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Efficacy and safety of new direct-acting antivirals in kidney transplant recipients with chronic hepatitis C: a single-center study

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Abstract

Background The recent interferon-free direct-acting antiviral (DAA) regimens have very good safety and efficacy profiles and are highly recommended for kidney transplant (KT) recipients with chronic hepatitis C (CHC).

Methods All KT recipients with CHC followed at our hospital and who received therapy with the current DAAs were included. At the baseline visit, demographic, clinical and laboratory variables before and after KT, as well as at the commencement of DAAs, at the end of antiviral therapy and the end of follow up, were recorded, including assessment of glomerular filtration rate (eGFR). The changes in eGFR (DGFR) between baseline and end of therapy (1st period), and between end of therapy and end of follow up (2nd period), were evaluated.

Results Twelve KT recipients were retrospectively evaluated: 2 had received antiviral therapy in the past; 4 (33.3%) patients had genotype 1 and 3 (25%) genotype 4 CHC. The median stiffness was 11.9 kPa (range 5-16.8), while 5 patients, none with decompensated cirrhosis, had stiffness >12.5 kPa. Eight patients received a sofosbuvir-containing antiviral regimen (Group 1) and 4 patients received an antiviral regimen without sofosbuvir (Group 2). Eleven (91.7%) patients achieved a sustained virological response (SVR). One patient discontinued DAAs early after treatment and did not achieve SVR. Otherwise, DAAs were well tolerated and no rejection episode was recorded. The DGFRs in the 1st period and 2nd period did not differ significantly between Group 1 and Group 2 patients.

Conclusion In this real-world study of KT recipients with CHC, the high efficacy and clinically acceptable tolerability of DAAs were confirmed.

Keywords Kidney transplantation, hepatitis C, direct-acting antivirals, chronic hepatitis C, kidney

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Introduction

It is estimated that 5-15% of kidney transplant (KT) recipients have chronic hepatitis C (CHC), associated with poor patient and graft survival after KT [1]. In particular, CHC after organ transplantation usually has a more aggressive course due to the necessary immunosuppressive therapy, as well as the more frequent development of post-transplant diabetes mellitus, cardiovascular disease and HCV-associated glomerulonephritis, while there is an increased risk of post-transplant lymphoproliferative disorders [2,3]. In the era before direct-acting antivirals (DAAs), there was hardly any therapeutic option for CHC in KT recipients, as interferon-based therapy, with or without ribavirin (RBV), was usually not recommended, or was even contraindicated because of the low rates of sustained virological response (SVR) and the high risk for the development of steroid-resistant acute allograft rejection [3]. After 2014, the introduction of DAAs in the

treatment of CHC has changed the landscape dramatically, as interferon-free and RBV-free oral DAA combinations given for a few weeks can achieve very high cure rates (>95% SVR), while having excellent tolerability and safety profile even in immunocompromised patients [2,3].

Currently, DAA combinations represent the standard therapeutic option for the treatment of all CHC subgroups, including those with renal dysfunction or KT. All current DAAs are eliminated mainly through the liver, except for sofosbuvir eliminated through the kidney and may be associated with an unfavorable safety profile in patients who have at least moderate-to-severe renal impairment [4]. Thus, sofosbuvir—and consequently its co-formulations, sofosbuvir/ledipasvir, sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir—are not recommended for use in patients who have an estimated glomerular filtration rate (eGFR) lower than 30 mL/min [4], although in the very recently updated guidelines of the American Association for the Study of Liver Diseases (AASLD), a daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) is considered as an option in this specific group of patients [5]. On the other hand, caution is required regarding the potential drug-drug interactions between immunosuppressive agents and DAAs in the KT setting, since calcineurin inhibitors (CNIs: tacrolimus and cyclosporine) and mammalian target of rapamycin inhibitors (sirolimus and everolimus) are substrates of cytochrome P450 and P-glycoprotein [6]. In fact, some DAAs should not be used and some others should be used with caution in combination with specific immunosuppressive drugs (e.g., protease inhibitors with cyclosporine, given the elevations in cyclosporine concentrations) [6]. The aim of the present study was to evaluate the efficacy, tolerability and safety of DAAs in KT recipients followed in a single center in Greece.

