RESEARCH ARTICLE

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Received: 16.12.2020
Acceptance: 14.01.2021
DOI: 10.18521/ktd.841747

Konuralp Medical Journal
e-ISSN1309–3878
konuralptipdergi@duzce.edu.tr
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The Effectiveness of Favipiravir Treatment in Severe COVID-19 Pneumonia: a Single Centre Experience

ABSTRACT

Objective: The aim of this study was to investigate the efficacy of favipiravir (FVP) in severe COVID-19.

Methods: This is a retrospective study of 142 COVID-19 patients with severe pneumonia signs, who received inpatient treatment between March 15 and May 20, 2020. The patients were divided into two groups according to the use of FVP treatment; group 1 (n = 99) included patients who treated with FVP and group 2 (n = 43) who didn't receive FVP.

Results: Mean age was 66.47 ± 11.89 in group 1, and 68.58 ± 14.78 in group 2. Forty patients (40.4%) in group 1 and 22 (51.2%) in group 2 were treated in the intensive care unit (P > 0.05). The proportion of eosinophil, tendency of increasing thrombocyte counts and eosinophil/neutrophil ratio in FVP group was significantly higher than non-FVP group (p < 0.05). In Group 1, patients had significantly reduced erythroid series, and elevated uric acid levels as side effects of FVP. With respect to complications during hospitalization, there was no significant difference among the groups for mechanical ventilator requirement, acute kidney injury, dialysis requirement and sepsis (P > 0.05). The mortality rates in Group 1 (n = 26 [26.3%]) were lower than those in group 2 (n = 16 [37.2%]), but it was not statistically significant.

Conclusions: While the treatment of COVID-19 pneumonia options were limited during the initial stages of the pandemic, the FVP may be effective in severe cases. To confirm this effect, randomized controlled studies are needed in patients of all disease severities.

Keywords: COVID-19 Treatment, Favipiravir, Laboratory Parameteres, Severe COVID-19

Şiddetli COVID-19 Pnömonisinde Favipiravir Tedavisinin Etkinliği: Tek Merkez Deneyimi

ÖZET

Amaç: Çalışmamızda, şiddetli COVID-19'da favipiravirin (FVP) etkinliğini araştırmak amaçlandı.

Gereç ve Yöntem: 15 Mart - 20 Mayıs 2020 tarihleri arasında yatarak tedavi gören, ağır pnömoni belirtileri olan 142 COVID-19 hastası retrospektif olarak analiz edildi. Hastalar FVP tedavisinin kullanımına göre iki gruba ayrıldı; grup 1 (n = 99) FVP ile tedavi edilen hastaları ve grup 2 FVP tedavisi almayan hastaları içeriyordu.

Bulgular: Grup 1'de ortalama yaş 66,47 ± 11,89, grup 2'de 68,58 ± 14,78 idi. Grup 1'de 40 hasta (% 40,4) ve grup 2'de 22 (% 51,2) yoğun bakım ünitesinde tedavi edildi (P> 0,05) . FVP tedavi grubunda eozinofil düzeyi, trombosit sayısı ve eozinofil / nötrofil oranı FVP tedvisi almayan gruba göre anlamlı olarak yüksek bulundu (p <0.05). Grup 1'de hastalarda FVP'nin yan etkileri olarak eritroid serileri önemli ölçüde azalmış ve ürik asit seviyeleri yükselmiştir. Hastanede yatış sırasındaki komplikasyonlar açısından mekanik ventilatör ihtiyacı, akut böbrek hasarı, diyaliz gereksinimi ve sepsis açısından gruplar arasında anlamlı fark yoktu (P> 0.05). Grup 1'deki mortalite oranları (n = 26 [% 26.3]), grup 2" deki hastalardan (n = 16 [% 37.2]) daha düşüktü, ancak istatistiksel olarak anlamlı değildi.

