DOI: 10.14744/cm.2022.03360
Comprehensive Medicine 2023;15(1):44-49

RESEARCH ARTICLE

The Effect of Favipiravir Initiation Time on Intensive Care Unit Admission Rate and Disease Progression

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ABSTRACT

Objective: No specific treatment has been reported for coronavirus disease-2019 (COVID-19). The use of broad-spectrum antivirals has come up again for COVID-19. We aimed to investigate the effect of favipiravir (FPV) onset time on intensive care hospitalization rate and progression in the treatment of COVID-19.

Materials and Methods: The data of 90 patients who used favipiravir in the isolation wards and intensive care units of our hospital in March, April, and May were reviewed retrospectively. According to symptom onset time, FPV onset time, hospitalization time in the intensive care unit, exitus time, recovery, and discharge time were recorded. In addition, as a laboratory, D-dimer, ferritin, C-reactive protein (CRP), white blood cell, lymphocyte, and fibrinogen counts were recorded. Using these data, the effect of FPV onset time on the progression of the disease was investigated.

Results: As a result of the statistical analysis, the mean age of those who were exitus (ex) was significantly higher than those who survived. The PCR positivity of the patients who were exitus was found to be significantly less than the survivors. The difference in CRP level increases as the time taken for the onset of FPV increases. If FPV is started late, the length of stay in the intensive care unit increases.

Conclusion: Nowadays, when the COVID-19 pandemic is thought to be over, there is still no effective treatment for COVID-19 in the world. The fact that FPV reduces the length of hospital stay has provided ease of treatment in pandemic days when the number of hospital beds is important. Therefore, more studies on FPV are needed.

Keywords: COVID-19, CRP, D-dimer, favipiravir, ICU

How to cite this article: Özdemir F, Şehirlioğlu S, Türkmen ÜA, Kamilçelebi N, Tezdönen M. The Effect of Favipiravir Initiation Time on Intensive Care Unit Admission Rate and Disease Progression. CM 2023;15(1):44-49

INTRODUCTION

The outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and coronavirus disease 2019 (COVID-19) caused by this virus was reported in China in December 2019.[1] There is currently no specific antiviral treatment for COVID-19. Therefore, identifying drug treatment options as soon as possible is critical for the response to the COVID-19 outbreak.[2] The use of broad-spectrum antivirals has come to the agenda again for COVID-19.

SARS-CoV-2 is a single-stranded RNA beta-coronavirus encoding an RNA-dependent RNA polymerase (RdRp) and proteases. Both RdRp and viral proteases are considered important targets for potential therapeutic agents. Favipiravir (FPV) stops viral replication by inhibiting RdRp. With a broad spectrum of activity, FPV is an oral drug approved in Japan in 2004 for the treatment of influenza.[3,4] In 2014, FPV was approved by the Pharmaceuticals and Medical Devices Agency of Japan under the brand name AVIGAN® for the treatment of new and re-emerging influenza virus infection.[5] Studies on FPV have described the efficacy of FPV against other RNA viruses such as ebolavirus, rhinovirus, and respiratory syncytial virus.[6] SARS-CoV-2 has a genome sequence that is 75–80% identical to SARS-CoV. Therefore, the idea that FPV may be useful in the treatment of COVID-19 has emerged.[7] *In vitro*, the 50% effective concentration (EC50) of FPV

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Received date: 09.08.2022
Revised date: 25.09.2022
Accepted date: 16.12.2022
Online date: 31.01.2023

against SARS-CoV-2, was 61.88 μM/L in Vero E6 cells.[8] FPV, therefore, has high potential to treat COVID-19 patients.

Initial reports from China suggest that more than 80% of those infected with SARS-CoV-2 develop mild or moderate illness, but, to date, there have been few studies investigating therapeutic interventions in this population.[9]

FPV was started to be used in our country on March 24, 2020, with the guidance of the Ministry of Health for COVID-19 treatment. In the first published guideline, patients were expected to be hospitalized in the intensive care unit to start FPV, but later, ward hospitalization was sufficient. Finally, it was recommended to start FPV in outpatient treatment in mild disease in the early period. In the last guideline, the use of FPV was left to the physician's preference. Based on these changes, we aimed to investigate the effect of the time of starting FPV treatment on the rate of intensive care unit hospitalization and progression in COVID-19 treatment.