Patients and methods

We included all KT recipients with CHC followed at our hospital who received therapy with the current DAAs. All KT recipients with positive antibodies against hepatitis C (anti-HCV) before transplantation were reassessed after KT with anti-HCV and serum HCV RNA to confirm the HCV infection. In patients with detectable serum HCV RNA, HCV genotype determination and baseline laboratory tests were performed. The choice of antiviral regimen was based on the availability of DAAs at the time of evaluation in relation to the HCV genotype and viral load, previous antiviral therapy, liver disease severity, eGFR, co-morbidities and co-medications.

Commercially available enzyme immunoassays were used for the detection of anti-HCV, while serum HCV RNA levels were determined by a commercially available quantitative polymerase chain reaction (PCR) assay. HCV genotype was also determined by a commercially available assay. Evaluation of liver severity was classified into the following subgroups: fibrosis stage F0-F1, F2, F3 and F4, and decompensated cirrhosis. The diagnosis of fibrosis stage F0-F4 was based on liver stiffness measurements (LSM) using 2-dimensional real-time shear-wave elastography (2D-SWE) performed by experienced operators according to the current guidelines (evaluation of the right lobe of the liver through the intercostal spaces with the fasting patient in the supine position). The Aixplorer ultrasound system (Supersonic Imagine S.A., Aix-en-Provence, France) with an abdominal 3.5 MHz curved array probe was used, as recommended. Ten reliable LSM were obtained from each patient, and the mean values were calculated. The standard deviation (SD) was <20% of the mean value of LSM. The recipients with reliable liver stiffness measurements of <7.0, 7.0-9.0, 9.1-12.5 and >12.5 kPa were considered to have fibrosis stage F0-F1, F2, F3 and F4, respectively. The diagnosis of decompensated cirrhosis was based on the presence of ascites, episodes of variceal bleeding, encephalopathy or non-obstructive jaundice diagnosed by clinical and/or radiological signs.

At the baseline visit, demographic and clinical variables were recorded: (a) before KT: duration of hemodialysis and indication for KT; and (b) after KT: rejection episodes, concomitant diseases (e.g., diabetes mellitus, arterial hypertension, hyperlipidemia, cardiovascular events) and immunosuppressive therapy, including dosage and blood concentrations of CNIs and everolimus, dosage of mycophenolate mofetil (MMF) and steroids.

In addition, several laboratory parameters were tested, including hematocrit, hemoglobin, white blood count, platelet count, serum creatinine (sCr), and aminotransferases (aspartate [AST] and alanine [ALT]). Renal function was assessed by eGFR calculated with the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) sCr-based formula. Evaluation of renal function was performed at baseline (initiation of DAAs), at the end of antiviral therapy and at the end of follow up. The changes in eGFR (DGFR) between baseline and end of therapy (1st period), and between end of therapy and end of follow up (2nd period) were also evaluated.

After the commencement of DAA therapy, all patients were followed every month and whenever clinically indicated, with or without laboratory evaluation. Adverse events and their management were recorded. At the end of therapy, clinical and laboratory re-evaluation was performed, with measurement of aminotransferases, serum HCV RNA, and renal function based on sCr and eGFR. SVR was evaluated at 3 months after stopping DAAs (SVR12) and was considered to have been achieved when serum HCV RNA was undetectable by PCR. Patients with serum HCV RNA undetectable at the end of treatment, but detectable subsequently, were considered as relapsed responders, while patients with detectable serum HCV RNA at the end of treatment were classified as non-responders.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was not supported by any external institution or agency. Informed consent was obtained from all participants before DAAs were initiated.

Statistical analysis

Continuous variables were represented as mean ± standard deviation (if normally distributed) or median with interquartile range (if non-normally distributed). Categorical variables were expressed as frequencies or percentages. Comparisons of

parameters between patients were performed using Student's *t*- or Mann-Whitney *U* tests, as appropriate, for continuous variables, and a corrected chi-square test for categorical variables. Chronic kidney disease was defined as eGFR<60 mL/min/1.73 m^2. A P-value <0.05 was considered to be statistically significant. Statistical analysis was conducted using SPSS software (IBM SPSS v.24.0 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.).