Sonuç: COVID-19 pnömonisinde tedavi seçenekleri pandeminin ilk aşamalarında sınırlı iken, ciddi vakalarda FVP etkili olabilir. Bu etkiyi doğrulamak için, tüm hastalık şiddetlerindeki hastalarda randomize kontrollü çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: COVID-19 tedavisi, favipiravir, laboratuvar parametreleri, şiddetli COVID-19

INTRODUCTION

While the fight against the novel type coronavirus (COVID-19) pandemic continues, the numbers of COVID-19 related deaths worldwide have exceeded one million cases. The mortality rates are higher in patients with advanced age, males, and presence of more than one comorbidity (1-3). Death rates in the intensive care units can be as high as 26-80% (4-6). To date, no vaccine or WHO-approved antiviral treatment for the new virus is available. Although numerous drugs have been suggested for treatment, their efficacies are still debated (7-9). One of the interesting antivirals suggested for COVID-19 treatment is FVP, which is effective against numerous RNA viruses including the ebola virus (10). FVP was first developed in Japan in 2014, against neuraminidase resistant influenza. It is a prodrug that first enters the infected cells via endocytosis, then transformed into active favipiravir ribofuranosyl phosphate (11). FVP has been shown to demonstrate a more efficient and rapid viral clearance in COVID-19 patients when compared to other antivirals (12). The most reported side effects are abnormal liver function enzymes, diarrhea, and hyperuricemia (13). There is limited information in the literature about the role of FVP in the treatment of COVID-19 pneumonia. We aimed to investigate the efficacy of FVP in patients diagnosed with severe COVID-19 pneumonia, whose symptoms did not improve despite treatment with hydroxychloroquine (HQ), oseltamivir, and azithromycin.

MATERIAL AND METHODS

Study Design and Patient's Population: This is a retrospective study of 142 COVID-19 patients with severe pneumonia signs, who tested positive on nasopharyngeal (NP) swabs and received inpatient treatment between March 15 and May 20, 2020. The present study protocol was conducted in accordance with the Declaration of Helsinki, and after approval of the Ethics Committee of Sakarya University Faculty of Medicine (No:71522473/050.01.04/261).

According to the algorithm constructed by the coronavirus scientific advisory board, set up by the Turkish Ministry of Health, the recommended first step treatment in patients diagnosed with COVID-19 pneumonia consisted of HQ, oseltamivir, and if necessary, azithromycin. FVP, tocilizumab, or convalescent plasma are applied in patients with respiratory failure or tachypnea, and need intubation or transfer to the intensive care unit. During the initial stages of the pandemic, patients had not received FVP due to the unavailability of the drug in Turkey.

The patients were divided into two groups according to the use of FVP treatment; group 1 (n = 99) included patients who treated with FVP and group 2 (n = 43) who didn't receive FVP. Both groups were compared by measurement of the biochemical parameters, including organ dysfunction assessments before and after treatment. Initial treatment prior to FVP, age, sex, comorbid disease status, and length of hospital stay were recorded. Also, the reasons for starting FVP, initiation of treatment in the ward or intensive care, and the data for deceased patients were recorded. Patients in Group 1 had received the following drugs prior to FVP: HQ in 99%, azithromycin in 77.8%, and oseltamivir in 67.8%. In Group 2, all patients had been given HQ, azithromycin and oseltamivir without any FVP treatment. The FVP doses were, 1600 mg twice daily in day 1, 600 mg twice daily in days 2 - 5.

The inclusion criterion was COVID-19 patients with severe pneumonia signs (Presence of pneumonia clinical signs plus one of the following: respiratory rate > 30 breaths/min, severe respiratory distress, or SpO2 < 90% on room air) (14). Patients aged below 18 or above 90 years, had active bacterial infections, elevated liver enzymes, used immunosuppressive medications, and had malignancies were excluded from this study.

Statistical Analysis: Statistical analysis was performed using the IBM SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max), or number and frequency. To compare the qualitative data, the chi-square test or Fisher's exact test (when chi-square test assumptions do not hold due to low expected cell counts) was used. The Mann–Whitney U test was used to compare the variables that were not normally distributed. On the other hand, Student's t test was used to compare the variables with normal distribution. The statistically significant two tailed p-value was considered as < 0.05.