MATERIALS and METHODS

Ethical approval for this study was obtained from Istanbul Gaziosmanpaşa Training and Research Hospital Clinical Research Local Ethics Committee on December 16, 2020 (Ethics Committee Decision No: 123). The principles of human experimentation outlined in the Helsinki Agreement adopted in 1975 were followed. In addition, permission was obtained from the Turkish Ministry of Health for anonymous analysis of the recorded patient data. The data of 90 randomly selected patients who received FPV in March, April, and May 2020 in the isolation wards and intensive care units of our hospital were retrospectively reviewed. Research data were recorded from patient files and the hospital information management system on the case report form. According to symptom onset time, FPV onset time, intensive care unit hospitalization time, exitus time, and discharge time with cure were recorded. In addition, D-dimer, ferritin, C-reactive protein (CRP), white blood cell (WBC), lymphocyte, and fibrinogen counts were recorded as laboratory parameters. Laboratory parameters were recorded before FPV, 7 days and 14 days after FPV. The 69 surviving patients and 21 patients with exitus were compared with each other with all these parameters. The parameters of the surviving and exitus patients were compared. With this information, the effect of FPV initiation time on disease progression was investigated.

All patients included in the study received hydroxychloroquine (HCQ), azithromycin, and oseltamivir according to the treatment guidelines of the Ministry of Health, except FPV (HCQ: 400 mg twice daily on day 1, 200 mg twice daily for the next 4 days, oseltamivir: 75 mg twice daily for 5 days, and azithromycin: 500 mg/day on day 1, and 250 mg/day for the next 4 days). FPV treatment was started when the patients were hospitalized in the isolation ward or intensive care unit as stated in the guidelines. The disease treatment guideline was published and updated by the Ministry of Health. FPV was included in patients who presented with severe pneumonia (tachypnea [>30 breaths/min] and/or hypoxia [SpO_2 <90% on room air] and/or bilateral diffuse ground-glass infiltrates) that did not respond to first-line treatment with HCQ or who developed bilateral diffuse ground-glass. FPV 200 mg tablets were started with a loading dose of 1600 mg twice daily, followed by oral administration of 600 mg twice daily for 5 days. The treatment approach was in line with the recommendations of the Guidelines for the Management of Adults with COVID-19 prepared by the Ministry of Health of the Republic of Turkey.[10]

Statistical Analysis

Statistical analyses were performed using SPSS 22.0 for Windows. Descriptive measures were presented as mean, standard deviation, and percentage distribution. The suitability of the data for normal distribution was checked by Kolmogorov–Smirnov test. Since parametric conditions were not met for the comparison of continuous variables between groups, Mann–Whitney U-test was used. K-square analysis was used to compare the distributions between the Survival and Exitus groups. Spearman correlation analysis was used to compare the correlation between FPV initiation time and changes in various laboratory results and length of stay in intensive care unit. The significance level was taken as $p<0.05$.

RESULTS

A total of 90 people participated in the study and the mean age of the participants was 58.7 ± 13.6 (min: 22, max: 66). Of the participants, 72.2% were male, 27.8% were female, 51.1% had comorbidities, 94.4% had CT positivity, and 67.8% had PCR positivity. About 33.3% of the participants were hospitalized in the intensive care unit. Exitus was observed in 23.3% of the participants (Table 1).

As a result of the statistical analysis, it was found that the median age of the exitus group was statistically significantly higher than that of the survivors, and the PCR test positivity of the exitus group was statistically lower than that of the survivors (Table 1).

As a result of the statistical analysis, it was found that the median D-dimer levels before FPV and D-dimer levels on day 7 after FPV, ferritin levels on day 7 after FPV, CRP levels before FPV and CRP levels on day 7 after FPV, and WBC levels on day 7 before FPV, day 7 after FPV, and day 14 after FPV were statistically significantly higher in patients with exitus than in survivors.

