Favipiravir Use in Kidney Transplant Recipients with COVID-19: A Single-Center Experience

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Abstract

Objectives: **Kidney transplant recipients are among the high-risk groups for severe COVID-19. To date, no specific antiviral agent has proved uniformly effective against SARS-CoV-2. Favipiravir, the recommended drug by the Turkish Ministry of Health, was uniformly supplied to all patients diagnosed with COVID-19 by a positive nasopharyngeal swab polymerase chain reaction test. The aim of our study was to retrospectively compare our kidney transplant recipients treated with favipiravir who developed COVID-19 infection versus those not treated with favipiravir during the clinical course of the disease, with a special emphasis on the occurrence of side effects and adverse events.**

Materials and Methods: **We included 37 consecutive kidney transplant recipients with a median age of 46 years (62.2% women). Recipients included 8 with deceased donors and 29 with living related donors; median posttransplant survival was 8.0 years (IQR, 5.5-12.5 years).**

Results: **Twenty-six patients (70.3%) received favipiravir, and 11 (29.7%) did not. There were no statistically significant differences between the groups for baseline demographic characteristics and clinical and laboratory data, except that the favipiravir-treated patients were older and had a higher requirement of oxygen treatment. There were no statistically significant differences between the 2 groups for the course and outcome of COVID-19 infection with regard to adverse side effects/events associated with favipiravir. Laboratory data at baseline, day 7, and day 30 were also comparable between the groups.**

Conclusions: **Although the efficacy of favipiravir for treatment of COVID-19 infection remains controversial, favipiravir is safe for kidney transplant recipients.**

Key words: *COVID-19 pandemic, Kidney transplantation, Severe acute respiratory syndrome coronavirus 2*

Introduction

The SARS-CoV-2 pandemic has affected more than 15 million people in 215 countries worldwide since early 2020. Although the course of COVID-19 infection is usually mild to moderate, it can be severe to very severe in approximately 10% to 15% of cases and fatal in approximately 1% to 3% of cases.[1,2] Advanced age and comorbidities such as hypertension, diabetes mellitus, chronic lung disease, and chronic kidney disease have been reported as risk factors for critical disease and unfavorable outcomes.[2]

Kidney transplant (KT) recipients are included in high-risk groups for severe COVID-19. Use of immunosuppressant drugs, concurrent comorbidities, and existing graft dysfunction increase the susceptibility of KT recipients to COVID-19 infection, and the outcomes for these patients are less favorable versus the general population.[3] The lack of specific antiviral treatment has led to a mandated evaluation of the efficacy of various drugs for treatment of patients with COVID-19. However, regional differences due to economic issues and logistic disparities have prevented the globalization of a uniform COVID-19 treatment with a specific set of agents. To date, several drugs including hydroxychloroquine, remdesivir, favipiravir, and lopinavir-ritonavir have been used in the treatment of COVID-19 infection.[4] Although remdesivir was approved by the US Food and Drug Administration for use in the treatment of COVID-19 infection, on the basis of available clinical trials, there remains no specific antiviral treatment with proven effectiveness against COVID-19.[5] Furthermore, the possible adverse interactions of these antiviral

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therapies with a transplant patient's typical immunosuppressive regimen, as well as the difficult management of adverse side effects and adverse events associated with antiviral therapy, have been major concerns in the transplant community.

Favipiravir, a guanosine purine nucleoside analogue, inhibits RNA-dependent RNA polymerase-mediated viral replication and has been used to treat patients with Ebola, Lassa fever, or rabies. Also, favipiravir has been shown to exhibit potent antiviral activity at high doses in a SARS-CoV-2 hamster model.[6] However, data for the efficacy and safety of favipiravir in the treatment of COVID-19 in humans are scarce. The established treatment guidelines from the Turkish Ministry of Health are based on the recommendations of the Coronavirus Scientific Advisory Board, who have, since the early periods of pandemic, recommended high-dose favipiravir as a first-line treatment agent.[7]

In this study, we report our experience with favipiravir treatment in KT recipients diagnosed with COVID-19 infection, with a special emphasis on adverse events.