RESULTS

Ninety-nine patients in Group 1 (mean age 66.47 ± 11.89) and 43 patients in Group 2 (mean age 68.58 ± 14.78 years) were evaluated. There were 55 males (55.6%) in group 1, and 24 (55.8%) in group 2. Forty patients (40.4%) in group 1 and 22 (51.2%) in group 2 were treated in the intensive care unit ($p > 0.05$). Mean time of hospitalization was 15.03 ± 8.50 days for group 1, and 13.49 ± 3.73 for group 2 ($p > 0.05$). Baseline characteristics and laboratory properties of all patients are presented in Table 1 and 2. Assessment of basal biochemical parameters revealed that patients in Group 1 were more hyponatremic and hypoalbuminemic, whereas Group 2 patients had lower eosinophils and eosinophil to neutrophil ratios ($p < 0.05$). After treatment; Group 1 patients had significantly increased eosinophil counts, reduced erythroid series and elevated uric acid levels ($p < 0.05$) (Table 2). Comparison of the complications during hospitalization, there was no significant difference among the groups for mechanical ventilator requirement, acute kidney injury, sepsis and requirement to renal replacement

therapy (RRT) ($p > 0.05$) (Figure 1). Also, the mortality rates in Group 1 (n = 26 [26.3%]) were lower than those in group 2 (n = 16 [37.2%]), it was not statistically significant.

Table 1. Baseline characteristics of patients according to disease groups

Variables	Group 1 (n=99)	Group 2 (n=43)	p value
Age (year)	66.47±11.89 (37.0-90.0)	68.58±14.78 (28.0-92.0)	0.370*
Sex (M/F) n, (%)	55/44 (55.6/44.4)	24/19 (55.8/44.2)	0.977**
Onset of Symptoms			
Fever	84 (84.8)	34 (79.1)	0.399**
Shortness breathing	81 (81.8)	33 (76.7)	0.490**
Cough	70 (70.7)	36 (83.7)	0.092**
Myalgia	27 (27.3)	12 (27.9)	0.938**
Diarrhea	12 (12.1)	7 (7.0)	0.553***
Sore throat	11 (11.1)	3 (7.0)	0.552***
Anosmia	4 (4.0)	1 (2.3)	0.521***
Comorbid situations (%)			
Hypertension	49 (49.5)	24 (55.8)	0.610**
Diabetes mellitus	27 (27.3)	12 (27.9)	1.000**
Heart disease	16 (16.2)	9 (20.9)	0.656**
COPD	4 (4.0)	5 (11.6)	0.130***
Antihypertensive use (%)			
ACEI	22 (22.2)	7 (16.3)	0.561**
ARB	15 (15.2)	7 (16.3)	1.000**
Smoking (yes/no) (%)	12/87 (12.1/87.9)	5/38 (11.6(88.4)	0.934**
The onset of O2 saturation			
Mean values ± SD	88.04±8.68	90.86±4.02	0.142****
(min.-max.)	(50.00-99.00)	(80.00-95.00)	
O2 recruitment (no) (%)	78 (78.8)	32 (74.4)	0.723**
Torax CT findings			
Unilateral/Bilateral (no) (%)	12/87 (12.1/87.9)	3/40 (7.0/93.0)	0.553***
Hospitalization to ICU (no) (%)	40 (40.4)	22 (52.28)	0.235**
Mean time of hospitalization (days)	15.03±8.50 3.00-46.00	13.49±3.73 6.00-22.00	0.784****
Time of symptoms onset to admission (days)	4.42±2.27 1.0-10.0	4.41±2.66 1.0-10.0	0.759***
The first line treatment was given before FVP treatment (%)			
Hydroxychloroquine	98 (99.0)	43 (100.0)	0.697***
Azathioprine	77 (77.8)	43 (100.0)	**<0.001****
Oseltamivir	68 (68.7)	43 (100.0)	0.794**

*Independent-Samples T test, **Chi Square test, ***Fisher's Exact test, ****Mann-Whitney U tests were used. COPD: Chronic obstructive pulmonary disease, ACEI: Angiotensin converting enzyme inhibitor, ARB: Angiotensin II receptor blocker, CT: Computerized tomography, ICU: İntensive care unit, FVP: Favipiravir

Table 2. Comparative analysis of laboratory values obtained during baseline and discharging of Favipiravir and control groups