Table 1. Comparison of various characteristics between right and ex groups

	Right		Ex		p
	Average hydrangea number	Standard deviation min-max%	Average hydrangea number	Standard deviation min-max %	
Age	56.8	13.9	65.0	10.0	0.02
	58.5	22–86	67.0	48–83	
Gender					
Male	48	69.6	17	81.0	0.31
Woman	21	30.4	4	19.0	
CT finding	65	94.2	20	95.2	0.86
PCR	51	73.9	10	47.6	0.02
ICU Length of Stay	9.9	2.9	8.9	6.2	0.210
	9	5–13	8.0	2–31	
OTE time	11.0	4.1	9.9	8.1	0.297
	12.5	5–14	9.0	2–41	
Favi Start Time	8.7	4.4	9.2	5.5	0.788
	8.0	2–20	8.0	4–30	
Before D-dimer Favi	1416.8	1565.1	4622.4	10755.4	0.028
	1004.0 (mg/dl)	459–8420 (mg/dl)	1630.0 (mg/dl)	0–43200 (mg/dl)	
D-dimer Day 7	1494.2	1232.1	10308.0	12768.0	0.006
	1072.0 (mg/dl)	482–4380.0 (mg/dl)	2710.0 (mg/dl)	0–39700 (mg/dl)	
D-dimer Day 14	2134.3	1912.5	3748.6	2437.5	0.100
	1912.5 (mg/dl)	486–5510 (mg/dl)	2437.5 (mg/dl)	1310–7330 (mg/dl)	
D-dimer 0–7	−1151.6	1686.9	2983.6	17097.9	0.343
	−922.0 (mg/dl)	−8420–790 (mg/dl)	1050.0 (mg/dl)	−40570–38764 (mg/dl)	
D-dimer 0–14	−1133.5	1990.0	−3707.1	11269.3	0.213
	−980.0 (mg/dl)	−8420–4638 (mg/dl)	−1600.0 (mg/dl)	−43200–5650 (mg/dl)	
Ferritin Pre-Favi	581.5	704.3	759.6	459.9	0.066
	385.0 (ml/ng)	15–4460 (ml/ng)	725.0 (ml/ng)	129–1500 (ml/ng)	
Ferritin Day 7	464.3	419.5	959.3	1104.9	0.005
	397.0 (ml/ng)	2.7 –2334.0 (ml/ng)	656.5 (ml/ng)	112–4000 (ml/ng)	
Ferritin Day 14	382.8	260.3	667.8	762.9	0.726
	282.0 (ml/ng)	99–925 (ml/ng)	395.0 (ml/ng)	120–2134 (ml/ng)	
Ferritin 0–7	44.3	513.8	420.9	957.7	0.241
	4.0 (ml/ng)	−1501–2191 (ml/ng)	66.0 (ml/ng)	−555–2500 (ml/ng)	
Ferritin 0–14	−216.9	543.3	231.5	1087.4	0.764
	−121.0 (ml/ng)	−1690–754 (ml/ng)	−91.0 (ml/ng)	−692–1800 (ml/ng)	
CRP Before Favi	116.3	94.6	184.8	64.7	0.001
	97.5 (mg/L)	0–503 (mg/L)	160.0 (mg/L)	79–323 (mg/L)	
CRP Day 7	49.2	58.8	173.9	136.9	0.001
	23.5 (mg/L)	0–290 (mg/L)	142.0 (mg/L)	11–489 (mg/L)	
CRP Day 14	43.4	53.2	51.9	55.5	0.452
	18.0 (mg/L)	0–159 (mg/L)	31.5 (mg/L)	0.06 –168 (mg/L)	
CRP 0–7	−73.9	110.7	−10.8	153.9	0.072
	−67.1 (mg/L)	−464–122 (mg/L)	0 (mg/L)	−312–315 (mg/L)	

Table 1. Cont.