Materials and Methods

Design and study participants

In this retrospective study, our aim was to compare the severity of COVID-19 infection and outcome and occurrence of adverse events in KT recipients who received favipiravir treatment versus those who did not. All KT recipients (for living related donors, from first-degree to fourth-degree relatives or spouses) older than 18 years old with functioning grafts who tested positive for SARS-CoV-2 by nucleic acid polymerase chain reaction with nasopharyngeal swabs between March 2020 and January 2021 were included in the study. Criteria for admission and treatment protocols were planned for all patients according to the guidelines for COVID-19 Treatment in Adult Patients, published by the Turkish Ministry of Health.[7]

Therapeutic approach

Immunosuppression was adjusted depending on the clinical presentation. Antimetabolite drug doses (mycophenolate mofetil or mycophenolic acid) were reduced or stopped in patients with symptomatic COVID-19 disease. Tacrolimus dose was adjusted to maintain a trough level of 4 to 6 ng/mL in hospitalized patients. Steroids were either continued at the maintenance dose or converted to intravenous dexamethasone depending on the disease severity.

Favipiravir treatment was initiated with 2 loading doses of 1600 mg each on day 1, followed by 600 mg twice daily for 5 days.[8] Tocilizumab, remdesivir, and convalescent plasma were also used in patients with progressive disease despite favipiravir treatment. Low-molecular-weight heparin was administrated in hospitalized patients.

Data collection

Treatment details were recorded and included in the analysis. Demographic characteristics, comorbidities, clinical signs and symptoms, and radiologic and laboratory findings were obtained from the hospital electronic archive system, patient files, and Turkey's National Health Information System. Laboratory values of the patients at the time of admission, on day 7, and on day 30 were recorded when available. Adverse events related to favipiravir were also recorded. Liver toxicity was classified as mild (<2-fold elevation in liver enzymes), moderate (2-fold to 5-fold elevation), and severe (>5-fold elevation) according to measurements of alanine transaminase. During favipiravir treatment, acute gout attacks or uric acid increases of >1 mg/dL were considered drug-related adverse events.

Ethical statement

This study was approved by the local ethics committee (protocol code 09.2021.134) and was conducted in accordance with the Declaration of Helsinki.

Statistical analyses

Descriptive statistics are reported as mean, median, IQR, and frequency, as appropriate for the various data. Statistical significance was assessed by independent sample *t* test for continuous variables and by chi-square test or the Fisher exact test for categorical variables. $P < .05$ was regarded as statistically significant. All analyses were performed with SPSS software (version 22).

Results

This was a retrospective observational study of 37 consecutive KT recipients diagnosed with COVID-19

infection. The median age of patients was 46 years (IQR, 41-61 years), and 23 of the 37 patients (62.2%) were women. Eight patients (22%) were recipients of a deceased donor transplant, and 29 (78%) were recipients of a living related transplant. The median duration of posttransplant survival was 8.0 years (IQR, 5.5-12.5 years). Most of the patients (n = 30) were on a triple-drug regimen of calcineurin inhibitors (CNI), antimetabolites, and corticosteroids. Twenty-four patients (64.9%) were hospitalized, and 3 patients (8.1%) were transferred to the intensive care unit (ICU) to receive mechanical ventilation during their stay in the hospital. The median duration of hospitalization was 6 days (IQR, 1-9 days). Twenty-seven patients (73.0%) had typical findings of lung involvement for COVID-19 infection, as shown by computed tomography (CT). At admission, the median creatinine level of the patients was 1.2 mg/dL (IQR, 1.0-1.6 mg/dL), median lymphocyte count was 0.9×10^3 cells/μL (IQR, 0.6-1.4 $\times 10^3$ cells/μL), and median ferritin level was 335 μg/L (IQR, 194-1300 μg/L).

