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Coronavirus Pandemic

The safety and adverse event profile of favipiravir in the treatment of COVID-19 patients, Turkey

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Abstract

Introduction: Favipiravir (FVP) is an antiviral and used to treat COVID-19. We aimed to document the safety and adverse events associated with FVP on the outcome of COVID-19 treatment.

Methodology: The study included 225 adult patients with moderate COVID-19 infection (World Health Organization scale-5). The adverse events (AEs) were evaluated using a grading scale supported by the Food and Drug Administration. Safety was assessed by the frequency of serious AEs.

Results: The AEs associated with FVP treatment were hepatotoxicity (87/225, 38.7%), weakness (32/225, 14.2%), nephrotoxicity (26/225, 11.6%), nausea (18/225, 8.0%), diarrhea (8/225, 3.6%), vomiting (5/225, 2.2%), and insomnia (4/225, 1.8%); rash was not detected. Hepatotoxicity was observed more frequently in patients who also developed nephrotoxicity (57.7% vs 36.2%, $p = 0.03$). The deceased patients were significantly older and had higher prevalence of hypertension, congestive heart failure (CHF), coronary artery disease, cancer, nephrotoxicity. and angiotensin- converting enzyme inhibitors/angiotensin receptor blocker use. While male gender (OR: 5.38 CI: 1.64-17.67) and CHF (OR: 6.8 CI: 1.92-24.74) were significantly associated with nephrotoxicity, age (OR: 1.06 CI: 1.02-1.10), cancer (OR: 3.9 CI: 1.10-14.22) and nephrotoxicity (OR: 5.5 CI: 1.74-17.74) were associated with mortality.

Conclusions: Serious AEs were detected at very low levels that would not require discontinuation of treatment or any AE-related death. Since SARS-CoV-2 itself and drug interactions may differ, FVP-related AEs might vary in COVID-19 patients. Our study shows that FVP can be used safely with a low AE profile. More extensive evidence is required to evaluate the long-term AEs of FVP.

Key words: favipiravir; safety; adverse events; COVID-19; hepatotoxicity; nephrotoxicity.

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Introduction

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and it has been declared a pandemic by the World Health Organization (WHO) [1]. It has become the worst global public health crisis in the past century. New and definitive therapeutic options are required. While no licensed therapy directly shows activity against COVID-19, broad-spectrum antivirals (remdesivir, darunavir/ritonavir, lopinavir/ritonavir, chloroquine, and favipiravir (FVP)) are being used in different combinations or alone [2]. One treatment option is FVP, an RNA polymerase inhibitor used previously for influenza and Ebola, which has shown promise for the treatment of COVID-19 [3,4]. Safety analysis for the use of FVP is vital for its widespread use. Meanwhile, a systematic risk-benefit assessment of FVP has yet to be carried out. The other important point is the adverse events (AEs) associated with FVP use in COVID-19-infected patients. The most serious AE of FVP is teratogenicity; others are hematological dysfunctions, liver enzyme abnormalities, and renal dysfunction. In a Japanese and international trial, the main AEs related to FVP treatment were hyperuricemia (4.8%), neutropenia (1.8%), diarrhea (4.8%), increased aspartate aminotransferase (AST) (1.8%) and alanine aminotransferase (ALT) (1.6%), and psychiatric disorders [5,6].

However, existing safety data and AEs for FVP usage in COVID-19 treatment are limited. In the

present study, we sought to document the safety and AEs of the clinical use of FVP and the effect on the outcome of COVID-19 treatment. This article is the first report to demonstrate the efficacy and AEs of FVP in such a large COVID-19 patient population.

Methodology

The study was conducted according to the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice. The study was approved by the ethics committee of Marmara University School of Medicine (approval ID: 09.2021.558). All the participants gave written informed consent.

This was an observational prospective study. Patients were selected from among adult patients (≥ 18 years of age) with SARS-CoV-2 virus confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) or suspected chest computed tomography (CT) findings. The patients with moderate COVID-19 infection with WHO scale-5 admitted to the Marmara University Pendik Training and Research Hospital from March through June 2020 were consecutively included in the study. Moderate cases with WHO scale-5 were defined as patients with an oxygen saturation ≤ 93% who needed oxygen support by mask or nasal prongs [7]. Pregnant patients were excluded. FVP was started within 48 hours after the onset of symptoms and admission to the hospital. FVP was ordered as 1600 mg twice on the first day, followed by 600 mg twice daily for four days. FVP treatment was maintained till the end of the fifth day in all patients, irrespective of the AEs. The standard care also comprised supportive oxygen, and low-molecular-weight heparin prophylaxis. In addition, antibiotics, dexamethasone and/or tocilizumab treatments were given when moderate COVID-19 infection was progressed into severe COVID-19 pneumonia with severe systemic inflammation.