Variables	Basal Group-1 mean values ± SD (min.-max.)	Basal Group-2 mean values ± SD (min.-max.)	p value	End of follow up Group-1 mean values ± SD (min.-max.)	End of follow up Group-2 mean values ± SD (min.-max.)	p value
White Blood Cells NV: 5.6-10.2 (K/uL)	8.76±5.64 (2.04-37.00)	8.57±4.56 (3.20-22.00)	0.972*	6.70±2.52 (2.27-14.00(	7.11±1.75 (4.28-9.07)	0.409*
Lymphocyte NV: 0.6-3.4 (K/uL)	1.29±0.98 (0.10-8.48)	1.38±0.69 (0.36-3.70)	0.333*	1.77±0.91 (0.32-4.76)	1.58±0.53 (0.91-2.35)	0.966**
Neutrophil/ Lymphocyte ratio	7.76±8.07 (0.75-38.15)	6.47±8.19 (1.14-44.44)	0.211*	3.01±1.84 (0.83-10.38)	2.85±1.96 (1.01-8.18)	0.488*
Eosinophil NV: 0-0.7 (K/uL)	0.06±0.10 (0.001-0.56)	0.02±0.06 (0.001-0.34)	**<0.001 ***	0.20±0.14 (0.002-0.91)	0.13±0.11 (0.00-0.51)	**0.008***
Eosinophil/neutrophil ratio	0.01±0.02 (0.00-0.19)	0.007±0.16 (0.00-0.008)	**0.002***	0.05±0.04 (0.00-0.22)	0.04±0.05 (0.00-0.23)	0.072*
Red Blood Cells NV: 4.04-6.13 (K/uL)	4.50±0.70 (2.66-6.00)	4.55±0.75 (1.41-5.90)	0.654**	4.09±0.57 (3.02-5.82)	4.22±0.94 (3.20-5.71)	**0.021****
Hemoglobin NV: 12.2-18.1 (gr/dl)	12.61±2.04 (6.20-17.20)	12.92±1.85 (6.70-16.90)	0.398**	11.57±1.48 (8.37-14.50)	12.05±2.32 (9.93-16.00)	**0.003****
Platelet NV: 142-424 (K/uL)	206.07±83.39 (52.60-555.0)	198.25±79.31 (68.2-507.0)	0.446*	272.38±102.24 (41.9-580.0)	270.17±76.02 (196.0-403.0)	0.563**
D-Dimer NV: 0-500 (ug/L)	1942.2±4559.8 (119.0-35100.0)	2291.7±48488 (110.0-29.5)	0.594*	1260.2±1202.3 (158.0-7630.0)	1618.1±1150.9 (320.0-3910.0)	0.599*
Ferritin NV: 21.8-274.6mcg/L	687.30±1237.0 (9.19-9587.0)	491.51±539.6 (46.0-2069.0)	0.780*	359.16±298.87 (23.8-1261.0)	417.00±326.51 (144.0-972.0)	0.942*
Serum creatinine NV: 0.67-1.17 mg/ml	1.15±1.41 (0.20-10.00)	1.15±0.86 (0.35-4.58)	0.632*	1.21±1.50 (0.40-10.00)	0.76±0.71 (0.28-2.16)	0.344*
Uric acid NV: 3.5-7.2 (mg/ml)	4.87±1.67 (2.3-10.9)	5.55±2.29 (3.20-13.0)	0.196*	5.68 2.36 (2.20-12.00	5.40±2.86 (2.20-10.10)	**0.006***
Sodium NV: 135-145 mEq/L	136.72±5.40 (124.0-165.0)	137.98±3.45 (130.0-147.0)	**0.032***	136.74±2.96 (128.0-142.0)	134.66±4.50 (128.0-141.0)	0.678*
Serum albumin NV: 35-52 (gr/L)	30.84±4.80 (17.0-44.0)	32.54±4.22 (22.20-40.20)	**0.019***	32.30±5.20 (21.40-44.90)	31.53±4.64 (27.30-38.70)	0.174**
Lactate dehydrogenase NV: 0-248 (U/L)	349.22±144.02 134.00-855.00	307.58±96.63 (137.0-591.0)	0.215*	285.72±90.53 (147.0-506.0)	252.00±65.78 (147.0-344.0)	0.156**
C-Reactive Protein NV: 0-5 (mg/L)	79.69 67.22 (2.14-286.00)	74.79 74.62 (3.55-298.0)	0.635*	22.89±23.56 (3.02-106.00)	39.15±47.05 (3.60-102.00)	0.815*