Twenty-six patients (70.3%) were treated with favipiravir while 11 (29.7%) were not. Among the patients who were not treated with favipiravir, the major reasons for the decision were personal preference (n = 9) and low glomerular filtration rate (GFR) (n = 2). Clinical and laboratory characteristics were compared for patients treated with favipiravir versus patients who did not receive favipiravir and are summarized in Table 1. Patients in the favipiravir group were older than the untreated group (56 years [IQR, 42-64 years] vs 41 years [IQR, 31-44 years], respectively; P = .008), and oxygen therapy was required for more favipiravir-treated patients versus the untreated patients (15 patients [57.7%] vs 2 [18.2%] patients, respectively; P = .036). The immunosuppressive drug regimens were similar in both groups. There were no significant differences between the groups with respect to sex, duration of posttransplant survival, comorbidity, hospitalization requirement, duration of hospital stay, ICU admission, or death. Seven patients in the favipiravir-treated group and 3 patients in untreated group had acute kidney injury (AKI) at hospital admission (P = 1.000). Antimetabolites were stopped or reduced in 88.4% of patients in the favipiravir-treated group and 90.9% of patients in the untreated group (P = .281). The laboratory data of the groups at admission, day 7, and day 30 are given in Table 2.

Table 1. Demographic and Clinical Characteristics of the Kidney Transplant Recipients With or Without Favipiravir Treatment

Variable	All Patients (n = 37)	Favipiravir (n = 26)	No Favipiravir (n = 11)	*P*
Age, median (IQR), y	46 (41-61)	56 (42-64)	41 (31-44)	.008
Sex, No. (%)				.663
Male	14 (37.8%)	11 (42.3%)	3 (27.3%)	
Female	23 (62.2%)	15 (57.7%)	8 (72.7%)	
BMI, median (IQR), y	27.3 (25.0-30.4)	27.3 (24.2-31.5)	27.3 (25.0-29.7)	.820
Posttransplant survival, median (IQR), y	8.0 (5.5-12.5)	8.5 (6.0-12.0)	7.0 (4.0-15.0)	.756
Hospitalization, No. (%)	24 (64.9%)	19 (73.1%)	5 (45.5%)	.143
Duration of hospitalization, median (IQR), d	6 (1-9)	6 (0-11)	0 (0-8)	.124
Transfer to ICU, No. (%)	3 (8.1%)	3 (11.5%)	0 (0.0%)	.540
Death, No. (%)	3 (8.1%)	3 (11.5%)	0 (0.0%)	.540
AKI at presentation, No. (%)	10 (27%)	7 (26.9%)	3 (27.3%)	1.000
AKI at day 7, No. (%)	3 (8.1%)	2 (7.7%)	1 (9.1%)	1.000
Donor type, No. (%)				1.000
Living	29 (78.4%)	20 (76.9%)	9 (81.8%)	
Deceased	8 (21.6%)	6 (23.1%)	2 (18.2%)	
Comorbidity, No. (%)				
Hypertension	27 (73%)	18 (69.2%)	9 (81.8%)	.688
Diabetes	11 (29.7%)	7 (26.9%)	4 (36.4%)	.699
Coronary heart disease	5 (13.5%)	4 (15.4%)	1 (9.1%)	1.000
Obesity	9 (24.3%)	7 (26.9%)	2 (18.2%)	.500
Immunosuppressive therapy, No. (%)				
CNI	34 (91.9 %)	24 (92.3%)	10 (90.9%)	1.000
Antiproliferative agents	33 (81.8%)	23 (88.5%)	10 (90.9%)	1.000
mTOR inhibitors	3 (8.1%)	2 (7.7%)	1 (9.1%)	1.000
Corticosteroids	36 (97.3%)	26 (100.0%)	10 (90.9%)	.297
ACEI/ARB, No. (%)	15 (40.5%)	11 (42.3%)	4 (36.4%)	1.000
Specific signs in thorax CT, No. (%)	27 (73%)	21 (80.7%)	6 (54.5%)	.096
Increase dose in corticosteroid, No. (%)	23 (62.2%)	19 (73.1%)	4 (36.4%)	.027
Antiproliferative treatment, No. (%)				.281
Cessation	28 (75.7%)	21 (80.7%)	7 (63.6%)	
Reduction	5 (13.5%)	2 (7.7%)	3 (27.3%)	
Other COVID-19 therapies, No. (%)				
Lopinavir-ritonavir	1 (2.7%)	0 (0%)	1 (9.1%)	.297
Remdesivir	1 (2.7%)	1 (3.8%)	0 (0.0%)	1.000
Hydroxychloroquine	7 (18.9%)	2 (7.7%)	5 (45.5%)	.016
Tocilizumab	2 (5.4%)	2 (7.7%)	0 (0.0%)	1.000
Convalescent plasma	2 (5.4%)	2 (7.7%)	0 (0.0%)	1.000
LMWH, No. (%)	23 (62.2%)	18 (69.2%)	5 (45.5%)	.268
Antibiotics, No. (%)	17 (45.9%)	13 (50.0%)	4 (36.4%)	.495
Oxygen, No. (%)	17 (45.9%)	15 (57.7%)	2 (18.2%)	.036
Mechanical ventilation, No. (%)	3 (8.1%)	3 (11.5%)	0 (0.0%)	.540
Vasopressors, No. (%)	3 (8.1%)	3 (11.5%)	0 (0.0%)	.540
RRT, No. (%)	1 (2.7%)	1 (3.8%)	0 (0.0%)	1.000
Elevated liver enzymes, No. (%)				.179
Mild	13 (35.1%)	9 (34.6%)	4 (36.4%)	
Moderate	8 (21.6%)	8 (30.8%)	0 (0.0%)	
Increase in uric acid >1 mg/dL, No. (%)	4 (10.8%)	3 (11.5%)	1 (9.1%)	.174