Table 1. Demographic features of patients.

Characteristics	N =225
Age, mean ± SD	60.36 ± 15.42
Male, %	144 (64)
Asthma, %	15 (6.7)
COPD, %	15 (6.7)
Pneumonia, %	2 (0.9)
Cancer, %	17 (7.6)
CRF, %	16 (7.1)
CHF, %	18 (8.0)
CAD %	51 (22.7)
CVD, %	9 (4.0)
HT, %	124 (55.1)
DM, %	72 (32.0)
Immunosuppression, %	11 (4.9)
ACE-ARB, %	104 (46.2)
Statin, %	55 (22.4)
Antibiotic, %	62 (27.6)
Charlson score (med, iqr)	2 (1-4)
Charlson score percent (med, iqr)	90 (53-96)
Obese, %	146 (64.9)
Deceased patients	35 (15.6)

COPD: chronic obstructive pulmonary disease; CRF: chronic renal failure; CHF: congestive heart failure; CAD: coronary artery disease; CVD: cerebrovascular disease; HT: hypertension; DM: diabetes mellitus; ACE-ARB: angiotensin-converting enzyme-angiotensin receptor blocker; med: median; iqr: interquartile range.

The patients' age, gender, comorbidities, drug use, body mass index (BMI, ≥ 30 kg/m^2), Charlson score, and outcomes were recorded. Laboratory assessments (C- reactive protein (CRP), ferritin, D-dimer, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, and troponin) were performed at admission to the hospital and daily during the five-day FVP treatment period by the same laboratory. Additional lab tests were performed when necessary.

Diarrhea, fatigue, insomnia, nausea–vomiting, rash, hepatotoxicity, and nephrotoxicity were questioned and noted as AEs related to FVP use. AEs in patients were evaluated using the guidance for industry: toxicity grading scale for healthy adults in clinical trials supported by the Food and Drug Administration (FDA) [8]. This scale provides an AE severity grading ranging from 1 to 5 with descriptions of mild, moderate, severe, life-threatening events and death. A severe AE was defined as ≥ grade 4. The patients were followed for AEs throughout their hospitalization and standard medical measures were taken when an AE was developed. Safety was assessed by the frequency of serious AEs. All cause-mortality and survival were evaluated as outcome.

Statistical analysis

Statistical analyses were performed by statistical software (SPSS 22.0 for windows, Chicago, IL). The distribution of data was assessed by using one-sample Kolmogorov–Smirnov test. Continuous data were expressed as medians and interquartile ranges while categorical data were expressed as numbers or percentages. Chi-squared test and Fisher exact test were used for the comparison of categorical variables. Wilcoxon test and Mann-Whitney U test were used to compare the nonparametric continuous variables. Logistic regression analysis was performed to explore the predictors of nephrotoxicity and all-cause mortality. The Hosmer-Lemeshow goodness of fit statistic was used to assess model fit. Statistical significance was accepted as a p value less than 0.05.

Table 2. Laboratory parameters during 5 days of FVP treatment.

Laboratory parameters	Basal (med-IQR) *	Day 5 (med-IQR)	*p* value
Lymphocytes, cells/μL	1000 (700-1400)	700 (1.8-1500)	0.003
CRP, mg/L	57.5 (21.25-114.50)	35 (15-92)	0.003
D-dimer, mg/L	0.7 (0.5-1.3)	1.08 (0.55-2.18)	0.005
Ferritin, μg/L	238.50 (100.50-470.25)	387 (197.75-689.75)	0.001
AST, U/L	36 (26-52)	41.5 (29- 61.25)	0.002
ALT, U/L	24 (16-38.5)	37.5 (21-75)	0.001
Creatinine, mg/dL	0.80 (0.7-1.1)	0.86 (0.67-1.08)	0.183
Troponin, ng/L	11 (5- 25.5)	15 (6.5- 33.5)	0.025

* median (interquartile range); CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Results