* Mann-Whitney test and, **Independent-Samples T test were used

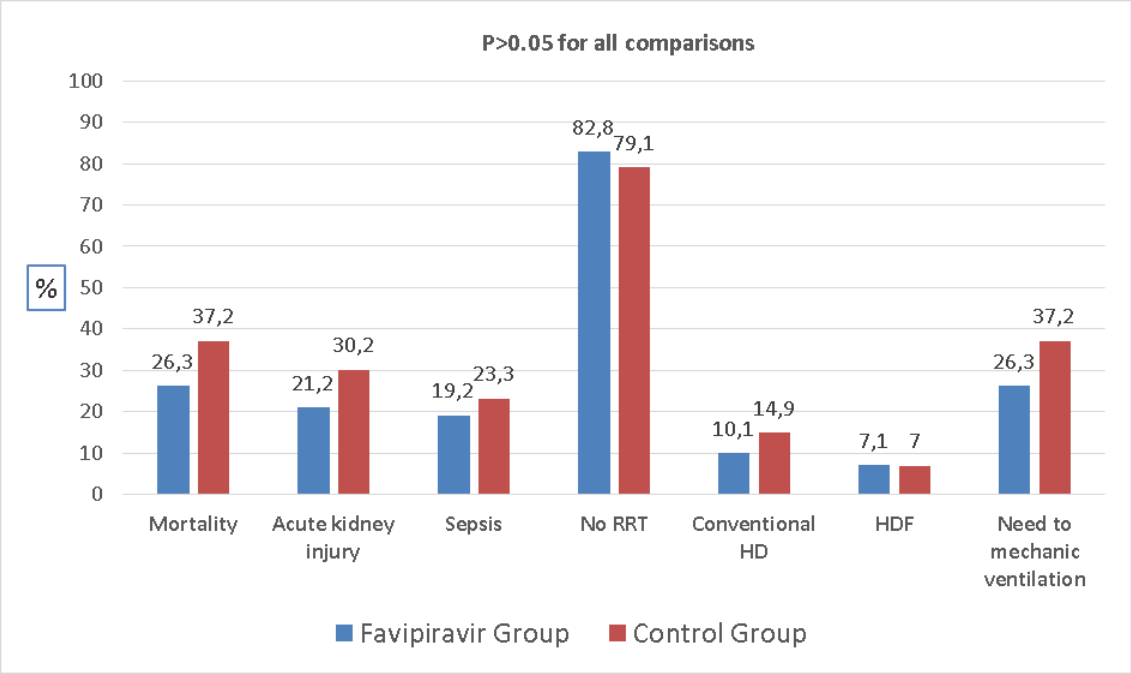

Figure 1. Comparison of two groups in terms of complications occurred during treatment period
RRT: Renal replacement therapy, HD: Hemodialysis, HDF: Hemodiafiltration

DISCUSSION

In our study, we compared FVP with some drugs used at the onset of the COVID-19 pandemic to investigate the efficacy of FVP in severe COVID-19 patients. There are no human studies that investigated the effects of FVP on COVID-19 related mortality in the literature. In the present study, although the mortality rates were lower in the FVP group compared to the Group 2, the difference was not significant ($p > 0.05$). It could be due to a small number of our patients. Because it is being used in the treatment of several RNA virus infections, FVP has been tested on numerous experimental and clinical studies (10,12,14). One non-randomized interventional small study that enrolled 80 non-severe COVID-19 patients investigated the efficacy of FVP treatment and reported a possible increase in viral clearance at day 7 with FVP (12). Our outcomes provide a comprehensive analysis of the demographic features, comorbidities, and laboratory abnormalities that are associated with mortality in COVID19 as in the literature (15,16). The important point was that the present study population included just patients who had severe disease criteria. Because there are no data related to the effect of FVP on mortality of COVID-19 infection, we believe this information is very important. FVP mortality studies were previously reported on non-COVID-19 patients. In a study that investigated the effect of high dose FVP (day 0: 6,000 mg; day 1 to day 9: 2,400 mg/d) against the Ebola virus, 99 patients were randomized by their cycle threshold (Ct) 20-value, and Ct 20 was adjusted to a RNA viral load of 7.7 log10 viral genome copies/ml. Mortality at day 14 of patients in the Ct ≥ 20-group was 20%, whereas mortality in the Ct < 20-group was 91%. These results showed that FVP treatment was highly effective in patients with high Ebola viral load (10). Another study that compared FVP monotherapy against FVP-oseltamivir combination in critically ill influenza patients did not find any significant differences (17).