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; AKI, acute kidney injury; ARB, angiotensin receptor blockers; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CNI, calcineurin inhibitors; CT, computed tomography; ICU, intensive care unit; LMWH, low-molecular-weight heparin; mTOR, mechanistic target of rapamycin; RRT, renal replacement therapy

$P < .05$ is statistically significant.

Table 2. Laboratory Data at Admission, Day 7, and Day 30, for Kidney Transplant Recipients With or Without Favipiravir Treatment

Characteristic	Favipiravir (n = 26)				No Favipiravir (n = 11)			
	Admission	Day 7	Day 30	*P*	Admission	Day 7	Day 30	*P*
Leukocytes, $\times 10^3$ cells/μL	6.3 (4.9-7.3)	8.3 (6.1-11.2)	6.9 (5.8-9.5)	.067	5.2 (4.3-9.7)	4.4 (4.3-11.0)	9.9 (6.3-11.1)	.421
Lymphocytes, $\times 10^3$ cells/μL	0.9 (0.6-1.3)	0.8 (0.4-1.6)	1.5 (1.0-2.2)	.004[a,b]	1.0 (0.5-1.4)	1.4 (0.6-4.4)	2.6 (1.6-3.5)	.214
Hemoglobin, g/dL	13.0 (11.7-13.6)	12.0 (11.2-12.1)	12.0 (11.6-12.8)	.063	11.9 (9.5-12.5)	11.8 (8.7-13.0)	12.7 (10.0-13.1)	.233
Platelets, $\times 10^3$ cells/μL	176 (142-219)	235 (168-321)	218 (172-283)	.038[c]	181 (143-279)	273 (142-312)	259 (234-308)	.433
Creatinine, mg/dL	1.0 (0.8-1.3)	1.2 (1.0-1.5)	1.1 (0.8-1.3)	.066	1.9 (0.9-4.6)	1.7 (1.3-3.8)	1.2 (1.0-3.1)	.358
AST, U/L	25 (21-36)	25 (21-38)	18 (14-31)	.194	18 (14-30)	17 (15-26)	16 (13-33)	.914
ALT, U/L	19 (14-34)	32 (15-50)	26 (15-55)	.248	15 (11-38)	14 (13-26)	14 (10-52)	.684
Uric acid, mg/dL	6.3 (5.5-7.2)	6.2 (4.4-8.0)	5.7 (5.0-6.8)	.393	5.4 (4.5-8.0)	7.0 (5.5-10.6)	6.9 (5.5-7.8)	.498
LDH, U/L	274 (215-258)	269 (240-521)	276 (217-374)	.478	206 (167-303)	201 (158-227)	230 (174-260)	.687
CRP, mg/L	48.5 (19.5-69.0)	31.5 (14.0-80.5)	9.0 (4.8-45.3)	.395	34.0 (15.8-86.3)	19.0 (5.8-25.0)	3.3 (2.7-16.7)	.217
D-dimer, μg/L	0.4 (0.3-0.8)	0.7 (0.5-1.5)	NA	.059	1.4 (0.5-2.2)	1.1 (0.6-1.6)	NA	.519
Ferritin, μg/L	309 (192-1338)	441 (223-1800)	259 (26-625)	.940	597 (257-2062)	773 (408-1368)	143 (27-419)	.164
Tacrolimus level, ng/mL	7.5 (4.2-9.2)	6.8 (4.2-8.3)	4.8 (3.9-6.3)	.015[a]	6.8 (2.3-9.1)	8.2 (3.7-10.5)	5.6 (4.2-8.1)	.941

