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Efficacy and Safety of Sofosbuvir and Ledipasvir for Hepatitis C in Kidney Transplant Recipients: A Single-center Retrospective Observational Study

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Background: Treatment using direct-acting antivirals provides high rates of sustained virologic response and a favorable safety profile for patients with chronic hepatitis C virus infection. However, data on the efficacy of direct-acting antivirals in kidney transplant recipients are still limited.

Aims: To evaluate the safety and efficacy of fixed-dose sofosbuvir/ledipasvir combination in kidney transplant recipients.

Study Design: Retrospective, observational, single-center study.

Methods: Data of 29 kidney transplant recipients who received a fixed-dose safety and efficacy of fixed-dose sofosbuvir/ledipasvir combination for 12 or 24 weeks with or without ribavirin were analyzed. The primary outcome was SVR12, which was defined as undetectable HCV-RNA levels 12 weeks after the treatment. Secondary outcomes were graft function, proteinuria, and calcineurin inhibitor trough level variability.

Results: The predominant hepatitis C virus genotype was 1b (n = 19, 65.6%). All patients achieved SVR12. No graft failures nor deaths were reported during the study period. Throughout and after the treatment, the levels of aspartate aminotransferase [21 (range: 18-29.5) to 16 (range: 14-20) U/l, $p < 0.001$] and alanine aminotransferase [22 (range: 15-34) to 14 (range: 12-17.5) U/l, $p < 0.001$] improved significantly, unlike bilirubin, hemoglobin, and platelet levels. Renal function remained stable. Dose adjustments for calcineurin inhibitors were required. Serious adverse events were not observed.

Conclusion: Safety and efficacy of fixed-dose sofosbuvir/ledipasvir combination was effective and safe in kidney transplant recipients with hepatitis C virus. However, cautious monitoring of trough levels of calcineurin inhibitorss is needed due to potential drug-drug interactions during the treatment episode.

INTRODUCTION

In developed countries, 1.8-8% of kidney transplant recipients (KTRs) have chronic hepatitis C virus (HCV) infection.[1] HCV is the primary cause of chronic liver disease after kidney transplantation (KTx) and poses an increased risk for liver failure, hepatocellular carcinoma, and death.[2] Moreover, it is associated with serious extrahepatic complications, including post-transplant diabetes, proteinuria, HCV-associated glomerular diseases, chronic transplant glomerulopathy, and chronic graft rejection.[3] Although patients who underwent KTx have better survival than patients with HCV on dialysis, n patient and graft survival is lower in patients who underwent KTx than KTRs without HCV infection, mainly due to liver failure and post-transplant diabetes.[4] Prior to the introduction

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of direct-acting antivirals (DAAs), pegylated interferon (peg-IFN) and ribavirin (RBV) were the gold standard in the treatment of HCV infection. However, peg-IFN-based therapy is contraindicated in KTRs due to a high risk of rejection, thus requiring its administration before transplantation. However, response rates before transplantation were modest.[5-8] With the development of DAAs, treatment against HCV entered a new era. In the general population, DAAs result in high response rates within different genotypes and a good safety profile. [9-13]

Various studies have examined the safety and effectivity of DAAs in KTRs and demonstrated their high efficacy.[14-18] Growing evidence indicates that DAAs play a central role in KTRs.[19-21] Based on the recent advances, the Kidney Disease: Improving Global Outcomes (KDIGO) now recommends that "all patients with chronic kidney disease (CKD), on dialysis, and KTRs with HCV be evaluated for DAA-based therapy".[22] As studies evaluating DAAs in different populations are few, we aimed to evaluate the efficacy and safety of the fixed-dose combination of sofosbuvir/ledipasvir (SOF/LDV) in KTRs in this single-center retrospective study.

MATERIALS AND METHODS

Patients

A total of 29 KTRs who were treated with SOF/LDV after KTx were included in the study. Patients who did not complete the therapy or lost to follow-up were excluded (n = 1). HCV genotypes, prior treatments for HCV before KTx, and DAA regimens and doses were recorded. At our institution, administration of DAAs on KTRs began as early as 2016, after the publication of the first reports regarding their use.[15,23] Accordingly, a fixed-dose combination of 400 mg SOF and 90 mg LDV once a day has been administered to all patients, and RBV is added by the expert hepatologist on a case-by-case basis. Treatment duration (12 or 24 weeks) and whether to use RBV are set at the discretion of the treating hepatologist until the recommendations were published in 2018. Subsequently, the European Association for the Study of the Liver guideline at the time of treatment was taken into consideration.[24,25]

All study procedures were conducted according to good medical and laboratory practices and the recommendations of the Declaration of Helsinki on biomedical research involving human subjects or its later amendments. This study was approved by the local ethical committee at our institution (2018/1587). All patients enrolled in the study provided written informed consent to extract their medical data from the center's research database.

