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The efficacy of favipiravir treatment in hemodialysis patients with COVID 19

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Introduction

Corona Virus 2 (SARS-CoV 2), a recent coronavirus was first discovered in Wuhan, China in December 2019 [1]. Previous coronavirus infections, namely Middle-East Respiratory Syndrome (MERS-CoV) and SARS-CoV have been reported to damage the respiratory system and cause serious outbreaks [2]. Major complaints are shortness of breath, cough, fever, and diarrhea [3,4]. Lung involvement is the most common form of infection, and is characterized by bilateral lung infiltrates [5,6]. The infection leads to cytokine storm and organ dysfunction and may consequently death. The diagnosis is suspected in presence of contact history, respiratory symptoms, fever, chest radiology, and biochemical parameters. The diagnosis is confirmed with Reverse Transcription-Polymerase Chain Reaction (RT PCR) positivity for COVID-19 in the nasopharyngeal swab [7]. It has been reported that elderly patients are more prone to severe coronavirus disease, just as in hemodialysis patients with additional comorbidities [5]. Since the immune system is low in Chronic Kidney Disease (CKD) patients, their tendency to infections is increased [8,9]. Good supportive treatment and infection treatment should be done [10]. CKD is also associated with an increased risk for pneumonia. Mortality rates related to lung infection in CKD seem to be 15-16 times higher than in the general population [9,11]. The use of several antiviral drugs, such as chloroquine phosphate, lopinavir/ritonavir, interferon-alpha, ribavirin has been studied, and some clinical trials focusing on virus RNA dependent RNA Polymerase (RdRp) inhibitors have been initiated. Favipiravir, a purine-nucleic acid analog and RdRp inhibitor which has been approved for use in influenza, is

also considered in clinical trials [12,13]. The data on dialysis-dependent patients with COVID-19 are limited, and recommendations are based on expert opinion and case series. There are no studies about the use of favipiravir in patients with renal failure in the literature. In this study, we aimed to describe our experience of favipiravir treatment in dialysis-dependent patients.

Materials and methods

This study was planned at two university hospitals. These hospitals provide medical services in the region, where 17 million people live.

Statement of ethics: The study complies with the Declaration of Helsinki, and institutional approval was obtained from the local ethical review committee (2020/514/178/3). The participants' identities were kept confidential. The informed consent has been taken on admission.

Patients

We examined all COVID-19 patients with CKD who underwent chronic Hemodialysis (HD) treatment between March 2020 and December 2020. Fifty HD patients were evaluated with the diagnosis of COVID 19. The patients were recruited prospectively, and previous hospital records were evaluated retrospectively. Sixteen PCR positive HD patients who were treated with favipiravir were enrolled in the study. Participants were followed up for a minimum of 5 days or until death after COVID 19 diagnosis.

Patients were categorized into two groups for the analysis in line with favipiravir response. Patients whose clinical and laboratory values improved, were considered as responsive to favipiravir treatment (group 1). Patients whose findings didn't improve were considered non-responsive to favipiravir treatment (group 2).

Data

The data were retrospectively collected from the medical records of the patients by a physician who was blinded to the results. Clinical data, comorbidities, hemodialysis information laboratory, radiological results, antiviral, anti-cytokine treatments were extracted. Nasal and oropharyngeal swab results were recorded. All patients underwent chest Computed Tomography (CT). All cases demonstrated multilobar and bilateral lung involvement at initial admission.

Patient management

The COVID-19 diagnosis was supported with contact history, symptoms, laboratory, and radiological findings. The positive RT PCR test was required to confirm the diagnosis. All patients were hospitalized due to the poor prognosis of COVID 19 in CKD. The indications for favipiravir treatment were moderate or severe pneumonia, and being unresponsive to hydroxychloroquine treatment.

Patient treatment

The treatment modalities were based on national guidelines prepared by the scientific board and published by the Ministry of Health. All patients were initially treated with hydroxychloroquine (400 mg BID for the primary day, then 200 mg BID for four days; oral) and azithromycin (500 mg QD for the primary day, and so 250 mg QD for the four days; oral). The cases, who showed progression of infection despite this treatment got Favipiravir (1600 mg BID for the primary day, then 600 mg BID for the four days; oral). Tocilizumab (400 mg QD for 2 days; intravenous) was employed for the treatment of cytokine release syndrome. Antibiotic therapy was administered in the presence or suspect of bacterial co-infection. The patients were monitored for adverse drug reactions. The QT intervals were regularly monitored.

Other treatment

Dose-adjusted low-molecular-weight heparin was employed to all patients unless contraindicated on dialysis-free days. Oxygen treatment was provided to the patients with oxygen saturation below 92%, with the nasal cannula, or with a mask with a reservoir if it had been insufficient. If the respiratory failure progressed despite these treatments, the patients underwent mechanical ventilation.