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein. LDH, lactate dehydrogenase; NA, not applicable

All data are shown as median values (with IQR). $P < .05$ is statistically significant. [a]Association between admission and day 30. [b]Association between day 7 and day 30. [c]Association between admission and day 7.

When the patients treated with favipiravir were compared with untreated patients, there were no differences in adverse events, including increased liver enzymes and uric acid levels. Mildly elevated liver enzymes were noted in 9 patients (34.6%) treated with favipiravir and in 4 patients (36.4%) with no favipiravir treatment. Moderately elevated liver enzymes were noted in 8 patients (30.8%) with favipiravir but in none of the patients with no favipiravir. These differences in liver enzyme levels were not statistically significant ($P = .179$). The median levels of uric acid were 6.3 mg/dL (IQR, 5.5-7.2 mg/dL) at baseline and 6.2 mg/dL (IQR, 4.4-8.0 mg/dL) on day 7 of favipiravir treatment. A uric acid increase of >1 mg/dL was seen in only 4 of the patients. There was no statistically significant difference in terms of the number of the patients with increased uric acid at day 7 between the 2 groups (3 patients [11.5%] in the favipiravir group vs 1 patient [9.1%] in the no favipiravir group; $P = .174$). None of the patients reported an acute gout attack or a uric acid level >10 mg/dL during or at the end of the favipiravir treatment. There was also no significant difference in AKI rates in the follow-up period between the 2 groups (2 patients [7.7%] in the favipiravir group vs 1 untreated patient [9.1%]; $P = 1.000$). None of the patients discontinued favipiravir due to adverse events.

Discussion

In this retrospective observational study, we analyzed our experience with favipiravir use in KT recipients diagnosed with COVID-19. To our knowledge, this is the first study that investigated the safety of favipiravir in KT recipients. In our cohort, a mild to moderate increase in liver enzymes was more frequent in patients treated with favipiravir versus untreated patients, although the difference was not statistically significant, which was probably result of the small number of participants in our study. Moreover, we did not observe any severe adverse events associated with favipiravir.

Reduction of the immunosuppression regimen is crucial for the management of COVID-19 infection in symptomatic KT recipients. Presently, there is no fully effective antiviral drug treatment for COVID-19. Favipiravir has been approved for the treatment of influenza in Japan since 2014.[9] It was also approved for investigative use against COVID-19 in China and Italy in March 2020.[10] Favipiravir was recommended as an antiviral treatment against SARS-CoV-2 in Turkey by the Turkish Ministry of Health in early 2020. Favipiravir has been used widely in Asian countries, whereas only very limited use has been reported in European countries, the US, and Australia.[11] A review of the literature has revealed several published papers on the efficacy of favipiravir in the general population. Cinarka and colleagues have shown that favipiravir is more effective than lopinavir-ritonavir in terms of mortality reduction in hospitalized patients with COVID-19.[12] In another study from Shenzhen, China, patients on favipiravir treatment had a significantly shorter viral clearance time and radiologic improvement was better versus patients on lopinavir-ritonavir treatment.[8] To date, there have been no studies published on favipiravir use in the KT population.

