Paritaprevir, ritonavir, ombitasvir, and dasabuvir treatment in renal transplant patients with hepatitis C virus infection

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ABSTRACT

Background/Aims: The Social Security System of our country reimburses only paritaprevir, ritonavir, ombitasvir, and dasabuvir (PrOD) regime in treatment-naive patients with hepatitis C regardless of kidney disease. Most of our renal transplant (RT) recipients were treated with PrOD. The aim of the present study was to investigate the efficacy and safety of PrOD in RT patients with hepatitis C virus (HCV) infection in a single center real-life experience.

Materials and Methods: RT recipients with a post-transplant follow-up of at least 1 year were included in the study. The patients were treated and monitored according to the guidelines. Blood levels of immunosuppressive patients were closely followed up and adjusted.

Results: A total of 21 (12 male and nine female) patients were assessed. The age of the patients was 50.8±8.5 years. Ten patients were infected with G1a, 10 patients with G1b, and one patient with G4 HCV. Two patients had compensated cirrhosis. Eighteen patients were treatment-naive, and three were peginterferon+ribavirin-experienced. Sustained virologic response (SVR12) was achieved in all patients. None of the patients discontinued the treatment. Cyclosporine (Csa) and tacrolimus (Tac) doses were reduced to once a day to once a week to maintain the blood level within normal range. The most common adverse effect was anemia in patients receiving ribavirin. Renal functions did not change during the treatment period.

Conclusion: In this real-life experience, all of the 21 PrOD-treated RT recipients reached SVR12. Tac or Csa serum levels were maintained within the normal range with close monitoring. PrOD regime can be successfully and safely used in RT recipients with HCV infection with close follow-up.

Keywords: Paritaprevir, ritonavir, ombitasvir, dasabuvir, renal transplant, hepatitis C

INTRODUCTION

The prevalence of hepatitis C virus (HCV) infection in renal transplant (RT) patients ranges from 10% to 65% depending on the clinic, the dialysis modality used prior to RT, the time since dialysis, and the number of blood transfusions (1). HCV infection in RT patients can cause a decline in both the longevity of the graft and the patient and can cause an increased risk of mortality due to infections, cardiovascular diseases, and liver diseases (2,3). Moreover, HCV infection in RT patients is associated with proteinuria, chronic rejection, transplant glomerulopathy, post-transplant diabetes, and HCV-associated glomerulonephritis (4). Immunosuppression after RT facilitates viral replication and may lead to the progression of liver disease, reactivation of the HCV infection, and acute hepatitis (5). Interferon-based therapy is not recommended for RT recipients due to the risk of allograft dysfunction and the low success rates of viral eradication (5). The development of direct-acting antiviral agents (DAAs) successfully revolutionized the treatment of chronic hepatitis C. Generally, new generation DAAs have achieved a sustained virologic response (SVR) rate of >90%.

RT recipients are often difficult to treat due to their impaired renal function and because of the adverse drug-drug interactions between DAAs and immunosuppressive drugs. However, sofosbuvir-based therapies have been successfully used in liver-transplant recipients (6). Paritaprevir, ritonavir, ombitasvir, and dasabuvir (PrOD) therapy is not frequently used due to its interaction with calcineurin inhibitors.

However, since the Social Security System of our country reimburses the PrOD regime in treatment-naive patients regardless of whether they underwent kidney transplant or not (7), most of the RT patients in our current study were treated with the PrOD regime.

The aim of the present study was to investigate the efficacy and safety of PrOD using data from a single center.

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To our knowledge, this is the first study to collect PrOD data in RT recipients from our country, and this is the largest cohort in which the PrOD regime was used.