Severe complications including the requirement to mechanical ventilation, acute kidney failure, sepsis, and RRT requirement were similar in both groups. The treatment protocol in our country was recommended FVP treatment in those patients who do not respond to treatment or who show disease progression, therefore FVP could be initiated only after a mean period of 5.0 ± 3.18 days. There are currently no studies that have investigated the start of FVP treatment in mild-moderate disease or before disease progression.

In our study, the proportion of eosinophil, coagulation parameters, tendency of increasing thrombocyte counts and eosinophil/neutrophil ratio in FVP group was significantly higher than non-FVP group. However, the reduction in erythroid series and hyperuricemia as side effects of FVP were significantly higher than group 2 ($p < 0.05$). Eosinophils constitute only 1-3% of the leukocytes in the circulation, they possess a proinflammatory potential and they appear at various levels in numerous diseases (18-20). A study that investigated eosinopenia as a marker for distinguishing COVID-19 pneumonia from non-COVID showed that it had 74.7% sensitivity, 68.7% specificity, and 67.3% positive predictive value (PPV). When assessed together with high

sensitive CRP, the sensitivity was 67.9%, specificity was 78.2%, and PPV was 72.8% (21). Another study found eosinopenia in 52.9% of COVID-19 patients. The eosinophil counts showed a positive correlation with lymphocyte counts in non-severe and severe patients ($r = 0.486$ and 0.469, respectively) ($p < 0.001$) (18). Similarly, we found that on the day of discharge the patients with severe disease receiving FVP treatment had improvements in eosinopenia, and eosinophil to neutrophil ratio values.

We recently showed that the using of standardized dose of FVP for five days reduced the erythroid series as side effects in a small study involving 62 COVID-19 positive patients (22). Also, FVP related hyperuricemia was reported previously (23).

In our patients, if FVP treatment had been initiated earlier, maybe more viral clearance could have been attained. An open-label non-randomized control study comparing FVP with lopinavir/ritonavir study in COVID-19 disease found a shorter viral clearance time for the FVP group versus the lopinavir/ritonavir group (median (interquartile range, IQR), 4 (2.5–9) day versus 11 (8–13) day, $p < 0.001$). The FVP group also showed significant improvement in chest computerized tomography compared with the control group, with an improvement rate of 91.43% versus 62.22% ($p = 0.004$). Also, FVP was independently associated with a faster viral clearance (12). However, it is not easy to talk about viral clearance with this small-scale study. Larger randomized controlled studies are needed to prove the antiviral clearance of FVP.

The limitations of the study are lack of patients with mild or moderate severity illness in either group, retrospective nature and, not adding the side effect information to the study data caused by lack of knowledge on side effects of the other drugs. In addition, because the study included patients at the outbreak onset, it was not compared with the results of patients receiving recently proven steroid therapy.

In conclusion, COVID-19 outbreak has been spreading quickly all over the world; while specific vaccine or drugs have not yet been consolidated for the time being. It is a controversial issue, at the beginning of present study, but not now, according to the algorithm determined by the scientific committee, it was deemed appropriate to start FVP treatment only in patients with severe disease criteria. Although we found lower mortality rates in severe patients using FVP, we did not find a significant difference between the two groups. In our opinion, to test the efficacy and reliability of FVP, randomized controlled studies in which the drug is given as a first line treatment to patients with different disease severities are needed.

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