Major risk factors for COVID-19-related mortality include advanced age, multiple comorbidities, and immunosuppressive therapy. In fact, the European Renal Association COVID-19 Database study has documented chronic kidney disease as the major risk factor for increased morbidity and mortality for SARS-Cov-2 infection.[13] Patients at increased risk of a severe COVID-19 infection are best treated with antiviral therapy.[14] Although the risk for severe COVID-19 infection is increased in KT recipients, there are various reasons for physicians' reluctance to use antivirals, including concern for serious adverse events and adverse drug interactions, as well as the lack of efficacy data.[9] In a study by Santeusanio and colleagues, only 7.9% of the KT recipients were treated with remdesivir; in a study by Pereira and colleagues, only 3% of the KT recipients received antiviral treatment.[15,16] In our cohort, 70.3% of the KT recipients with COVID-19 infection received favipiravir treatment. The advantages of favipiravir are that it (1) can be orally administered, (2) does not require hospitalization, and (3) has a lower financial cost. Remdesivir was not available in Turkey during the early period of the pandemic, and its use presently remains restricted to special indications. The lack of access to remdesivir combined with the easy availability of favipiravir resulted in the higher use of the favipiravir in our study population. Mortality rates of COVID-19 infection in KT recipients have ranged between 12.8% and 28% in different series.[17-19] According to a multicenter study from Turkey by Oto and colleagues, 49% of the KT recipients were treated with favipiravir, and there was a total mortality of 12.8% in the whole group.[17] Overall mortality in our cohort was low (8.1%). The 3 patients who died in our study had been admitted to the ICU and had been treated with favipiravir. Overall, there were 5 patients treated with favipiravir who received additional therapy: 1 patient received remdesivir, 2 patients received tocilizumab, and 2 patients received convalescent plasma, in addition to favipiravir. All patients with adjuvant therapies died from progressive disease. The relatively low number of adjuvant therapies suggests that favipiravir therapy may help limit disease progression in some patients.

Drug toxicity due to interactions with a patient's existing medications or favipiravir itself may result in serious problems in KT recipients. In our study, we observed that favipiravir treatment is safe for KT recipients with regard to side effects or other adverse events. None of the patients had a severe increase in liver enzymes. A mild liver enzyme elevation was observed in 34.6% of the patients, and moderate liver enzyme elevation was observed in 30.8% of the patients. All of these patients with mildly or moderately elevated liver enzyme profiles showed improvement in these scores on day 30, except for the patients who died. For patients who are older adults or who are in need of hospitalization, elevated liver enzyme profiles may be a direct effect of COVID-19 rather than an effect of favipiravir.

Elevated levels of uric acid have been reported as another important adverse side effect of favipiravir, but we could not find a difference between our 2 study groups with respect to uric acid levels. None of the patients had a uric acid level >10 mg/dL at day 7. Uric acid increase (>1 mg/dL) developed in only 11.5% of the favipiravir-treated patients, and this rate is comparable with previous reports.[10] Favipiravir has been recommended as a short-term treatment for patients with COVID-19. Therefore, we conclude that the observed effects on blood uric acid levels and its consequences may be subclinical. Nevertheless, clinicians should remain cautious when treating KT recipients who have graft dysfunctions, because patients with a history of gout and/or advanced kidney dysfunctions have not been included in the favipiravir studies.

Although some studies have recommended against favipiravir for patients with GFR <30 mL/min, other studies have recommended in favor of favipiravir for patients with chronic kidney disease with no need for adjustment of renal dose.[20,21] In our cohort, favipiravir treatment was withheld from only 2 patients due to a GFR of <30 mL/min. One of these patients was treated with lopinavir-ritonavir, and her course was complicated with calcineurin toxicity. There is not much information about the direct renal toxicity of favipiravir, although favipiravir treatment has been associated with AKI due to high uric acid levels.[22] Nevertheless, favipiravir treatment for patients with end-stage kidney disease or patients who require renal replacement therapies has also been reported.[23,24] Both remdesivir and lopinavir-ritonavir treatments were restricted at a GFR level of <30 mL/min.[25-27]

