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Favipiravir in Kidney Transplant Recipients With COVID-19: A Romanian Case Series

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ABSTRACT

Background. Favipiravir (FPV) is an orally administrable antiviral drug that selectively inhibits its RNA-dependent RNA polymerase and has been repurposed for COVID-19 treatment. There is limited information on the use of FPV in kidney transplant recipients (KTx), who often have multiple comorbidities and run a higher risk for death from COVID-19.

Methods. We retrospectively reviewed all KTx at our institution who got sick with COVID-19 between March 1, 2020, and May 31, 2021, and who received FPV (loading dose of 1800 mg × 2 on day 1, maintenance dose 2 × 800 mg/d for 5-14 days) as part of their COVID treatment. We analyzed demographics, clinical course, laboratory data, management, and outcome.

Results. Nine KTx with COVID-19 received FPV; all were hospitalized. The median age was 52 years (range, 32-60 years), and women were predominant (77.7%). Eight KTx had pulmonary involvement on chest radiograph. On admission 1 patient had mild, 5 had moderate, 2 had severe, and 1 had critical disease. Leukopenia and increased creatinine were universally noted. Three patients had disease progression under treatment. Seven patients (77.7%) required additional oxygen, and 4 (57.1%) needed intensive care unit admission. Three KTx died, resulting in an overall mortality of 33.3%. Survivors did not show increased transaminases or creatinine during or after FPV treatment; leukocytes, neutrophils, and platelets improved on discharge compared with admission values.

Conclusions. FPV appears well tolerated by KTx with COVID-19, but its clinical benefit remains unclear. Larger analyses are needed.

DURING the first year of the COVID-19 pandemic there was a frustrating and protracted lack of effective antiviral treatments, so that supportive therapy and decreasing immunosuppression remained the cornerstones of COVID-19 management in transplant recipients. Repurposed drugs such as hydroxychloroquine, antiretrovirals, and remdesivir have also been used with negative, conflicting, or inconclusive results [1,2].

Favipiravir (FPV) is a synthetic prodrug approved in Japan for the management of the emerging 2014 influenza pandemic, which has also been repurposed and tested in COVID-19. It inhibits the RNA-dependent RNA polymerase leading to termination of viral protein synthesis [3]. The influenza dosing regimen in Japan is a loading dose of 3200 mg on day 1, followed by a maintenance dose of 600 mg twice daily on days 2 to 5. Apart for its known teratogenic effect, FPV appears to have a good safety profile. However, hyperuricemia, diarrhea, reduced neutrophil count, transaminitis, and QTc prolongation have been reported as potential adverse effects [4]. The limited experience with FPV for COVID treatment suggests that this drug induces viral clearance by 7 days and contributes to clinical improvement within 14 days, especially in patients with mild to moderate illness, and that FPV may be an option for moderate

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COVID-19 pneumonia treatment [5−8]. However, the risk of adverse events requires careful consideration.

So far, the literature on the use of FPV in kidney transplant recipients (KTx) with COVID-19 is limited to 1 retrospective series and several case reports, totaling less than 70 patients [9−12]. There is no documented benefits of FVP in this group of patients because of the limited number of studies, most of them being case reports. In addition, the results are difficult to interpret because of simultaneous administration of other medications. Thus, the efficiency and safety of FPV in transplant recipients remain unclear. We herein report our experience with 9 KTx infected with SARS-CoV-2 treated with FPV.

MATERIALS AND METHODS

We retrospectively reviewed all KTx who underwent transplant at the Clinical Institute of Urology and Renal Transplantation in Cluj-Napoca, Romania, who got sick with COVID-19 between March 1, 2020 and May 31, 2021. COVID-19 was defined as a positive result for SARS-CoV-2 RNA on real-time polymerase chain reaction assay of a nasopharyngeal swab and typical COVID-19 symptoms. We identified all the patients who were treated with FPV at any stage of their treatment and retrieved demographic and clinical data including age, sex, comorbidities, duration of symptoms, clinical course, and laboratory data.