Statistical analysis

The Statistical Package for Social Sciences Software (SPSS trial version, Chicago, Illinois) was accustomed compare demographic and clinical variables. Quantitative variables were shown as median (minimum-maximum). The numbers and percentage values were used for expression of categorical variables. For continuous variables, the Mann-Whitney U test was wont to compare groups. For categorical variables, the X2 test or the Fisher exact test was used as appropriate. The differences were considered significant at the 2-sided P<0 .05 level.

Results

Demographical-Clinical Characteristics

Fifty HD patients with COVID-19 were analyzed. Favipiravir treatment was ordered for 16 of them. Sixteen patients (10 female and 6 male) were reviewed for a median follow-up of 15 days (interquartile range 25th to 75th percentiles, 5-57 days) after admission. The demographic characteristics were shown in Table 1. All patients with severe pneumonia were admitted to the hospital. Eleven patients (68.8%) responded to the favipiravir treatment. No significant differences were observed between the two groups in terms of gender, age, comorbidities, hemodialysis duration (Table 1). Cough (n=8), fever (n=10) and dyspnea (n=9) were the most frequent. The symptoms were similar in two grups. The serum acute phase reactants were found to be elevated in both groups (Table 2). Significant differences were found in post-treatment oxygen saturation values (85% [min-max, 83%-88%] and 95% [min-max, 90%-98%]; p=0.013, respectively) , pre-treatment CRP values (216 mg/L [min-max,154 mg/L -271 mg/L] and 132 mg/L [min-max, 53 mg/L -304 mg/L]; p=0.01, respectively) and post-treatment CRP values (146 mg/L [min-max, 98 mg/L -254 mg/L] and 56 mg/L [min-max, 26 mg/L -123 mg/L]; p=0.04, respectively). (Table 3)

Outcomes

Eleven patients responded to favipiravir treatment. Five patients (31.3%) were deceased during the ICU follow-up. Four patients died due to respiratory failure, and one patient died due to multi-organ failure, associated with the cytokine-release

Table 1: The demographic characteristics of the patients.

	All patients (n=16)	Response to treatment (n=11)	Non response to treatment (n=5)	p-value
Age (Mean±SD, year)	65,3 ± 13.8	64.5 ± 15.2	67.2 ± 9.8	0.95
Sex (N, %)				
Male	6 (40%)	6 (54.5%)	0 (0%)	
Female	10 (60%)	5 (45.5%)	5 (100%)	0.93
Etiology of CKD (N, %)				
Hypertensive nephropathy	4 (25%)	2 (18.2%)	2 (40%)	0,63
Diabetic nephropathy	8 (50%)	6 (54.5%)	2 (40%)	0,59
Sekondary amyloidosis	1 (6.25%)	0 (0%)	1(20%)	0,14
Unknown	3 (18.75%)	3 (27.3%)	0 (0%)	0,34
Comorbidities (N, %)				
Pre-existing lung disease	2 (12.5%)	2 (18.2%)	0(0%)	1
Previous heart disease	6 (37.5%)	4 (36.4%)	2(40%)	0.77
Chronic hypertension	16 (100%)	11(100%)	5 (100%)	
Usage of RAS blockage	8 (50%)	6 (54.5%)	2 (40%)	1
Smoking	5(31.25%)	5(45,5%)	0(0%)	0.1
Hemodialysis duration (months, Min-max)	7 (1-122)	10 (2-122)	3 (1-121)	0.33

Table 2: Clinical characteristics; laboratory values; duration of hospitalization of patients and relation between response to treatment and onset time of favipiravir.

Time (Day)	All patients (n=16)	Response to treatment (n=11) Group 1	Do not response treatment (n=5) Group 2	p-value
Duration of Hospitalization (day)	15 (5-57)	15 (5-57)	12 (5-23)	0.16
Time from onset of symptom to favipiravir treatment(day)	5.5 (1-17)	7 (1-17)	5 (5-16)	0.31
Time from hospitalization to favipiravir treatment (day)	2 (1-13)	2 (2-13)	5 (1-8)	0.16
Presentation symptoms				
Fever	10 (62.5)	2(20)	8 (80)	0.29
Cough	8(50)	2(25)	6 (75)	1
Dyspnea	9 (56.3)	1 (11,1)	8 (88.9)	0.16
Diarrhea	3 (18.7)	2 (66.7)	1 (33.3)	0.24
Initial examination findings				
Pulse rate	84 (64-120)	82 (65-112)	89(64-118)	0.90
SpO_2 value	96 (88-98)	95 (88-98)	96 (88-97)	0.013
Respiratory rate	22(18-32)	18 (22-32)	20 (18-32)	0.64
Blood Pressure				
Systolic	127 (100-170)	140(170-100)	120 (100-140)	0.97
Diastolic	80 (60-90)	80 (70-90)	70 (60-90)	0.74
Fever (^{0}C)	37.2(36.1-39)	36.9(36-38)	37.3(36.3-39)	0.30