MATERIALS AND METHODS

This retrospective, non-interventional, single center study was performed in patients during routine clinical practice. Adult RT patients who were undergoing PrOD treatment between July 2016 and September 2017 were enrolled in the present study. The study was approved by the clinical trials ethics committee of Ege University School of Medicine, a tertiary level health care center (approval no.: 70198063-050.06.04, dated: April 9, 2018). Patients with or without compensated liver diseases who were infected with genotype 1 and genotype 4 HCV at least 1 year after the transplant were included in the study. Both treatment-naive patients and those previously treated with pegylated interferon+ribavirin (RBV) were also included. Patients who had decompensated cirrhosis, were co-infected with hepatitis B virus or human immunodeficiency virus, or were undergoing hemodialysis were excluded from the study. Patients with genotype 1a HCV were treated with PrOD+ribavirin according to the guidelines. Patients with genotype 1a HCV but without cirrhosis were treated for 12 weeks, whereas those with cirrhosis were treated for 24 weeks. All of the patients infected with genotype 1b HCV were treated with PrOD. Patients infected with genotype 4 were treated with paritaprevir, ritonavir, ombitasvir, and ribavirin for 12 weeks. Before treatment, demographic characteristics, liver function test results, urea levels, creatinine levels, HCV RNA levels, and blood levels of tacrolimus (Tac), everolimus, or cyclosporine (Csa) were recorded for each enrolled patient. Liver function tests, renal functions, and HCV RNA levels were determined at 4 weeks, 12 weeks, and if applicable, 24 weeks after the initiation of treatment and 4 weeks and 12 weeks after the end of treatment. Blood levels of Tac, everolimus, and Csa were obtained once every week for the first 4 weeks and every 2 weeks thereafter; drug doses were adjusted according to these levels. Impaired renal function was defined as a >25% increment in serum creatinine levels and a >25% decline in estimated glomerular filtration rate (eGFR) levels compared with baseline. Virologic failure was defined as virologic breakthrough or detectable HCV RNA at the end of treatment or during follow-up.

HCV RNA levels were determined via real-time polymerase chain reaction (Abbott Molecular, Des Moines, IA, USA; lower detection limit 12 IU/mL).

Statistical analysis

As this was a retrospective study, no sample size calculation was performed. Results were determined via an intent-to-treat analysis with descriptive statistics. Continuous variables were expressed as mean and standard deviation or as minimum-maximum, as appropriate, and descriptive variables were expressed as frequency and percentage (%). Categorical variables were analyzed via chi-square test or Fisher's exact test. For quantitative variables, group differences were analyzed using Student's t-test. A p value <0.05 was considered as significant.

RESULTS

In our center, there were 39 patients infected with HCV who underwent RT >1 year ago. Of the 39 patients, 4 patients who were undergoing hemodialysis, nine patients who were on sofosbuvir-based treatment, one patient with unstable renal functions, and one patient who refused treatment were excluded from the study. Patients who were treated with sofosbuvir-based regime were not switched from PrOD, four patients provided the drugs from other countries, and five patients received the drugs with the permission of the Ministry of Health. Of the remaining 24 patients, 3 patients did not yet begin treatment at the time of publication (Figure 1). The remaining 21 patients received PrOD treatment and completed the treatment period. All of the patients completed the study for 12 weeks following treatment. One patient with liver cirrhosis who was infected with G1a HCV received therapy for >24 weeks, whereas all of the other participants received therapy for 12 weeks.

The characteristics of the 21 patients receiving PrOD treatment are presented in Table 1. Briefly, of the 21 patients, 12 were male. The mean age of the patients was 50.8±8.5

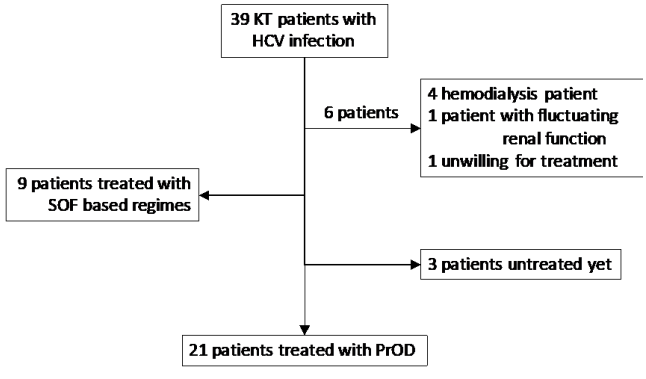

Figure 1. Patient disposition and trial profile.

Table 1. Baseline characteristics of patients who received PrOD.

Features	
Sex (M/F)	12/9
Age (mean±SD, years)	50.8±8.5
Donor characteristics (living/cadaveric)	12/9
Transplantation age (median; range, years)	3.5 (1-23)
HCV-positive donor number	1
Pre-/post-transplantation DM number	2/1
Hypertension	15 (71%)
Post-transplant malignancy	2 basal cell carcinomas
Crohn's disease	1
Years elapsed since the diagnosis of hepatitis C (median; range)	8.8 (1.1-27.0)
HCV genotype (1a/1b/4)	10/10/1
Log HCV RNA	6.10±0.72
Treatment-naive/experienced	18/3
Cirrhosis	2

PrOD: paritaprevir, ritonavir, ombitasvir, and dasabuvir; HCV: hepatitis C virus.

