroquine sulfate and 92% azithromycin were started for the treatment of COVID-19. The risk of hepatotoxicity for hydroxychloroquine sulfate is 1-0.1%, while it is 1-2% for azithromycin. A rare side effect for oseltamivir, hepatotoxicity is seen in the range of 1-11% for lopinavir/ritonavir. There is a risk of hepatotoxicity for other drugs used, as well, but not close to the ratios found in our study (17). Consequently, the effects of the study drugs with regard to hepatotoxicity are minimal.

Study Limitations

An important limitation of our study is the liver involvement as a result of COVID-19, which requires elevated liver function tests (18). Moreover, other medications (those used for chronic conditions or other medicines used for COVID-19) may increase the hepatotoxicity risk of favipiravir. Another limitation is that in our hospital, favipiravir is administered to all patients who present with a severe course and are in need of oxygen; therefore, a control group that does not receive favipiravir from patients with the same clinical picture cannot be established.

Conclusion

It is observed that GGT, AST, and ALT, biochemical markers of hepatotoxicity, increase following favipiravir loading dose. This is considered a medication-related toxic effect. Therefore, close monitoring of patients for hepatotoxicity is recommended in a treatment with favipiravir, especially after the loading dose.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Türkiye Hamidiye Scientific Research Ethics Committee on May 15, 2020 with the session no: 2020/5 and resolution no: 4/5. Furthermore, the study was approved by the Ministry of Health Scientific Research Platform.

Informed Consent: Since our study was planned retrospectively, patient consent was not obtained.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.A.I., B.S., Concept: S.A.I., B.S., Design: S.A.I., Data Collection or Processing: S.A.I., B.S., Analysis or Interpretation: S.A.I., B.S., Literature Search: S.A.I., Writing: S.A.I.

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