Outcomes and Evaluation

The primary outcome was sustained virologic response (SVR), which was defined as undetectable HCV-RNA levels 12 weeks after the treatment. Secondary outcomes were graft function, proteinuria, and calcineurin inhibitor (CNI) trough level variability. Serious adverse events (AEs) requiring hospitalization, discontinuation of treatment, or addition of new medications to treat the AEs were recorded.

HCV-RNA was measured by reverse transcriptase real-time polymerase chain reaction (rt-qPCR) (Artus HCV QS-RGQ kit-Qiagen; Hilden, Germany), and the limit of detection was 0.19 IU/μl. HCV genotyping was performed using the Ampliquality HCV Type Plus kit-AB Analitika (Padua, Italy). HCV-RNA levels were measured before and after 12 weeks after the completion of the treatment. Laboratory parameters representing liver and kidney functions, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum bilirubin and albumin, prothrombin time, platelet counts, serum creatinine levels, and proteinuria, were measured using standard laboratory techniques. Estimated glomerular filtration rates (eGFRs) were calculated using The CKD Epidemiology Collaboration (CKD-EPI) 2009 formula.[26] The urine protein-to-creatinine ratio in the first morning specimen was used to estimate proteinuria. Serum trough levels of CNIs were checked at every outpatient visit, also before and after the treatment.

Statistical Analysis

Statistical analyses were performed by using SPSS for Windows (SPSS version 26.0, IBM Corp., Armonk, NY). Normality assumptions were checked with histograms and Shapiro-Wilk's test. Results were expressed as mean ± standard deviation when normally distributed or median [interquartile range (IQR)]. Categorical variables are shown as frequencies (%). One-way analysis of variance or Friedman's test was used to compare various features before, during, and after the treatment according to the distribution pattern. Post-hoc analyses of Friedman's test were computed using the Wilcoxon signed-rank test with Bonferroni correction. Missing data were considered to be pairwise missing in the analyses and were not imputed. All tests were two-sided, and a *p*-value of 0.05 or less was considered as statistically significant. Graphics were generated using MedCalc for Windows (MedCalc version 19.0, MedCalc Software, Ostend, Belgium).

RESULTS

Baseline Characteristics

The mean age of all patients was 39.8 ± 11.8, and 17 (58.6%) were male. The most frequent etiology of end-stage kidney disease was chronic glomerulonephritis, which was seen in 10 patients (34.5%), followed by 8 (27.5%) patients with unknown causes. In most patients, KTx was performed from living donors (68.9%). Only one patient was in the first 6 months after transplantation, and one had re-transplantation. None of the KTRs had liver cirrhosis.

The predominant HCV genotype in the study participants was 1b (n = 19, 65.6%). Seven patients received peg-IFN, and one received peg-IFN+RBV before KTx. No patient had a history of DAA use. All patients were treated with SOF/LDV, and two received additional RBV. Twelve- and 24-week treatment regimens were used in 20 (69%) and 9 (31%) patients, respectively. One patient had a coinfection with hepatitis B virus (HBV), and was using lamivudine with negative HBV-DNA levels. A 24-week regimen was administered to patients with a history of HCV (n = 8) or HBV treatment (n 0 = 1), and RBV was used in 12-week regimens in two patients had received HCV therapy. Treatment

was not discontinued. The baseline characteristics of the patients are shown in Table 1.

Study Outcomes

The median pre-treatment HCV-RNA load was 2.06 x 10^6 (IQR: 1.03 x 10^6-5.93 x 10^6) IU/ml. The primary outcome was achieved in all patients, and no graft failures nor deaths were reported during the study period. Median pre-treatment AST, ALT, and bilirubin levels were 21 (18-29.5) U/l, 22 (15-34) U/l, and 0.4 (0.29-0.76) mg/dl, respectively. AST and ALT declined throughout and after the treatment to 16 (14-20) and 14 (12-17.5) U/l, respectively ($p < 0.001$ for both), but bilirubin levels had the same course ($p = 0.998$). Serum albumin levels were mildly increased ($p = 0.047$), but no pairwise differences were found with Bonferroni correction. Prothrombin times, INR levels, leukocyte, hemoglobin, and platelet counts were not significantly different throughout the treatment. The laboratory characteristics of the patients are summarized in Table 2.