Another important advantage of favipiravir is the lack of adverse drug-to-drug interactions. Favipiravir is mainly metabolized in the liver by aldehyde oxidase, which may explain its lack of interaction

with CNI. The combination of lopinavir with ritonavir has also been used to treat SARS-CoV-2, although subsequent studies reported no benefit. Lopinavir is a protease inhibitor, whereas the addition of ritonavir increases the plasma half-life of lopinavir through its inhibition of cytochrome P450 and directly interferes with CNI metabolism, which is metabolized with the same enzyme system. Therefore, the lopinavir-ritonavir combination is not preferred for KT recipients. Strict drug level monitoring is therefore essential during lopinavir-ritonavir treatment in KT recipients. Furthermore, lopinavir-ritonavir is not suitable for patients followed at home and can result in AKI due to CNI toxicity. Remdesivir, on the other hand, has the best reported efficacy for the treatment of SARS-CoV-2; unfortunately, remdesivir not available for general use in Turkey.

The small sample size and retrospective nature are the major limitations of this study. Insufficient data for uric acid levels in some patients is another limitation of the study. This is mainly due to the limited laboratory data in patients who were not hospitalized. Additionally, electrocardiographic monitoring for QT prolongation was not regularly recorded, since not all patients were hospitalized. Although prolongation of QT interval has been reported as an adverse event associated with favipiravir, a recent study has shown no association between QT prolongation and favipiravir in COVID-19 treatment.[28]

Conclusions

With this small retrospective study, we conclude that early initiation of favipiravir treatment of COVID-19 infection may result in better control of disease progression with a safe drug profile. Regarding the widespread use of favipiravir in the Turkish general population, the effectiveness and safety of favipiravir in KT recipients should be evaluated with large, multicenter studies.