	Right		Ex		p
	Average hydrangea number	**Standard deviation min-max%**	**Average hydrangea number**	**Standard deviation min-max %**	
CRP 0–14	−99.7	74.6	−146.9	97.1	0.104
	−96.0 (mg/L)	−259–43 (mg/L)	−123.0 (mg/L)	−322–4 (mg/L)	
WBC Pre-Favi	7.2	2.7	10.3	4.9	0.006
	6.8 (10e3/uL)	2.2–15.1 (10e3/uL)	9.7 (10e3/uL)	1.3–20.0 (10e3/uL)	
WBC Day 7	7.4	3.2	10.1	5.3	0.017
	6.9 (10e3/uL)	2.5–16.7 (10e3/uL)	10.3 (10e3/uL)	1.1–20.0 (10e3/uL)	
WBC Day 14	8.3	2.5	13.9	8.3	0.016
	8.6 (10e3/uL)	4–13.6 (10e3/uL)	12.2 (10e3/uL)	1.8 –32.0 (10e3/uL)	
WBC 0–7	−1.2	4.6	−2.1	6.1	0.669
	−0.2 (10e3/uL)	−13.4–6.8 (10e3/uL)	−1.6 (10e3/uL)	−14.1–5.9 (10e3/uL)	
WBC 0–14	0.6	2.7	3.8	5.6	0.138
	0.5 (10e3/uL)	−3.1–7.0 (10e3/uL)	3.8 (10e3/uL)	−3.9–12.0 (10e3/uL)	
Lymphocyte % before Favi	1.1	0.5	0.9	0.3	0.007
	1.0	0.3–2.2	0.8	0.3–1.7	
Lymphocyte % Day 7	1.4	0.6	0.7	0.3	0.001
	1.5	0.3–2.8	0.6	0.1 –1.3	
Lymphocyte % Day 14	1.5	0.5	1.2	1.0	0.100
	1.4	0.8 –2.3	1.0	0.4–3.7	
Lymphocytes 0–7	0.2	0.7	−0.2	0.3	0.002
	0.3	−1.7–1.7	−0.3	−0.7–0.4	
Lymphocyte % 0–14	0.4	0.7	0.2	0.9	0.215
	0.6	−1.0–1.5	0.1	−0.6–2.5	
Fibrinogen Before Favi	432.7	93.1	436.8	96.2	0.192
	408.0 (mg/dL)	261–727 (mg/dL)	469.0 (mg/dL)	208–545 (mg/dL)	
Fibrinogen Day 7	374.5	93.4	455.9	209.9	0.386
	383.5 (mg/dL)	102–552 (mg/dL)	401.0 (mg/dL)	181–768 (mg/dL)	
Fibrinogen Day 14	279.7	96.1	331.4	89.5	0.189
	235.0 (mg/dL)	174–441 (mg/dL)	323.0 (mg/dL)	230–495 (mg/dL)	
Fibrinogen 0–7	−117.9	176.9	−42.3	221.7	0.693
	−34.0 (mg/dL)	−451–133 (mg/dL)	−115.0 (mg/dL)	−260–445 (mg/dL)	
Fibrinogen 0–14	−285.5	106.5	−109.0	212.2	0.060
	−304.0 (mg/dL)	−390– (−20) (mg/dL)	−172.0 (mg/dL)	−323–142 (mg/dL)	

P<0.05 for significance level Mann Whitney U test-Chi-square test. CT: Computed tomography; PCR: Polymerase chain reaction; ICU: Intensive care unit; OTE: Orotracheal intubation; CRP: C-reactive protein; WBC: White blood cell

The median lymphocyte levels of the survivors before FPV and on day 7 were statistically significantly higher than those of the exitus patients.

Laboratory results before FPV were compared, it was determined that only the lymphocyte level on the 7th day after FPV decreased by an average of −0.2 in those who died before FPV, while there was an increase of 0.2 in those who survived, and this difference was statistically significant.

As a result of Spearman correlation analysis, a statistically significant positive correlation was found between the dura-

Table 2. Correlation between Favipiravir initiation time and change in various laboratory results and length of ICU stay

	D-dimer 0–7	D-dimer 0–14	Ferritin 0–7	Ferritin 0–14	CRP 0–7	CRP 0–14	WBC 0–7	WBC 0–14	Fibrinogen 0–7	Fibrinogen 0–14	Length of ICU hospitalization	Length of hospitalization[a]
Favipiravir start time	−0.052 0.745	−0.128 0.427	0.014 0.921	0.361 0.129	0.310 0.009	0.135 0.360	−0.064 0.563	0.092 0.649	−0.084 0.600	−0.043 0.850	0.727 0.001	0.569 0.001

P<0.05 for significance level spearman correlation analysis. CRP: C-reactive protein; WBC: White blood cell

tion of FPV initiation, the difference between CRP before FPV and day 7 and the duration of ICU stay. Accordingly, the difference in CRP level, ICU stay, and length of hospitalization increased as the time to start FPV increased (Table 2).