FPV (FluGuard, Alliance Health care, Romania) treatment was started on admission. All patients received FPV with a loading dose of 2 × 1800 mg and a maintenance dose of 2 × 800 mg for 5 to 7 days. An experienced transplant nephrologist adjusted the immunosuppression regimen according to the ERA−EDTA Developing Education Science and Care for Renal Transplantation in European States expert opinion [13]. Dexamethasone, tocilizumab, antipyretics, cough suppressants, and antibiotics were given at the discretion of the medical teams attending the patients. All patients received anticoagulant therapy with low-molecular-weight heparin during the hospital stay.

Acute kidney injury was defined as an increase in serum creatinine by ≥ 0.3 mg/dL within 48 hours or an increase to 1.5 times or more from baseline based on the definition of Kidney Disease: Improving Global Outcomes. Disease severity was classified from mild to critical according to the National Institutes of Health guidelines [14]. The comorbidity assessment was performed using the age-adjusted Charlson Comorbidity Index [15]. Baseline kidney graft function (estimated glomerular filtration rate) was assessed on data collected at the last check-up before COVID-19 using the Chronic Kidney Disease Epidemiology Collaboration formula. The study was reviewed and approved by the Institutional Review Board of the Clinical Institute of Urology and Renal Transplantation (1/2021).

Statistical Analysis

Discrete data were described by their frequency expressed as a percentage. Continuous data were expressed as median and range unless otherwise stated. Given the small group size and data distribution, Wilcoxon signed-rank test was used for data analysis. A P value $< .05$ was considered significant.

RESULTS

Patients

Nine KTx diagnosed as having COVID-19 during the study period received FPV, all during the second wave of the pandemic (autumn/winter 2020). The patients in this series had a median age of 52 years (range, 32-60 years) and were predominantly women (77.7%). All but 1 were deceased donor kidney recipients and had a median time since transplant of 57 months (range, 4-319 months). Eight patients were being administered tacrolimus therapy, mycophenolate mofetil, and prednisolone at the time of COVID-19 diagnosis, whereas 1 was on monotherapy with azathioprine. Basiliximab was used for tolerance induction in 8 cases. The characteristics of all 9 patients are detailed in Table 1.

All KTx but 1 had bilateral opacities typical for COVID-19 noted on initial chest radiography. The pulmonary involvement ranged from 10% to > 75% of the lung parenchyma.

Laboratory data at the time of diagnosis frequently revealed leukopenia with median white blood cell count of 4.16 × 10^3/mL (range, 2.1-10.62 × 10^3/mL), median neutrophil count of 2.74 × 10^3/mL (range, 1.06-9.45 × 10^3/mL), and median lymphocyte count of 915/mL (range, 400-1690/mL). At admission, liver function tests were largely within normal range, with median alanine aminotransferase of 26 IU/L (range, 14-34 IU/L) and median aspartate aminotransferase of 39 IU/L (range, 13-52 IU/L), whereas median creatinine was 1.36 mg/dL (range, 1.23-2.92 mg/dL). We recorded a wide variation in admission values for ferritin (median, 893 ng/mL; range, 40.5-3920 ng/mL), D-dimers (median, 4.24 mg/L FEU; range, 0.26-1437 mg/L FEU), and lactate dehydrogenase (median, 205 U/L; range, 136-673 U/L).

Management and Outcome

All patients were hospitalized. Immunosuppression regimen was modified in all but 1 patient: antimetabolites (mycophenolate

Table 1. Demographic and Clinical Data of the Patients Included in the Study

Patient No.	Age	Sex	Time After Transplant, mo	BMI	CCI	Baseline eGFR	Symptoms	Length of Symptoms Before Admission, d	Disease Severity at Admission
1	52	F	33	32.8	4	51	Fever, cough, malaise	11	Moderate
2	42	M	21	20.3	2	73	Fever, diarrhea, cough, anosmia	2	Moderate
3	56	F	23	22.1	3	21.8	Fever, SOB, diarrhea, malaise	9	Moderate, progression to severe
4	60	F	61	28.5	4	42	Fever, cough, SOB, anosmia, diarrhea	10	Severe
5	58	M	62	24.5	3	64.2	Fever, cough, malaise	3	Moderate
6	40	F	4	31.7	3	18.8	Fever, cough, SOB, diarrhea, malaise	2	critical
7	39	F	306	28.1	2	44	Cough, pharyngitis	2	Mild
8	52	F	57	28.6	3	68.5	Fever, cough, SOB, malaise,	3	Severe, progression to critical
9	32	F	58	27.3	3	73	Cough, SOB, malaise	9	Moderate, progression to severe

BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CCI, Charlson Comorbidity Index; eGFR, estimated glomerular filtration rate; F, female; M, male; SOB, shortness of breath.

mofetil, mycophenolic acid) were stopped in all but 1 patient (#7), and tacrolimus was reduced in all KTx receiving the drug. In 4 patients with severe or critical disease, all receiving high-dose dexamethasone, immunosuppression was completely withdrawn.