During the study period, 225 COVID-19 patients were included in the study. While all the patients received FVP for 5 days; antibiotics, dexamethasone and/or tocilizumab treatments were given to 62, 55 and 60 patients, respectively. The patients' age, gender, comorbidities, drug use, body mass index (BMI), Charlson score, and outcomes are summarized in Table 1. The most common comorbidity was obesity, and others were hypertension (HT), diabetes mellitus (DM) and coronary artery disease (CAD). In order of frequency, the identified AEs of FVP treatment were hepatotoxicity in 87 patients (38.7%), weakness in 32 patients (14.2%), nephrotoxicity in 26 patients (11.6%), nausea in 18 patients (8.0%), diarrhea in 8 patients (3.6%), vomiting in 5 patients (2.2%), and insomnia in 4 patients (1.8%), while rash was not detected (Figure 1). The most common severe (≥ grade 4) AEs were hepatotoxicity, nephrotoxicity, and weakness. The hepatotoxicity was observed more frequently in patients who also developed nephrotoxicity (57.7% vs 36.2%, $p = 0.03$). Fatigue was determined to occur in patients with asthma ($p < 0.01$), while diarrhea and nausea were found to occur in patients who subsequently used ACEI/ARB ($p = 0.02$) and statins ($p = 0.04$) (Figure 2).

Compared to admission day, the patients' lymphopenia became overt ($p = 0.003$), and their CRP levels decreased significantly in the fifth day ($p = 0.003$), although their D-dimer, AST, ALT, ferritin and troponin levels all increased significantly ($p = 0.005$, $p = 0.002$, $p = 0.001$, $p = 0.001$ and $p = 0.025$, respectively) (Table 2).

Figure 1. Possible adverse events of FVP according to the grading system.

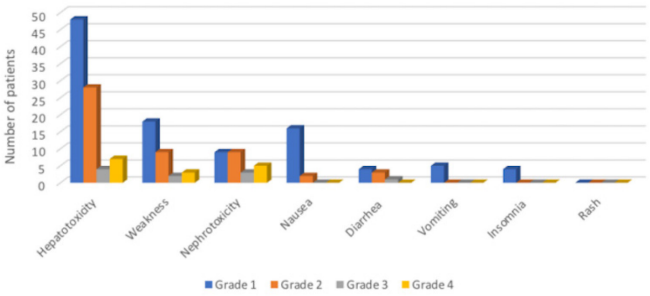

Figure 2. The course of hepatotoxicity in patients with increased creatinine.

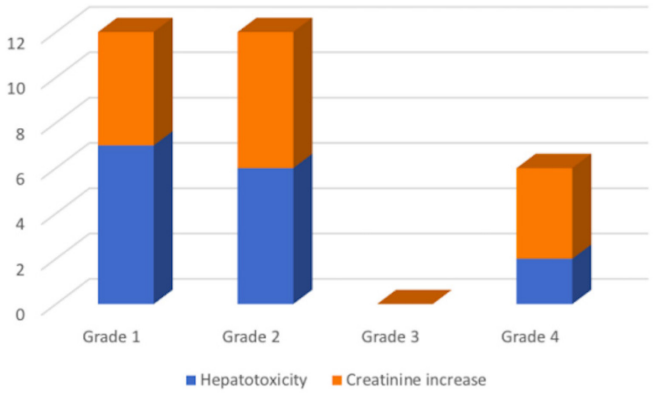

Table 3. The associated factors with nephrotoxicity are age, HT, CHF, CRF, and ACEI/ARB.

	Nephrotoxicity + (n = 26)	Nephrotoxicity – (n = 199)	*p*
Male gender (n%)	21 (80.8%)	123 (61.8%)	0.058
Age	**66.8 ± 15.6**	**59.5 ± 15.2**	**0.024**
HT	**21 (80.8%)**	**103 (51.8%)**	**0.005**
DM	12 (46.2%)	60 (30.2%)	0.100
CAD	8 (30.8%)	43 (21.6%)	0.294
CHF	**7 (26.9%)**	**11 (5.5%)**	**<0.001**
CRF	**5 (19.2%)**	**11 (5.5%)**	**0.025**
ACEI/ARB	**18 (69.2%)**	**86 (43.2%)**	**0.012**

HT: hypertension; DM: diabetes mellitus; CAD: coronary artery disease; CHF: congestive heart failure; CRF: chronic renal failure; ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

Table 4. The associated factors with mortality are age, HT, CAD, CHF, ACEI/ARB, cancer, nephrotoxicity.

	Mortality (n = 35)	Surviving (n = 190)	*p*
Male gender (n%)	20 (57.1%)	124 (65.3%)	0.358
Age	**72.1 ± 12.5**	**58.2 ± 15.0**	**< 0.001**
HT	**27 (77.1%)**	**97 (51.1%)**	**0.004**
DM	10 (28.6%)	62 (32.6%)	0.636
CAD	**15 (42.9%)**	**36 (18.9%)**	**0.002**
CHF	**8 (22.9%)**	**10 (5.3%)**	**< 0.001**
CRF	5 (14.3%)	11 (5.8%)	0.082
ACE/ARB	**22 (62.9%)**	**82 (43.2%)**	**0.032**
Cancer	**7 (20%)**	**10 (5.3%)**	**0.002**
Nephrotoxicity	**12 (34.3%)**	**14 (7.4%)**	**< 0.001**

HT: hypertension; DM: diabetes mellitus; CAD: coronary artery disease; CHF: congestive heart failure; CRF: chronic renal failure; ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

There was no significant increase in the creatinine level ($p = 0.183$) and no patient required dialysis.