(median: 39, range: 19-57) years. The median duration of hepatitis C after diagnosis was 8.8 years, and treatment was initiated on average 3.5 years after the RT. Ten patients were infected with G1a HCV, 10 patients were infected with G1b HCV, and one patient was infected with G4 HCV. Only two of the 21 included patients had compensated cirrhosis. Eighteen patients were treatment-naive, and three patients had received peginterferon treatment prior to the transplantation, which failed in all three cases.

Virological response

The mean HCV RNA level was 6.10±0.72 log IU/mL at the initiation of treatment (Table 2). After 4 weeks of treatment, HCV RNA was reported to be negative in 6 (28.5%) patients, <12 IU/mL in 8 (38.1%) patients, and <100 IU/mL (but detectable) in 7 (33.3%) patients. Following treatment, HCV RNA was negative in all of the patients. All of the patients achieved SVR12 after 12 weeks of treatment.

Safety

Laboratory values of all of the included patients during the treatment period are presented in Table 2. Hemoglobin levels were reduced in 11 patients infected with G1a and G4 4 weeks after the initiation of treatment due to ribavirin, but these levels returned to normal following treatment. The most common side effect was anemia (n=6, 28.5%), which was due to RBV in 5 (83%) patients. Three patients required recombinant erythropoietin treatment (1 of them had received erythropoietin prior to receiving antiviral therapy), and 3 (14.3%) patients received blood transfusions. Three of the six patients with anemia during therapy received azathioprine, and the other three received mycophenolate mofetil (MMF) as an immunosuppressant. The ribavirin dose was reduced to 600 mg/day in three patients who received blood transfusion.

Eleven (52%) patients had impaired renal functions (eGFR <60 mL/min), and one patient was undergoing erythropoietin treatment at baseline. No significant changes were found in creatinine levels or in 24-hour proteinuria levels during or after the treatment. Nevertheless, creatinine levels were higher 12 weeks following treatment than basal levels. As expected, eGFR levels also increased after 12 weeks of treatment. There were no significant differences in thrombocyte and albumin levels before or after treatment.

Compared with reference values, alanine aminotransferase (ALT) levels were significantly decreased during and following treatment. However, three patients experienced an increase in ALT levels 4 weeks after the initiation of treatment. For example, one patient with a reference ALT level of 21 U/l increased to 218 U/l 4 weeks after the initiation of treatment but did not experience an increase in bilirubin or prothrombin time. Within 1 week, the patient's ALT level reduced to 128 U/l and then returned to normal range.

Immunosuppressive doses during the pretreatment period and during treatment are presented in Table 3. As expected, there were no dose adjustments made for prednisolone, azathioprine, and MMF during treatment. Ten patients were using Csa (seven patients on 100 mg/day and three patients on 125 mg/day) in the pretreatment period. These 10 patients had a mean Csa blood level of 92.4±29.7 ng/mL with these doses. Csa was stopped in one patient during treatment. The other nine patients were monitored so that their Csa blood levels were maintained at 94.8±42.0 ng/mL by dose adjustment (50 mg/week-25 mg/day), which is not significantly different from the pretreatment level. The seven patients who were taking tacrolimus in the pretreatment period were given doses between 1 and 4 mg, and their

Table 2. Changes of laboratory findings pre-/post-treatment.

		Pretreatment[a]	Week 4[b]	End of the treatment[c]	Post-treatment week 12[d]	p	Groups with significant difference
Hb	Mean±SD	12.3±1.7	11.3±1.9	11.2±1.4	12.0±1.8	0.04	a-c; c-d
	Median	12.5	11.5	11.7	12.4		
Plt	Mean±SD	230.2±113.7	243.2±94.3	228.0±101.7	210.8±112.6	0.523	
	Median	223	239	206	205		
Kr	Mean±SD	1.61±0.80	1.62±0.72	1.51±0.63	1.62±0.59	0.037	a-d
	Median	1.37	1.41	1.41	1.51		
eGFR	Mean±SD	59.3±32.4	58.1±32.7	62.5±36.0	53.9±27.3	0.037	a-d
	Median	55	48	51.7	46.7		
Alb	Mean±SD	4.13±0.45	4.20±0.39	3.98±1.02	4.38±0.41	0.334	
	Median	4.15	4.3	4.1	4.4		
ALT	Mean±SD	40.9±48.5	32.4±48.8	14.8±11.3	12.2±6.0	<0.0001	a-c; a-d; b-c; b-d
	Median	23	14	9.5	11		
HCV RNA		12-100	7	0	0		
		<12	8	0	0		
		Negative	6	21	21		