Acute kidney injury developed in 2 patients, both developing critical disease and ultimately requiring renal replacement therapy. Seven of 9 patients (77.7%) required additional oxygen and 4 (57.1%) were admitted to the intensive care unit. Three of these patients ultimately died, resulting in an overall mortality of 33%. All the other patients are alive, with a follow-up of at least 6 months. A detailed account on the clinical course of each patient is presented in Table 2.

On discharge, survivors did not show increased transaminases, and creatinine level was lower that at admission in all patients (median, 1.18 mg/dL [range, 0.84-1.3 mg/dL]; $P = .06$). In addition, leukocytes, neutrophils, and platelets have all improved in absolute numbers ($P = .06$).

DISCUSSION

Organ transplant recipients are considered a risk group for unfavorable outcome regarding COVID-19, with reported mortality frequently exceeding 20% [1,16,17]. This disproportionately high mortality is most likely because of the lifelong immunosuppression affecting both the cellular and humoral immunity as well as the frequent comorbidities such as diabetes, overweight, cardiovascular diseases, and poor renal function.

Although administered on hospitalization, FPV was given relatively late in the course of the disease, most patients reporting COVID symptoms for longer than 1 week before seeking medical assistance. Joshi et al, in a preliminary report on 2158 COVID-19 cases from a Japanese observational registry where FPV was started within 3 days from diagnosis, reported the rates of clinical improvement at 7 days from the start of FPV therapy as 73.8%, 66.6%, and 40.1% for mild, moderate, and severe disease, respectively, whereas at 14 days it was 87.8%, 84.5%, and 60.3%, respectively [18]. Likewise, Doi et al found that viral clearance within 6 days occurred in 66.7%, whereas median time until SARS-CoV-2 clearance was 12.8 days [19]. Although incomplete, the current results mirror well these findings and suggest FPV treatment does not always result in rapid virus clearance.

Two of the 3 nonsurvivors already had a poor graft function before their SARS-CoV-2 infection. This has rapidly resulted in acute kidney failure requiring renal replacement therapy. It is unlikely that FPV has contributed to this worsening because an improvement in renal function tests was universally seen in all survivors receiving a similar regimen.

The most frequent adverse effects of FPV include gastrointestinal and psychiatric symptoms, decrease of the neutrophil count, and increase of liver enzymes (aspartate aminotransferase and alanine transaminase), uric acid, or blood triglycerides [4,5]. FPV seems to have been well tolerated with no biochemical abnormalities attributable during or at the completion of the treatment.