The characteristics of the patients who had nephrotoxicity is listed in Table 3. Those who developed nephrotoxicity were significantly older and had higher prevalence of hypertension (HT), congestive heart failure (CHF), chronic renal failure and angiotensin-converting enzyme-angiotensin receptor blocker (ACEI/ARB) use. The characteristics of the deceased patients are shown in Table 4. Similarly, the deceased patients were significantly older and had higher prevalence of HT, CHF, and ACEI/ARB use. They also had higher prevalence of CAD, cancer and nephrotoxicity. Logistic regression analysis was performed to determine the independent predictors of nephrotoxicity and mortality (Table 5). While male gender (OR: 5.38 CI: 1.64-17.67) and CHF (OR: 6.8 CI: 1.92-24.74) were significantly associated with nephrotoxicity, age (OR: 1.06 CI: 1.02-1.10), cancer (OR: 3.9 CI: 1.10-14.22) and nephrotoxicity (OR: 5.5 CI: 1.74-17.74) were associated with mortality.

Discussion

The most common AEs were hepatotoxicity, weakness, and nephrotoxicity (38.7%, 14.2%, and 11.6%, respectively) in our study. In previous studies where FVP was used in the treatment of influenza and COVID-19, the frequency of liver enzyme abnormalities was between 3.4% and 8.5% [5,9]. Compared to these studies, we detected a higher percentage (38.8%) of hepatotoxicity. Many studies that evaluated COVID-19-associated liver function variations have showed elevated liver enzyme levels between 14% and 58.5% [10-13]. This result suggests the presence of liver damage directly associated with COVID-19 infection. Depending on the severity of COVID-19, hepatocyte swelling, dilatation of the endoplasmic reticulum, and hepatic apoptosis may also develop [14]. The hepatotoxicity mechanism may include liver hypoxia secondary to thrombotic context and virus-induced inflammation. Direct hepatotoxic damage from the virus may also have shown an additive effect on the higher hepatotoxicity results in our study. FVP is mainly metabolized into a hydroxylated form by aldehyde oxidase found in the liver. Patients with severe liver dysfunction have previously been found to have a 6.3-fold increase in the area under the curve (AUC) (6.3-fold) for hepatotoxicity. In light of this information, it may prove necessary to reduce the dose

Table 5. The predicted factors associated with nephrotoxicity are male gender and CHF while risk factors associated with mortality are age, cancer and nephrotoxicity.

Characteristics	Nephrotoxicity			Mortality		
	p	OR	95% CI	*p*	OR	95% CI
Male gender	**0.005**	**5.388**	**1.643 - 17.672**	0.772	0.870	0.340 – 2.229
Age	0.115	1.030	0.993 - 1.068	**< 0.001**	**1.064**	**1.028 – 1.102**
HT	0.138	3.371	0.677 - 16.797	0.493	1.664	0.388 – 7.138
DM	0.795	1.141	0.423 - 3.077	0.119	0.445	0.160 – 1.233
CAD	0.262	0.534	0.178 - 1.600	0.153	2.114	0.758 – 5.896
CHF	**0.003**	**6.885**	**1.916 - 24.741**	0.116	2.949	0.766 – 11.351
CRF	0.145	2.797	0.701 - 11.166	0.759	0.809	0.209 – 3.134
ACE/ARB	0.823	0.854	0.214 - 3.407	0.426	0.585	0.156 – 2.193
Cancer				**0.035**	**3.961**	**1.103 – 14.220**
Nephrotoxicity				**0.004**	**5.571**	**1.749 – 17.749**

HT: hypertension; DM: diabetes mellitus; CAD: coronary artery disease; CHF: congestive heart failure; CRF: chronic renal failure; ACEI/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

of FVP given to patients with severe hepatic impairment [15].