Results

Patient characteristics

Our study was a case series of 12 KT recipients with CHC (6 male, age 57±12 years) who received therapy with DAAs. Table 1 depicts their baseline features. Six (50%) patients had known CHC before KT, but only 2 (16.6%) had received antiviral therapy in the past. One patient with CHC genotype 4 had used pegylated interferon and RBV before KT, and another patient with CHC genotype 4 had received sofosbuvir plus RBV after KT. Both cases had discontinued antiviral therapy shortly after its initiation, because of adverse events (anemia/leukopenia and anemia, respectively). A total of 4 (33.3%) patients were infected with genotype 1 (3 with 1b and 1 with 1a), 3 (25%) with genotype 4, and 2 with genotype 3 (16.7%), whereas the genotype was unknown in 3 (25%) patients. The median baseline serum HCV RNA was 3.68×10^6 IU/mL in the study population. The median stiffness was 11.9 (range 5-16.8) kPa and 5 patients had stiffness >12.5 kPa, i.e., had fibrosis F4 (cirrhosis) based on elastography. None of the patients had evidence of decompensated cirrhosis. At the commencement of DAA administration, 9 (75%) patients were under triple immunosuppressive therapy with CNIs plus MMF and methylprednisolone, 2 (16.7%) patients were under a combination of everolimus and methylprednisolone (1 with tacrolimus and 1 with MMF), while 1 (8.3%) patient was receiving no immunosuppressive agent. Regarding comorbidities, 12 (100%) patients had arterial hypertension, 6 (50%) diabetes mellitus, and 6 (50%) coronary artery disease (Table 1).

Table 1 Baseline characteristics of 12 kidney transplant (KT) recipients with chronic hepatitis C (CHC) who received antiviral therapy with direct acting antivirals (DAAs)

Variable (unit)	Patients, n=12
Age (years), mean±SD	57±12
Male sex (%)	6 (50)
Time under hemodialysis until KT (months), median (range)	36 (12-120)
Donor age (years), mean±SD	34.7±12
Patients with episodes of rejection before DAAs, n (%)	3 (25)
Number of rejection episodes before DAAs, n (%)	3 (25)
Known CHC before KT, n (%)	6 (50)
Antiviral therapy before baseline, n (5%)	2 (16.6)
Immunosuppressive therapy, n (%)	
Calcineurin inhibitors-based	9 (75)
Everolimus-based	2 (16.7)
No immunosuppression	1 (8.3)
Comorbidities at baseline, n (%)	
Diabetes mellitus	6 (50)
Arterial hypertension	12 (100)
Coronary artery disease	6 (50)
Antiviral therapy with DAAs, n (%)	
Sofosbuvir-based	8 (66.6)
Without sofosbuvir	4 (33.4)
Immunosuppression levels at baseline (ng/ml), mean±SD	
Tacrolimus (trough levels)	4.8±2.1
Cyclosporine (peak levels)	480±170
Everolimus levels (trough levels)*	-

*Only 2 recipients were under everolimus

Therapy with DAAs

Therapy with DAAs was initiated at a median of 189 (range: 1-339) months after KT. One patient started antiviral therapy after the diagnosis of acute cholestatic hepatitis C confirmed by liver biopsy at 20 months after KT. Eleven patients were treated for 12 weeks and 1 patient received therapy for 16 weeks. Eight patients received a sofosbuvir-containing antiviral regimen (Group 1) and 4 patients received an antiviral regimen without sofosbuvir (Group 2). In Group 1 patients, sofosbuvir was given with ledipasvir (n=3; 1 patient had received sofosbuvir plus RBV after KT), velpatasvir (n=2) and daclatasvir (n=3; 1 patient had received pegylated interferon plus RBV before KT). RBV was added in 1 patient with genotype 3 treated with sofosbuvir plus daclatasvir. In Group 2, 2 patients received the combination of elbasvir/grazoprevir and 2 the combination of ombitasvir/paritaprevir/ritonavir plus dasabuvir (3D regimen; together with RBV in 1 patient).

Eleven (91.7%) patients achieved SVR with undetectable serum HCV RNA at 12 weeks after the end of therapy. These 11 patients were followed for a median 30 (range: 3-49) months after the end of therapy and all remained in good clinical condition with undetectable serum HCV RNA. SVR was not achieved in only one patient (8.3%) treated with 3D plus RBV who discontinued DAAs early after treatment onset because of a serious adverse event (Table 2).

Safety profile of DAAs

Interestingly, no significant changes were observed between baseline and 12 weeks after the end of therapy regarding proteinuria (218.8±53.6 vs. 358.5±69.4 mg/24h, P=0.49), serum phosphate (3.25±0.48 vs. 3.09±0.65 mg/dL, P=0.51), calcium (9.74±0.88 vs. 9.71±0.69 mg/dL, P=0.93), sodium (139.2±3.43 vs. 138.66±2.42 mmol/L, P=0.68), potassium (4.3±0.41 vs. 4.27±0.42 mmol/L, P=0.84) or uric acid (7.97±1.42 vs. 8.3±2.41 mg/dL, P=0.69).