TABLE 1. Clinical Characteristics of all Patients at the Baseline

		n (%)
Sex	Female	12 (41.4)
	Male	17 (58.6)
Primary kidney disease	Chronic GN	10 (34.5)
	Unknown etiology	8 (27.5)
	Vesicoureteral reflux	6 (21)
	Chronic pyelonephritis	1 (3.4)
	Membranoproliferative GN	1 (3.4)
	Crescentic GN	1 (3.4)
	HELLP syndrome	1 (3.4)
	UPJ obstruction	1 (3.4)
Donor type	Deceased	9 (31.1)
	Living	20 (68.9)
HCV genotype	1b	19 (65.6)
	1a	6 (20.7)
	3	1 (3.4)
	4	1 (3.4)
	Record not available	2 (6.9)
Ribavirin	No	27 (93.1)
	Yes	2 (6.9)
Antiviral treatment before DAAs	No	21 (72.5)
	Peg-IFN	7 (24.1)
	Peg-IFN + ribavirin	1 (3.4)
Maintenance immunosuppression	Tac+MPA/AZA+PRDL	11
	CsA+MPA/AZA+PRDL	9
	Tac+mTORi+PRDL	1
	CsA+mTORi+PRDL	1
	Double therapies	
	- Tac+MPA/AZA	1
	- CsA+MPA/AZA	1
	- MPA/AZA+PRDL	3
	- mTORi+PRDL	2

AZA, azathioprine; CsA, cyclosporine; DAA, direct-acting antiviral; GN, glomerulonephritis; HCV, hepatitis C virus; HELLP, hemolysis, elevated liver enzymes, low platelets; IFN, interferon; MPA, mycophenolic acid; mTORi, mTOR inhibitor; PRDL, prednisolone; Tac, tacrolimus; UPJ, ureteropelvic junction.

Median pre-treatment serum creatinine, eGFR, and proteinuria levels were 106.1 (92.8-150.3) µmol/l, 58.2 (46.4-79.8) ml/min/1.73 m^2, and 0.1 (0.1-0.2) g/day, respectively. All of them demonstrated similar courses throughout and 12 weeks after the treatment (Table 2).

Blood trough levels and dosages were not significantly different before, during, and after treatment for both tacrolimus and cyclosporine. Moreover, tacrolimus concentration-dose ratios were similar during and immediately after the treatment ($p = 0.168$ and $p = 0.138$, respectively, by Wilcoxon with Bonferroni correction), compared with pre-treatment levels. Twelve weeks after treatment completion, the ratio remained similar in comparison with the pre-treatment ($p = 0.546$) (Figure 1). The cyclosporine concentration-dose ratio was retained throughout and after the treatment. The dose of tacrolimus was adjusted in six patients: five needed an increase, while one needed a decrease. In two patients on cyclosporine, the doses were changed: one needed an increase, while the other was decreased. No allograft rejection during DAA treatment nor serious AEs were reported.

DISCUSSION

In this retrospective single-center study, we evaluated 29 KTRs with chronic HCV infection who received fixed-dose SOF/LDV combination with or without RBV for 12 or 24 weeks to assess the safety and efficacy of this regimen in this patient population. This study confirmed that treatment with SOF/LDV in KTRs with HCV infection was safe and highly effective. The rate of SVR reached 100% with no serious AEs. Previous clinical trials showed an SVR rate of 94%-99% in patients with native kidneys.[11,27,28] Lacking randomized clinical trials, SOF/LDV and other DAAs are increasingly used in KTRs due to its high efficacy and tolerability. Thus, we believe our findings from the Turkish