Hb: hemoglobin; Plt: platelet; eGFR: estimated glomerular filtration rate; Alb: albumin; ALT: alanine aminotransferase; HCV: hepatitis C virus.

mean blood tacrolimus level was 7.2±1.9 ng/mL. Tacrolimus was stopped in one patient during treatment. The remaining six patients were monitored so that their tacrolimus blood levels were maintained at 7.8±0.8 ng/mL by dose adjustment (0.5 mg/every 2 weeks to 0.5 mg/week). There were no significant differences in the tacrolimus blood levels between the pretreatment period and during treatment.

DISCUSSION

Although chronic hepatitis C has a benign course in hemodialysis patients and in RT patients, extensive studies and meta-analyses have shown that HCV infection causes a decline in both the longevity of the graft and the patient in RT patients (8,9). However, there is insufficient evidence to show that the progress of hepatic fibrosis is more rapid in RT patients with HCV infection than in immunocompetent patients (10,11). RT patients with HCV are known to have an increased risk of mortality due to cardiovascular disease, cancer, and hepatic insufficiency; a decreased survival rate; an increase in the risk of de novo glomerulonephritis and chronic allograft nephropathy; and decreased graft longevity.

Immune complex diseases are known to be a major cause of glomerulonephritis. HCV-positive RT receivers have a 3-8 fold higher risk of glomerulonephritis risk than HCV-negative RT receivers (12,13). In addition, it should be noted that diabetes often results in loss of kidney function (14). Therefore, all RT patients should undergo treatment for HCV. However, this can prove to be quite difficult, as interferons can stimulate the immune system, causing an increased risk of kidney rejection. A small number of studies have shown that SVR rate was <20%, and that there were serious corticosteroid-resistant rejections in patients on interferon treatment.

The introduction of DAAs revolutionized the treatment of RT patients with HCV, together with the treatment of general hepatitis C. Despite the lack of large-scale, randomized controlled studies dedicated to RT patients with HCV, case series have reported that DAAs produce persistent virological responses in RT patients, with similar rates as obtained in immunocompetent patients (5,15-17). For example, a meta-analysis including six studies reported the results of a total of 360 patients (17). Of the 360 patients, 235 patients received a combination

Table 3. Immunosuppressive doses of patients pre/during treatment and blood levels of Csa and Tac.

	Pretreatment							During treatment						
Patient no.	Pred	Aza	MMF	Csa	Blood level of Csa	Tac	Blood level of Tac	Pred	Aza	MMF	Csa	Blood level of Csa	Tac	Blood level of Tac
1	2.5	100		125	148			2.5	100		50 qod	131		
2	2.5	50						2.5	50					
3	5	50						5	25					
4	5		1000	125	76			5		1000	25 qd	94		
5	7.5							5						
6	5		1000			1.0	7.5	5		1000			0.5 q10d	9
7	5	75						5	50					
8	5		1080			1.0	5.3	5		1080			Stop	
9	5		1000	100	70			5		1000	50 qw	70		
10	5		720			1.0	6	5		1080			0.5 qw	6.6
11	2.5	25		100	107			5	50		50 qw	57		
12	2.5			100	117			5	25		50 qw	62		
13	5		500			4.0	5	5		500			0.5 qw	8
14	5		720			1.5	9.9	5		720			1.5 q10d	8.1
15	5	75		100	70			5	100		50 qw	55		
16	5		720			2.0	7	5		720			0.5 q2wk	7
17	2.5		750	125	130			5		750	50 qod	171		
18	5		750	100	50			5		1000	50 bw	63		
19	5	100		100	80			5	100		50 bw	150		
20	2.5		1000			2.0	10	5		1000			0.5 q2wk	7.9
21	5		2000	100	76			5		1000	Stop			