Table 2 Characteristics of antiviral therapy with direct acting antivirals (DAAs) in kidney transplant (KT) recipients with chronic hepatitis C (CHC)

Variable (unit)	Patients, n=12
Duration of antiviral therapy, n (%)	
12 weeks	11 (91.6)
16 weeks	1 (8.4)
Sofosbuvir-based antiviral therapy, n	
Sofosbuvir/ledipasvir	3
Sofosbuvir/velpatasvir	2
Sofosbuvir plus daclatasvir	2
Sofosbuvir plus daclatasvir plus ribavirin	1
Non-sofosbuvir based antiviral therapy, n	
Elbasvir/grazoprevir	2
3D	1
3D plus ribavirin	1
Antiviral therapy according to the genotype	
1b (n=3)	Elbasvir/grazoprevir, 3D, 3D plus RBV
1a (n=1)	Sofosbuvir/ledipasvir
3 (n=2)	Sofosbuvir plus daclatasvir plus RBV, Sofosbuvir/velpatasvir
4 (n=3)	Sofosbuvir/ledipasvir (n=2), Sofosbuvir plus daclatasvir
Unknown (n=3)	Sofosbuvir/velpatasvir, Sofosbuvir plus daclatasvir, Elbasvir/grazoprevir
Sustained virological response (SVR), n (%)	11 (91.7)
Discontinuation of antiviral therapy, n (%)	1 (8.3)
Change in dosage of immunosuppression during antiviral therapy, n (%)	1 (8.3)

3D, ombitasvir/paritaprevir/ritonavir plus dasabuvir

The only serious adverse event was observed in the patient treated with the 3D plus RBV combination, who developed drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, resulting in permanent withdrawal of DAAs. The DRESS syndrome was attributed to the DAA therapy, since no other medication was changed or added during the last months in this patient. After DAA discontinuation, the patient received appropriate symptomatic management and improved rapidly, but he refused to take any other DAA regimen.

In the remaining 11 patients, therapy with DAAs was generally well tolerated. Only mild non-specific adverse events were reported (e.g., fatigue, headache, diarrhea) in 4 patients. All these mild adverse events were of short duration and required no specific therapeutic manipulation, treatment discontinuation or hospitalization. No patient received a blood transfusion during antiviral therapy, while 4 patients under erythropoietin before therapy continued the same erythropoietin dosage during and after DAA therapy (Table 2).

The dosages and levels of immunosuppressive agents did not change significantly during treatment with DAAs in all but 1 patient who received 3D therapy and had to decrease the dosage of cyclosporine. Otherwise, CNIs and everolimus trough levels were measured more frequently during DAAs therapy, but no other change was required. No rejection episode was recorded (Table 2).

Subgroup analysis at baseline and changes during antiviral therapy

The patients (n=8) who received a sofosbuvir-containing regimen (Group 1), compared to those (n=4) who received a regimen without sofosbuvir (Group 2), were more frequently under CNI-based immunosuppression (7/8 or 87.5% vs. 1/4 or 25%, P=0.03) and had better renal function at baseline (sCr: 1.2±0.2 vs. 1.8±0.3, P=0.028; eGFR: 58±16 vs. 35±6, P=0.007), end of therapy (sCr: 1.2±0.3 vs. 2.1±0.6, P=0.05; eGFR: 59±19 vs. 32±8, P=0.007), and end of follow up (sCr: 1.2±0.3 vs. 3.0±1.3, P=0.016; eGFR: 55±21 vs. 23±10, P=0.017). However, the changes in eGFR between baseline and end of therapy (1st period), and between end of therapy and end of follow up (2nd period), did not differ significantly between Group 1 and Group 2 patients (P=0.15 and P=0.073, respectively) (Table 3). Finally, the patients (n=5) who showed improvement in eGFR (DGFR>0) in the 1st period, compared to those without improvement (n=7), had significantly better renal function at the end of follow up (eGFR: 67.7±18 vs. 38.5±11, P=0.028).