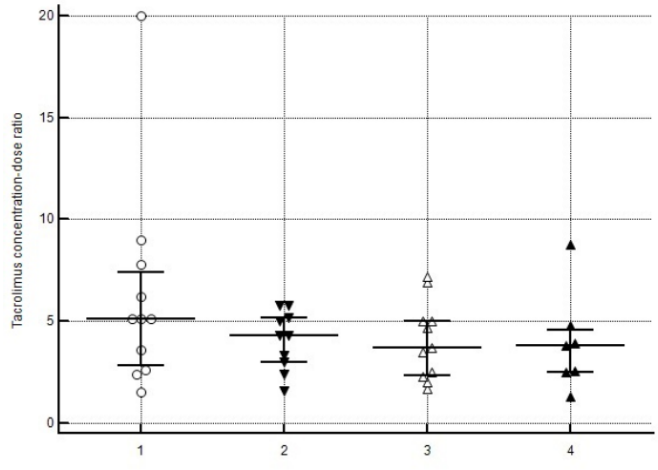

FIG. 1. Tacrolimus concentration-dose ratio before **(1)**, during **(2)**, immediately after **(3)**, and 12 weeks after the treatment **(4)** (1 vs 2: $p = 0.168$, 1 vs 3: $p = 0.138$ and 1 vs 4: $p = 0.546$ by Wilcoxon signed-rank test with Bonferroni correction).

population are valuable addition to the literature. The SVR rates in this study were generally consistent with the previous findings in the transplantation setting.[14-16,23]

RBV is a known cause of anemia in patients with CKD. In this study, no severe AEs were reported because of the limited use of RBV, while in other studies, RBV-containing regimens were administered, which resulted in high rates of anemia[14,18] Mild AEs such as fatigue, headache, nausea, and lightheadedness have been reported in 40% of patients, but serious AEs are not treated with frequent DAA treatment, similar to our results.[29] The treatment was overall well tolerated, and discontinuation did not occur in any patient.

In our study, pre-and posttreatment CNI dose and trough levels were not different, and concentration-dose ratios to monitor any dose modifications did not change. However, five patients on tacrolimus needed a dose increase, indicating a faster CNI metabolism after DAA treatment; CNI dose modifications are reported in previous studies. Colombo et al.[15] and Eisenberger et al.[30] exclusively included patients who received SOF/LDV and reported that 18% and 55% of them required either a reduction or an increase in CNI doses, respectively. In contrast, other studies administered different drug combinations and reported dose modifications in 6%-55% of the patients[14,31,32] SOF does not interact with cytochrome P450, but significant drug-to-drug interactions are possible when it used as a combination with LDV.[33] Moreover, improved liver functions result in better metabolism of CNIs.[34] We found a significant improvement in AST and ALT levels after DAAs, suggesting that liver injury was somewhat present. Nevertheless, none of the patients had cirrhosis, and serum markers of liver functions such as transaminase levels, bilirubin, and prothrombin time were within normal limits. Careful monitoring of serum concentrations and adjustment of drug doses are necessary during and after DAA therapy due to various reasons.

Graft dysfunction is an issue when starting treatment with novel drugs. Recent studies have conflicting results; Kamar et al.[23] showed no significant differences in serum creatinine, GFR, and proteinuria levels at the end of the treatment compared to the baseline, although three patients had a decrease in posttreatment GFR. Fernández et al.[14] reported that graft functions decreased in 17 (16%) patients, 10 of whom had rejection due to decreased CNI trough levels or acute kidney injury due to pre-renal and post-renal acute kidney injury, CNI toxicity, infections, nephrotoxic medications, cytomegalovirus, and BK virus nephropathy. Therefore, causality between DAAs and worsening of graft functions cannot be proved. On the other hand, SOF is expelled by the kidneys and causes a higher exposure in patients with kidney impairment.[35] In a study of 1,789 patients, the use of SOF-containing regimens in patients with a baseline eGFR ≤ 45 ml/min/1.73 m^2 (n = 45) resulted in more severe AEs and deterioration in kidney function compared with patients with a baseline eGFR > 45 mL/min/1.73 m^2. Nevertheless, it is still unclear whether SOF is the cause of kidney injury.[36] Recently, Liu et al.[37] investigated the nephrotoxicity of SOF in carefully selected patient and control groups who received SOF-based and SOF-free regimens, respectively. They excluded patients with stage 4-5 CKD, decompensated cirrhosis, concomitant HBV infection, and organ transplantation and their results demonstrated a decline in eGFR during treatment on SOF-based DAAs. Advanced age, more advanced CKD, and SOF-based DAAs were associated with the decline in kidney functions. Fortunately, this effect seemed to be reversible. In addition, the eGFR levels at SVR12 and SVR24 were higher than the baseline eGFR levels,