Hyperuricemia is the most common AE (4.8%-84.1%) related to FVP [5,6], but in our study we could not evaluate hyperuricemia because we could not monitor uric acid levels routinely. Gastrointestinal complaints such as diarrhea and nausea are rare [4,5,16]. The frequency of nausea in our cases was 8%, similar to previous studies. Psychiatric symptoms, hypertriglyceridemia, and neutropenia are other AEs attributed to FVP in many studies [5,6,9]. Although it has been reported that skin rashes develop during COVID-19, it cannot be distinguished whether skin rashes are directly related to the virus or the treatments used [17]. In a review evaluating the effects of agents used in the treatment of COVID-19 on skin reactions, it was emphasized that FVP does not cause a skin reaction [18]. Skin rash did not develop in our cases, either.

FVP is an already approved antiviral for pandemic influenza in Japan and has an established safety profile [19]. Pilkington *et al*. showed a well-characterized safety profile with more than 4000 patients. The AEs were hyperuricemia, AST elevation, ALT elevation, gastrointestinal complaints, and psychiatric symptoms [20]. FVP has an effective concentration (EC_{50}) of 61.88 μM and a cytotoxic concentration (CC_{50}) of > 400 μM [21]. The wide range between the EC_{50} and CC_{50} may provide a comfortable margin for a high dose of FVP. An experimental FVP dosing scheme for FVP in Ebola infection was a loading dose of 6000 mg on the first day followed by 2400 mg/day [4]. All patients achieved normal values of biochemical markers on treatment. This study suggests that FVP can be used at high doses.

In the efficacy and AE studies comparing FVP with lopinavir-ritonavir, it has been shown that FVP has more reliable efficacy and a lower AE profile than lopinavir-ritonavir (11.4% versus 55.6%) [22,23]. None of the patients needed to discontinue FVP therapy in these studies. Although cases of QT prolongation with FVP have been reported, it has been shown that cardiac AEs do not develop [24,25].

In line with multiple studies [26,27], we demonstrated that comorbidities cause a worse prognosis incrementally in our study. In univariable analysis, mortality was associated with age, HT, CAD, congestive heart failure, cancer, nephrotoxicity and ACEI/ARB use while logistic regression analysis revealed only age, cancer and nephrotoxicity as the independent predictors of mortality. Age-dependent failure of immune cells, causing a more vigorous inflammatory response, has been suggested as a hypothesis for the higher mortality in older patients [28].

FVP and its active metabolites are renally eliminated. Plasma active metabolites of FVP are two- to three-fold higher in patients with chronic renal failure (eGFR 30-50), but that level is expected to be safe. Although trials exclude patients with end-stage chronic renal failure (CRF), many cases of patients with an estimated glomerular filtration rate (eGFR) < 20 have reported using FVP without AEs [29]. There are no clear data on dose adjustment in patients with CRF. It has been shown that continuous venovenous hemofiltration (CVVH) did not affect FVP clearance in a patient who underwent CVVH [30]. During CVVH, the dose of FVP may not need to be reduced. No cases of FVP-related creatinine increase have been reported in the literature. In our study, 11.6% of the patients had increased creatinine. According to univariate analysis, age, HT, congestive heart failure, chronic renal failure, and ACEI/ARB usage were associated with nephrotoxicity while multivariate analysis showed gender and congestive heart failure as independent predictors of nephrotoxicity. Comorbidities rather than FVP might also have an effect on the creatinine increase in our cases. Besides, different AEs might be seen in the same patients. Hepatotoxicity was seen more in the patients who developed nephrotoxicity. This situation may require attention to hepatotoxicity in patients who receive FVP and have concomitant CRF.

Study limitations

This was a single center study. The lack of a control group consisting of patients who did not receive FVP was another study limitation. The AEs seen in the patients were related with FVP treatment. However, the COVID-19 infection itself and other drugs used, as well as the comorbidities of the patients, might also cause the AEs. We only included patients with moderate COVID-19 infection with WHO scale-5 who were hospitalized. The outpatients were not given FVP treatment at the moment. Therefore, the results of our study might not be attributed to those mild COVID-19 patients.

Conclusions

According to our analysis and other studies conducted on FVP for COVID-19 therapy, FVP appears to be a relatively safe drug. Since SARS-CoV-2 itself and drug interactions may differ, FVP-related AEs might vary in COVID-19 patients. Our study shows that FVP can be used safely with a low AE profile. More

extensive evidence is required to evaluate the long-term AEs of FVP.

Authors' contributions

ETT designed the study, analyzed, and drafted the manuscript. HPG, BO did the statistical analysis. ETT, BES, BB, BB, FG were responsible for the methodology. BO, VK, ZO conceptualized the study and revised the article for intellectual content. All authors contributed to the writing of the final manuscript. All the authors approved the final version of the manuscript to be published.

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Ethical approval

This study complied with the principles of the Declaration of Helsinki and was approved by Institutional Research Ethics Board of Marmara University School of Medicine.

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