Regarding aminotransferases, AST remained unchanged between baseline and end of therapy, regardless of antiviral (regimen with or without sofosbuvir) or immunosuppressive therapy (CNIs vs. non-CNI-based therapy). In contrast, ALT levels decreased in the total cohort (P=0.05) and in the subgroup of patients who received a sofosbuvir-containing regimen (P=0.031) (Table 3).

Discussion

Currently, only few studies in the literature, most of which included relatively small numbers of patients, have focused on KT recipients with CHC treated with DAAs (Table 4) [7-26].

Table 3 Characteristics of patients under sofosbuvir-based and non–sofosbuvir-based antiviral therapy in kidney transplant (KT) recipients with chronic hepatitis C (CHC) at baseline and during antiviral therapy

Characteristics	Sofosbuvir-based therapy (n=8, 66.6%)	Therapy without sofosbuvir (n=4, 33.4%)	P-value
Age (years), mean±SD	59±5	54±9	0.21
Male sex, (%)	4 (50)	2 (50)	>0.99
Diabetes mellitus, n (%)	5 (62.5)	1 (25)	0.22
CNI-based immunosuppression, n (%)	7 (87.5)	1 (25)	0.03
eGFR at baseline (mL/min), mean±SD	58±16	35±6	0.007
eGFR at EOT (ml/min), mean±SD	59±19	32±8	0.007
eGFR at end of follow-up (mL/min), mean±SD	55±21	23±10	0.017
DGFR (mL/min), median (range)			
Between baseline and EOT	0 (-13 – 15)	-3 (-6 – -1)	0.15
Between EOT and end of follow up	-5 (-9 – 13)	-14 (-3 – -20)	0.073
AST(IU/L), mean±SD - at baseline	18.1±3	17.5±4	>0.05
- at EOT	18.5±4	16.5±4	>0.05
ALT (IU/L), mean±SD - at baseline	18.5±6	15.5±3	0.031
- at EOT	16.5±5	15.5±4	>0.05

CNI, calcineurin inhibitors; eGFR, estimated glomerular filtration rate; DGFR, difference in estimated glomerular filtration rate; EOT, end of therapy

In our study, 11 (91.7%) of 12 patients achieved SVR under DAA combination therapy. Notably, RBV was given in only 2 (16.7%) patients and the vast majority (11/12 or 91.7%) of the KT recipients received 12 weeks of antiviral therapy. The only treatment failure was observed in 1 patient who developed DRESS syndrome shortly after 3D plus RBV initiation, leading to premature discontinuation of therapy. Thus, HCV eradication was achieved in all (11/11 or 100%) patients who received the full antiviral regimen. Our findings confirm previous studies from other centers (Table 4) that DAAs are highly effective in KT recipients, offering SVR rates comparable to those achieved in the non-transplant setting and therefore representing major progress in the elimination of HCV infection in this setting.

Importantly, DAAs in our cohort showed a satisfactory safety profile and were usually well-tolerated, since withdrawal of antiviral therapy was recorded only in the patient who developed DRESS syndrome, possibly attributable to the 3D plus RBV combination. No further serious clinical or laboratory adverse event and/or even transient discontinuation of DAAs was observed. It should be mentioned that all adverse events were non-specific, such as fatigue and headache, and of mild severity, requiring no specific therapeutic manipulation. Interestingly, no rejection episode was recorded during antiviral therapy or until the end of the 12-week follow up, while adjustment of immunosuppression was needed in only 1 KT recipient. In that patient, high levels of cyclosporine were measured during antiviral therapy with the 3D combination and the cyclosporine dosage was reduced, with no further consequences for patient or graft outcome. Thus, changes in immunosuppressive drugs were rather infrequent during DAA therapy in our cohort, although antiviral regimens with protease inhibitors were used in another 3 patients. Contradictory data have been reported on this issue: some studies recorded no need for significant changes in the dosage of immunosuppressive drugs, with stable immunosuppression levels during DAA therapy [17,18,20-22], while in other studies [9,19] a high proportion of patients were reported to require dose adjustment (Table 4). Nevertheless, in accordance with current guidelines, more frequent monitoring of immunosuppressive drug levels is recommended during and after the end of DAA therapy to avoid drug toxicity and/or rejection episodes. In the same context, development of anemia was not reported in our KT recipients under RBV, possibly reflecting careful escalation of the RBV dosage and close laboratory monitoring. Finally, since we performed a real-world study, all the patients in our cohort had comorbidities and were receiving several other drugs, usually related with components of metabolic syndrome. However, no evidence of clinically significant drug–drug interactions was observed, since no adjustments in co-medications were needed during DAA therapy.