TABLE 2. Laboratory Characteristics of All Patients

Characteristics	Before treatment	On treatment	Immediately after treatment	12 weeks after treatment	*p*
CNI values					
Tac dosage (mg/day)	1.5 (1-2.5)	1.25 (1-1.94)	1.5 (1.06-2.5)	1.5 (1-2.5)	0.234
Tac blood trough level (ng/ml)	6.9 ± 1.5	5.5 ± 1.8	6.0 ± 1.8	6.3 ± 1.4	0.319
Tac concentration-dose ratio	5.1 (2.6-7.80)	4.3 (2.85-4.35)	3.7 (2.3-5)	3.8 (2.5-4.8)	0.510
CsA dosage (mg/day)	87.5 (75-106.25)	87.5 (75-100)	75 (62.5-100)	100 (75-125)	0.392
CsA blood trough level (ng/ml)	59 (51.5-100.5)	69.5 (62.3-73)	49 (43-58)	86 (85-101.5)	0.392
CsA concentration-dose ratio	0.8 (0.5-1.15)	0.81 (0.7-0.9)	0.6 (0.43-0.8)	0.85 (0.78-1)	0.290
Laboratory values					
Serum bilirubin (mg/dl)	0.4 (0.29-0.76)	0.47 (0.35-0.64)	0.48 (0.38-0.75)	0.4 (0.26-0.6)	0.998
Prothrombin time (sec)	11 (10.75-11.4)	11 (10.8-11.4)	10.8 (10.8-11.0)	10.95 (10.8-11)	0.107
INR	0.90 (0.9-0.96)	0.97 (0.92-1)	0.92 (0.9-0.96)	0.9 (0.9-1)	0.711
AST (U/l)	21 (18-29.5)	19 (15-21)	18 (16-22.5)	16 (14-20)	**<0.001**
ALT (U/l)	22 (15-34)	15.5 (13.3-23.3)	13 (11.5-17.3)	14 (12-17.5)	**<0.001**
Serum albumin (g/dl)	4.3 ± 0.3	4.4 ± 0.3	4.6 ± 0.4	4.5 ± 0.3	**0.047**
Serum creatinine (μmol/l)	106.1 (92.8-150.3)	106.1 (88.4-132.6)	110.1 (88.4-123.8)	106.1 (97.2-148.1)	0.935
eGFR (ml/min/1/73 m^2)	58.2 (46.4-79.8)	70.5 (54.8-86.3)	65.5 (61.5-74)	61.5 (48.6-73.8)	0.305
Proteinuria (g/day)	0.1 (0.1-0.2)	0.1 (0.07-0.9)	0.13 (0.08-0.28)	0.15 (0.08-0.28)	0.581
Leukocyte count (per mm^3)	8,069 ± 1,376	8,113 ± 1,540	8087 ± 1797	8379 ± 1747	0.829
Hemoglobin level (g/dl)	13.4 ± 1.6	13.0 ± 1.7	13.1 ± 1.7	12.9 ± 1.6	0.086
Platelet count (per mm^3)	235,897 ± 64,156	246,875 ± 75,153	240,363 ± 66,384	239,786 ± 58,794	0.924

AST, aspartate aminotransferase; ALT, alanine aminotransferase; CNI, calcineurin inhibitor; CsA, cyclosporine; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; Tac, tacrolimus; All values were reported as mean ± standard deviation when normally distributed or median (interquartile range) otherwise.

which implies a favorable effect of HCV eradication on kidney functions.[37] However, another study that included exclusively stage 4 and 5 CKD patients revealed that eGFR at baseline and SVR12 were stable and severe AEs were associated with DAAs.[38]

The present study had some limitations. First, the nature of the study was retrospective. Second, patients with liver failure or severe kidney impairment were not included. Third, mild AEs such as fatigue, sleep disturbances, and loss of appetite were not recorded; therefore, the true frequency of AEs remains unknown.

In conclusion, DAAs appeared to be efficacious and safe in KTRs. However, dose modifications of CNIs are required during treatment with DAAs and we suggest close follow-up of CNI trough levels.

Ethics Committee Approval: Ethics Commitee of İstanbul Medical Faculty (2018/1587).

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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