Laboratory results at admission				
Leucocyte count (/mm³)	8800 (5700-18.800)	9300 (700-21100)	9400 (8500-16200)	0.42
Lymphocyte count (/mm³)	1200 (500-3700)	1000 (500-3700)	1500 (900-1800)	0.25
Hemoglobin count (g/dl)	10 (8-12)	9 (8-11)	11 (10-12)	0.24
Platelet count (/mm³)	218 (101-426)	185 (101-426)	237 (176-392)	0.39
Serum CRP levels (mg/L)	103 (10-195)	103 (10-95)	123 (92-154)	1
Serum LDH levels (IU/L)	257 (198-370)	320 (190-1150)	558 (260-945)	0.15
Serum D-Dimer levels (ng/ml)	11.86(0,19-5610)	605 (3.8-4104)		
Serum Ferritin levels (ng/ml)	358 (173-992)	876 (272-2000)	1075 (598-1343)	0.69
Serum procalcitonin (ng/ml)	0.2 (0.1-0.3)	38(4-44)	1(1-1)	0.18

The results are presented as median and min to max, and number (N) and percent (%)

Table 3: Laboratory findings before and after favipiravir treatment.

	RESPONSE TO TREATMENT GROUP 1			NONRESPONSE TO TREATMENT (GROUP 2)		
	BEFORE TREATMENT Median (min-max)	AFTER TREATMENT Median (min-max)	P	BEFORE TREATMENT Median (min-max)	AFTER TREATMENT Median (min-max)	P
SpO_2 value (%)	87 (85-89)	96 (92-99)	0.013	88 (84-96)	85 (83-88)	0.42
Leucocyte count (/mm³)	8200 (5700-18800)	8900 (4800-21.400)	0.79	13.500 (8500-14.600)	14.200 (8600-8.000)	0.43
Lymphocyte count (/mm³)	1000 (500-2500)	1100 (800-2400)	0.09	1150 (600-1900)	800 (600-1400)	0.78
Serum CRP levels (mg/L)	132 (53-304)	56 (26-123)	0.01	216 (154-271)	146 (98-244)	0.04
Serum LDH levels (IU/L)	315 (200-2459)	255 (125-628)	0.12	414 (234-540)	488 (214-1434)	0.69
SerumD-Dimer levels (ng/ml)	13.85 (0.23-5485)	9.92 (0.4-3110)	0.39	16.50 (1.2-4300)	35 (10.9-4710)	0.86
Serum Ferritin levels (ng/ml)	1171 (460-7777)	804 (345-1375)	0.42	560 (398-1568)	1754 (237-4000)	0.54

syndrome. Tocilizumab therapy was given to three patients (18.75%). One of the patients who was treated with tocilizumab died in ICU. One of the patients responsive to favipiravir treatment was followed up in the intensive care unit with mechanical ventilation. He was consequently weaned from mechanical ventilation and transferred to the COVID-19 ward. Regarding adverse events of favipiravir treatment, none of the adverse reactions including increased liver enzymes were detected during the follow-up.

Discussion

COVID 19 is a global life-threatening respiratory infection. SARS CoV 2 often causes lower respiratory tract infections requiring hospitalization in dialysis-dependent patients. In our study, we analyzed 16 HD-dependent CKD patients treated with favipiravir for COVID 19 for a median follow-up of 15 days. The study group had radiographically confirmed multilobar and bilateral pneumonia. All the patients were followed up in the hospital, either in a dedicated Covid-19 ward or in the ICU. Five patients died in the ICU. Both cytokine-targeted therapy and favipiravir were administered to three patients.

We have clinically observed that within the responsive group, favipiravir was initiated prior to the opposite group. However, the difference wasn't found to be statistically significant. This fact is often considered to be associated with the low number of patients in our study. for sure, in the favipiravir responsive group, post-treatment oxygen values were more than the others. within the responsive group, pre-treatment and post-treatment CRP values were not up to the opposite group. The CRP response led us to think that earlier favipiravir treatment may provide a simpler response. In the favipiravir responsive group, the speed of mechanic ventilation (27%, 60% respectively) and death (27%, 80% respectively) was but the non-responsive group.

One limitation of our study is that the study population consists of the low number of patients. Still, we have clearly observed the advantage of early initiation of favipiravir in HD patients.

Conclusions

In hemodialysis patients, the COVID-19 death rate is above the normal population. there's not enough information about the utilization of favipiravir in hemodialysis patients within the literature consistent with data of both the planet Health Organization and National Registry, the COVID-19 fatality rate is 2.76% in Turkey. The death rate is lower in our country than in many other countries. This low morbidity may well be associated with early treatment including favipiravir. In line with this data, we observed that early treatment and low mortality rates seem to be correlated even in chronic HD patients.

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