In our cohort, most of the KT recipients (n=8, or 66.6%) received a sofosbuvir-containing regimen. Sofosbuvir was given in combination with daclatasvir, ledipasvir and velpatasvir, reflecting the evolution of antiviral regimens according to the guidelines and the availability of DAAs in Greece during recent years. Although our cohort was small, no difference in the effectiveness and safety profile was observed among the different sofosbuvir-containing regimens. In addition, literature studies have shown that sofosbuvir might have a negative impact on eGFR, particularly in high-risk patients, such as KT recipients and/or patients under CNIs [3]. In our cohort, patients treated with a sofosbuvir-containing regimen had baseline mean eGFR 58±16 mL/min and they were more frequently under CNI-based immunosuppression (7/8 or 87.5%). Interestingly, their median DGFR while receiving the sofosbuvir-containing regimen was 0 (range: -13 – 15) indicating that sofosbuvir had an overall neutral renal safety profile in these patients. On the

Table 4 Studies of direct acting antivirals (DAAs) for treatment of hepatitis C virus infection in kidney transplant recipients

First author [Ref], year	Patients, *n*	Patient characteristics	Regimen: Patients number	Sustained virological response at 12 wk, *n/N*	Adverse events, *n*
Gendia [7], 2018	13	GT1: 9 patients (1b: 7) Age: 47 years	SOF/LDV: 4 SOF/VEL: 1 SOF+DCV: 2 SOF+RBV: 6	12/13	Therapy discontinuation: 0 Rejection: 0 immunosuppression adjustment: 1 Proteinuria: 2
Kawagishi [8], 2019	11	GT1: 9 patients (1b: 9) Age: 59.8 years	SOF/LDV: 6 SOF+RBV: 1 EBG/GZR: 3 GLE/PIB: 1	11/11	Anemia: 1 immunosuppression adjustment: 2 switching to tacrolimus: 2
Musialikl [9], 2019	40	GT1: 28 patients (1b: 28) Age: 49 years	SOF-based	40/40	Moderate anemia: 20 immunosuppression adjustment: 28
El Maghrabi [10], 2019	50	GT1: 5 patients Age: 41.4 years		49/50	Anemia: 7 Rejection: 4
Özer Etik [11], 2019	12	GT1: 12 patients (1b: 9) Age: 51 years	3D±RBV: 9 SOF/LDV±RBV: 3	11/12	Therapy discontinuation: 2 Anemia: 1 Rejection: 1
Duerr [12], 2019	16	GT1: 16 patients (1b: 15) Age: 51.5 years	SOF+DCV: 16	15/16	immunosuppression adjustment: 11
Weigert [13], 2018	23	GT1: 18 patients (1b: 13) Age: 56.7 years	SOF/LDV±RBV: 18 SOF+DCV±RBV: 3 EBG/GZR: 2	23/23	No serious adverse events
Xue [14], 2017	6	GT1: 4 patients (1b: 4) Age: 45 years	SOF+DCV: 6	6/6	No serious adverse events
Saxena [15], 2017	55	GT1: 44 patients (1b: 22) Age: 57 years	SOF/LDV±RBV: 44 SOF+DCV±RBV: 2 3D±RBV: 9	52/55	Therapy discontinuation: 4
Goel [16], 2017	6	GT1: 4 patients Age: 41 years	SOF/LDV: 2 SOF+DCV: 1 SOF+RBV: 3	6/6	Therapy discontinuation: 1
Beinhardt [17], 2016	8	GT1: 6 patients (1b: 5) Age: 56.3 years	SOF/LDV: 1 SOF+DCV: 5 SOF+SMV: 3	8/8	No serious adverse events
Lin [18], 2016	24	GT1: 21 patients (1b: 4) Age: 60 years	SOF/LDV±RBV: 8 SOF+RBV: 4 SOF+SMV±RBV: 12	21/24	No serious adverse events
Fernández [19], 2017	103	GT1: 85 patients (1b: 76) Age: 55 years	SOF/LDV±RBV: 59 SOF+DCV± RBV: 18 3D±RBV: 10 SOF+SMV±RBV: 8 SMV+DCV±RBV: 6 SOF+RBV: 2	101/103	Therapy discontinuation: 0 Anemia: 23 Rejection: 3 immunosuppression adjustment: 57
Huang [20], 2019	19	GT1: 16 Age: 48.3 years	SOF+DCV	19/19	No serious adverse events
Zhang [21], 2019	26	GT1: 21 (1b: 21) Age: 49 years	SOF/LDV: 17 SOF+DCV: 8 SOF: 1	26/26	No serious adverse events
Sawinski [22], 2016	20	GT1: 17 (1a: 7) Age: 57 years	SOF+SMV: 9 SOF/LDV: 7 SOF+RBV: 3 SOF+DCV: 1	20/20	No serious adverse events

(Contd...)