DISCUSSION

In the review published in December 2022, FPV, among other drugs, has gained importance since 2020 due to the COVID-19 pandemic and its versatility as a broad-spectrum antiviral that inhibits RdRp and targets viral replication. While its benefit has been demonstrated in several clinical trials, other studies have not yielded clear results. The efficacy of the drug in the treatment of COVID-19, including the optimal timing of administration, dosage, and duration of treatment, has not yet been established. Adverse drug reactions among patients included hyperuricemia, prolongation of the QT interval, and elevation of hepatic enzymes. Finally, the possibility of FPV as a post-exposure prophylactic agent in COVID-19 remains to be tested.[11]

In our study, a significant decrease in CRP level was observed. Similarly, in another study, while CRP, procalcitonin, LDH, and D-dimer levels were high before FPV treatment, CRP, procalcitonin, and LDH levels decreased significantly after treatment.[12] However, in both studies, it is difficult to determine whether the CRP decrease was related with the course of the disease or was due to FPV treatment.

According to the results of our study, the duration of hospitalization in the intensive care unit and ward increased as the start time of FPV increased. A study supporting our study suggests that early oral FPV administration in patients with mild-to-moderate severity may reduce the duration of clinical signs and symptoms.[13]

A clinical trial initiated on FPV for the treatment of COVID-19 has achieved promising results. Preliminary results from a total of 80 patients (including the experimental group and control group) showed that FPV has a stronger antiviral effect than lopinavir/ritonavir. No significant adverse reactions were recorded in the FPV treatment group and it had significantly fewer side effects than the lopinavir/ritonavir group.[7] Therefore, we think that it is worth conducting studies on FPV with more patient groups.

In our study, there was no difference between the two groups when we compared the patients who survived and those who died according to the start time of FPV. Similar results to our study in a systematic review of 12 studies investigating the efficacy of FPV in COVID-19, there is no evidence that FPV reduces mortality or the use of mechanical ventilation in moderate and severe patients with COVID-19.[14] Randomized clinical trials or high-quality observational studies involving moderate and severe patients with appropriate sample sizes are needed to define the efficacy of FPV in COVID-19.

In a study on the association of FPV with mortality and accelerated discharge, FPV was associated with clinical benefits, including accelerated discharge rate and less progression to mechanical ventilation; however, no mortality benefit was observed.[15] In our study, the length of ICU stay and hospitalization increased as the time to initiation of FPV increased. Although FPV does not reduce mortality, it reduces the length of hospitalization.

Early treatment with oral FPV had no effect on reducing the incidence of mechanical ventilation, intensive care unit admission, and mortality during hospitalization in 500 COVID-19 patients with comorbidities.[16]

According to a meta-analysis, FPV induced viral clearance within 7 days and contributed to clinical improvement within 14 days. The results showed that FPV has a strong likelihood of treating COVID-19, especially in patients with mild-to-moderate disease. Additional well-covered studies, including examining the dose and duration of treatment, are crucial to reach definitive conclusions.[17]

CONCLUSION

There is still no effective treatment for COVID-19 in the world today when the COVID-19 pandemic is thought to have come to an end. Although FPV is used in a large patient group in our country, there are few studies. The fact that FPV reduces the duration of hospitalization has provided ease of treatment during pandemic days when the number of hospital beds is crucial. Therefore, more studies on FPV are needed.

Disclosures

Ethics Committee Approval: The study was approved by the Gaziosmanpaşa Training and Research Hospital Clinical Research Ethics Committee (No: 123, Date: 16/12/2020).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer reviewed.

Authorship Contributions: Concept: F.Ö.; Design: N.K.; Supervision: F.Ö.; Funding: Ü.A.T.; Materials: F.Ö.; Data Collection or Processing: S.Ş.; Analysis or Interpretation: N.K.; Literature Search: M.T.; Writing: F.Ö.; Critical review: Ü.A.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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