Pred: prednisolone; Aza: azathioprine; MMF: mycophenolate mofetil; Csa: cyclosporine; Tac: tacrolimus. Doses of drugs are in mg.

of grazoprevir/elbasvir, and none of them received PrOD treatment. SVR12 was found in 98.3% of the patients, and only four patients had serious adverse effects. However, it should be noted that the biggest problem in patients treated with DAA is the interaction of DAA with immunosuppressive drugs (18). Among the most commonly used regimens, simeprevir reduces tacrolimus levels, but ritonavir (part of the PrOD regime) and elbasvir/grazoprevir cause serious increases in tacrolimus levels. Therefore, we suggest that tacrolimus levels should be monitored closely while using these drugs. These aforementioned drugs can cause a severe increase in Csa and sirolimus levels, so until now, sofosbuvir regimens, particularly the sofosbuvir/ledipasvir combination, were used to treat patients who underwent RT.

Until recently, there has been very little research studying PrOD regimens in RT patients. In Cohort 5 of the CORAL I study sponsored by AbbVie, the PrOD regimen was used in nine patients without cirrhosis with genotype 1a HCV and three patients with genotype 1b HCV (19). The patients underwent treatment for 12 weeks, and those infected with G1a HCV also received ribavirin. One of the 12 patients was prematurely removed from the study due to nausea and vomiting, and another patient was removed due to acute renal failure and respiratory distress, as they could not achieve SVR. A third patient died from a tacrolimus overdose. Nine patients completed the trial and achieved SVR. The SVR ratio was 75% in ITT analysis. Based on the results of that study, the PrOD regimen does not appear to be a good treatment choice for that patient group.

The largest series of DAA treatment in RT patients infected with HCV was reported from Spain. In that retrospective study, 10 of the 103 patients were treated with the PrOD regimen (4). Three of those 10 patients discontin-

ued the study prematurely due to reasons unassociated with adverse effects, but they did achieve SVR. There was no premature discontinuation of treatment due to adverse effects. The SVR ratio was determined to be 98% in this population. This study did not mention any adverse effects specific to the PrOD regimen, premature discontinuation, or changes in immunosuppressive doses.

Our current study includes the largest number of RT patients with HCV on PrOD treatment. Ten patients in our study also received ribavirin as they were infected with G1a HCV, and one patient also took ribavirin as he was infected with G4 HCV. One patient with G1 cirrhosis underwent treatment for 24 weeks, whereas the rest of the patients were treated for 12 weeks. No patients discontinued the medication due to adverse effects. All of the patients, including two with compensated cirrhosis, achieved SVR12. The most common adverse effect was anemia, which occurred in patients on ribavirin. No renal function impairment was reported during treatment. Tac was stopped in one of the six tacrolimus-treated patients, and the dose was reduced to 0.5 mg/every 7-10 days in the others. In seven patients on Csa, the dose was reduced to 25 mg/day-50 mg/week, and blood levels were maintained at a normal range. No dose adjustments were required for prednisolone, azathioprine, and MMF.

It has been reported that ALT can be increased in patients receiving the PrOD regimen, and this can be fatal, particularly in patients with cirrhosis (20). In our current study, only one patient had a 10-fold increase in ALT compared with reference values, but there was no decompensation, rise in bilirubin, or increase in international normalized ratio prolongation.

International guidelines do not suggest PrOD treatment for RT patients. For example, the HCV guideline of the American Association for the Study of Liver Diseases (published September 21, 2017) suggests a combination of glecaprevir/pibrentasvir and a combination of ledipasvir/sofosbuvir for RT receivers infected with HCV (21). According to the politics of the Social Security System reimbursement foundation, the PrOD regimen was fully paid for in treatment-naive patients with compensated hepatitis in our country. Patients with renal failure, renal transplantation, or liver transplantation were not considered in this payment plan. Therefore, most of the RT patients who were followed up within our center underwent PrOD treatment. Three patients who underwent pretreatment with immunosuppressives were also given the PrOD regimen as these drugs have no interaction with PrOD.

This retrospective data included the largest cohort of PrOD-treated patients showing that PrOD treatment is safe and effective in RT patients, even those with compensated cirrhosis, as long as the patients are closely monitored.

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Informed Consent: N/A.

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