References

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323(13):1239-1242. doi:10.1001/jama.2020.2648
3. Phanish M, Ster IC, Ghazanfar A, et al. Systematic review and meta-analysis of COVID-19 and kidney transplant recipients, the South West London Kidney Transplant Network Experience. *Kidney Int Rep*. 2021;6(3):574-585. doi:10.1016/j.ekir.2020.12.013
4. World Health Organization. Solidarity Trial PLUS: An international randomised trial of additional treatments for COVID-19 in hospitalised patients who are all receiving the local standard of care. April 11, 2021. https://www.who.int/publications/m/item/solidarity-trial-plus-protocol
5. WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed antiviral drugs for Covid-19: Interim WHO Solidarity Trial results. *N Engl J Med*. 2021;384(6):497-511. doi:10.1056/NEJMoa2023184
6. Kaptein SJF, Jacobs S, Langendries L, et al. Favipiravir at high doses has potent antiviral activity in SARS-CoV-2-infected hamsters, whereas hydroxychloroquine lacks activity. *Proc Natl Acad Sci U S A*. 2020;117(43):26955-26965. doi:10.1073/pnas.2014441117
7. Ministry of Health. COVID-19 Guide. COVID-19 Information Platform. Republic of Turkey. https://covid19.saglik.gov.tr/TR-66301/covid-19-rehberi.html
8. Cai Q, Yang M, Liu D, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. *Engineering (Beijing)*. 2020;6(10):1192-1198. doi:10.1016/j.eng.2020.03.007
9. Kiso M, Takahashi K, Sakai-Tagawa Y, et al. T-705 (favipiravir) activity against lethal H5N1 influenza A viruses. *Proc Natl Acad Sci U S A*. 2010;107(2):882-887. doi:10.1073/pnas.0909603107
10. Pilkington V, Pepperrell T, Hill A. A review of the safety of favipiravir a potential treatment in the COVID-19 pandemic? *J Virus Erad*. 2020;6(2):45-51.
11. Kaur RJ, Charan J, Dutta S, et al. Favipiravir use in COVID-19: analysis of suspected adverse drug events reported in the WHO database. *Infect Drug Resist*. 2020;13:4427-4438. doi:10.2147/IDR.S287934
12. Cinarka H, Gunluoglu G, Cortuk M, et al. The comparison of favipiravir and lopinavir/ritonavir combination in COVID-19 treatment. *Turk J Med Sci*. 2021;51(4):1624-1630. doi:10.3906/sag-2012-189
13. Council E-E, Group EW. Chronic kidney disease is a key risk factor for severe COVID-19: a call to action by the ERA-EDTA. *Nephrol Dial Transplant*. 2021;36(1):87-94. doi:10.1093/ndt/gfaa314
14. Boretti A. Favipiravir use for SARS CoV-2 infection. *Pharmacol Rep*. 2020;72(6):1542-1552. doi:10.1007/s43440-020-00175-2
15. Santeusanio AD, Menon MC, Liu C, et al. Influence of patient characteristics and immunosuppressant management on mortality in kidney transplant recipients hospitalized with coronavirus disease 2019 (COVID-19). *Clin Transplant*. 2021;35(4):e14221. doi:10.1111/ctr.14221
16. Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: Initial report from the US epicenter. *Am J Transplant*. 2020;20(7):1800-1808. doi:10.1111/ajt.15941
17. Oto OA, Ozturk S, Turgutalp K, et al. Predicting the outcome of COVID-19 infection in kidney transplant recipients. *BMC Nephrol*. 2021;22(1):100. doi:10.1186/s12882-021-02299-w
18. Hilbrands LB, Duivenvoorden R, Vart P, et al. COVID-19-related mortality in kidney transplant and dialysis patients: results of the ERACODA collaboration. *Nephrol Dial Transplant*. 2020;35(11):1973-1983. doi:10.1093/ndt/gfaa261
19. Akalin E, Azzi Y, Bartash R, et al. Covid-19 and kidney transplantation. *N Engl J Med*. 2020;382(25):2475-2477. doi:10.1056/NEJMc2011117
20. Marra F, Smolders EJ, El-Sherif O, et al. Recommendations for dosing of repurposed COVID-19 medications in patients with renal and hepatic impairment. *Drugs R D*. 2021;21(1):9-27. doi:10.1007/s40268-020-00333-0
21. Maggiore U, Abramowicz D, Crespo M, et al. How should I manage immunosuppression in a kidney transplant patient with COVID-19? An ERA-EDTA DESCARTES expert opinion. *Nephrol Dial Transplant*. 2020;35(6):899-904. doi:10.1093/ndt/gfaa130
22. Mishima E, Anzai N, Miyazaki M, Abe T. Uric acid elevation by favipiravir, an antiviral drug. *Tohoku J Exp Med*. 2020;251(2):87-90. doi:10.1620/tjem.251.87

23. Koshi E, Saito S, Okazaki M, et al. Efficacy of favipiravir for an end stage renal disease patient on maintenance hemodialysis infected with novel coronavirus disease 2019. *CEN Case Rep.* 2021;10(1):126-131. doi:10.1007/s13730-020-00534-1
24. Hirai D, Yamashita D, Seta K. Favipiravir for COVID-19 in a patient on hemodialysis. *Am J Kidney Dis.* 2021;77(1):153-154. doi:10.1053/j.ajkd.2020.09.007
25. Adamsick ML, Gandhi RG, Bidell MR, et al. Remdesivir in patients with acute or chronic kidney disease and COVID-19. *J Am Soc Nephrol.* 2020;31(7):1384-1386. doi:10.1681/ASN.2020050589
26. Thakare S, Gandhi C, Modi T, et al. Safety of remdesivir in patients with acute kidney injury or CKD. *Kidney Int Rep.* 2021;6(1):206-210. doi:10.1016/j.ekir.2020.10.005
27. Binois Y, Hachad H, Salem JE, et al. Acute kidney injury associated with lopinavir/ritonavir combined therapy in patients with COVID-19. *Kidney Int Rep.* 2020;5(10):1787-1790. doi:10.1016/j.ekir.2020.07.035
28. Cap M, Bilge O, Isik F, et al. The effect of favipiravir on QTc interval in patients hospitalized with coronavirus disease 2019. *J Electrocardiol.* 2020;63:115-119. doi:10.1016/j.jelectrocard.2020.10.015