Table 2. Management and Outcome

Patient No.	Immunosuppression Change	Immunomodulation	Anticoagulation	Antibiotic Therapy	Other Treatments	Antihypertensive Drugs	PCR on Discharge/ Death	Acute Kidney Injury	Oxygen Therapy	Hospitalization, d	ICU Admission	Outcome
1	MMF Ø, tacrolimus ↓	Dexa	ENOX	CTR	APAP, ALP, PPI, Statins	CCBs, BBs	Negative	No	No	14	No	Discharged
2	MMF Ø, tacrolimus ↓	PRED 5 mg	ENOX	CTR	Calciferol, probiotics, hepatoprotectors	-	Negative	No	No	14	No	Discharged
3	MMF Ø, tacrolimus Ø	Dexa, TCZ	ENOX	MEM, VAN	Calciferol, L-ascorbic acid, Zn	CCBs	Negative	RRT	Yes	28	Yes	Dead
4	MMF Ø, tacrolimus Ø	Dexa, TCZ	ENOX	MEM	PPI, calciferol, L-ascorbic acid, statins, probiotics, ALP	CCBs, BBs, ARBs	Negative	No	Yes	18	Yes	Discharged
5	MMF Ø, tacrolimus ↓	PRED 5 mg	ENOX, ASP	CIP	Calciferol, L-ascorbic acid, Zn, NAC	CCBs, BBs	Negative	No	Yes	14	No	Discharged
6	MMF Ø, tacrolimus Ø	Dexa, TCZ	ENOX, ASP	MEM, LIN	FCZ, calciferol, L-ascorbic acid, PPI, APAP, Ins, diuretics,							
NE, Aa	-	NA	RRT	Yes	7	yes	Dead					
7	None	Dexa	ENOX	MEM	Calciferol, L-ascorbic acid, NAC, bronchodilators, Aa, Ins	CCBs	NA	No	No	6	No	Discharged
8	MMF Ø, tacrolimus Ø	MPS	ENOX	CTR	APAP, PPI	-	NA	No	Yes	8	Yes	Dead
9	MMF Ø, tacrolimus ↓	Dexa	ENOX	-	APAP, L-ascorbic acid, statins, PPI	CCBs, BBs	NA	No	Yes	14	No	Discharged

Aa, amino acids; ALP, allopurinol; APAP, acetaminophen; ARB, angiotensin II receptor blocker; ASP, aspirin; BBs, beta blockers; CCB, calcium channel blocker; CIP, ciprofloxacin; CTR, ceftriaxone; Dexa, dexamethasone; ENOX, enoxaparin; FCZ, fluconazole; ICU, intensive care unit; Ins, insulin; LIN, linezolid; MEM, meropenem; MMF, mycophenolate mofetil; MPS, methylprednisolone; NA, not available; NAC, N-acetyl cysteine; NE, norepinephrine; PCR, polymerase chain reaction; PPI, proton pump inhibitor; PRED, prednisone; RRT, renal replacement therapy; TCZ, tocilizumab; VAN, vancomycin; Zn, zinc; Ø, discontinued.

This case series lacks a control group. making it difficult to establish the efficiency of FPV compared with other treatments. Finding a proper control group matching the age, sex comorbidities, and, above all, disease severity would have been difficult or impossible. For these reasons, we did not perform direct comparisons with patients receiving other treatments such as remdesivir and standard supportive therapy. Previous analyses in similar, larger patient groups showed an in-hospital mortality during the second COVID wave at around 27% [20,21]. Because the overall mortality in this series was 33.3%, it does not appear that FPV obviously impacted mortality, although this statement is purely speculative in the absence of adequate comparisons with a well-matched control group. The mortality in a group of Turkish KTx with COVID pneumonia similarly treated with FPV was almost identical (35.7%) [9].

The dramatic clinical course of a recipient who has recently undergone transplant, with a duration between symptom start to death of only 9 days, further underscores the negative impact of immunosuppression. It is customary that more intense immunosuppression is applied in the first months after transplant, which together with the persistent effect of the induction therapy on the cellular immunity may explain the rapid progression toward death. Two large Spanish analyses confirmed a significantly higher risk for death in recipients who have recently undergone transplant (within 12 months from transplant) [1,20].

The present study has several other limitations besides the absence of a control group. This was a retrospective observational study reporting on a small number of patients, and selection bias might have occurred. Although two-thirds of patients presented with mild and moderate disease, which is the typical disease severity when FPV is currently used, some patients were sicker or progressed toward more severe forms. The use of FPV in severe and critical cases was probably motivated by the limited availability of remdesivir during the second wave, although it is unlikely that other treatments including remdesivir would have significantly improved the mortality.

Secondly, time to viral clearance and viral load was not assessed uniformly during the hospitalization but only on discharge or around the time of patient death. Whereas this could have been interesting from epidemiologic and academic standpoint, it is known that SARS-CoV-2 can be detected in the respiratory samples of over half of the patients with severe disease up to the fourth week after symptom onset, and even longer time from other sampling locals [22,23].

CONCLUSIONS

This small case series does not allow firm conclusions about the efficiency of FPV on disease progression or mortality but suggests that a brief treatment is well tolerated by KTx. Further studies and larger meta-analyses are mandated to explore a potential clinical benefit of FPV in this vulnerable patient group.

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