Table 4 *Continued*

First author [Ref], year	Patients, *n*	Patient characteristics	Regimen: Patients number	Sustained virological response at 12 wk, *n/N*	Adverse events, *n*
Moreno [23], 2016	12	GT1: 11 (1b: 7) Age: 53 years	SOF+SMV: 1 SOF/LDV: 8 SOF+DCV: 3	11/12	Therapy discontinuation: 1
El-Halawany [24], 2016	11	GT1: 10 (1b: 0) Age: 57.6 years	SOF+SMV: 2 SOF/LDV: 8 SOF+RBV: 1	10/11	No serious adverse events
Colombo [25], 2016	114	GT1: 104	SOF/LDV	112/114	Therapy discontinuation: 1 Serious adverse events: 12
Kamar [26], 2015	25	GT1: 19 (1b: 15) Age: 54 years	SOF/LDV±RBV: 10 SOF+DCV: 4 SOF+SMV±RBV: 7 SOF+RBV±PEG: 4	22/25	No serious adverse events Significant decrease in calcineurin inhibitor levels was observed after HCV clearance
Our study	12	GT1: 4 (1b: 3) Age: 57 years	SOF/LDV: 3 SOF+DCV±RBV: 3 SOF/VEL: 1 EBG/GZR: 2 3D±RBV: 2	11/12	Therapy discontinuation: 1 (DRESS syndrome) immunosuppression adjustment: 1

DCV, daclatasvir; GT, genotype; RBV, ribavirin; LDV, ledipasvir; PEG, pegylated interferon-α; SMV, simeprevir; SOF, sofosbuvir; 3D, ombitasvir/paritaprevir/ritonavir plus dasabuvir; 2D, ombitasvir/paritaprevir/ritonavir

other hand, antiviral regimens without sofosbuvir were given to recipients with renal dysfunction at baseline (mean eGFR: 35±6 mL/min) who were more frequently under everolimus-based immunosuppression (3/4 or 75%). Interestingly, eGFR worsened in Group 2 patients, under a sofosbuvir-free DAA regimen, i.e., DAAs with a theoretically more favorable renal profile (Table 3). However, this group had pre-existing renal dysfunction and the decline in GFR could not be attributed to DAA administration. Nevertheless, in both Group 1 and 2 patients there was no change in eGFR during either the 1st (between baseline and end of therapy) or the 2nd (between end of therapy and end of follow up) period (Table 3), confirming previous studies that DAAs do not adversely affect renal function in KT recipients (Table 4). In addition, DGFR was not associated with the type of immunosuppression used during antiviral therapy or the presence of comorbidities, such as diabetes mellitus or arterial hypertension (data not shown).

Finally, regarding liver function tests, all patients had AST and ALT within normal ranges (<40 IU/L) at baseline; thus, only minor changes in aminotransferase levels were observed at the end of antiviral therapy and after hepatitis C eradication. Only ALT levels significantly decreased from baseline to the end of therapy in the total cohort (P=0.05) and in the subgroup of patients who received a sofosbuvir-containing regimen (from 18.5±6 to 16.5±5 U/L, P=0.031) (Table 3).

Our study is not without limitations, since it was a small observational single-center study that included only Caucasian patients. Nevertheless, although only 12 patients were included in our study, most studies in the literature were characterized by a small sample size (Table 4). Moreover, we were not able to evaluate more sensitive markers of renal dysfunction, such as neutrophil gelatinase-associated lipocalin, before and after DAA therapy. Nevertheless, it was a real-world study of KT recipients with several comorbidities and co-medications, and therefore patients at high risk for drug–drug interactions, in whom DAA therapy showed high efficacy and clinically acceptable tolerability, with only a few non-specific adverse events.

Summary Box

What is already known:

- In the era before direct-acting antivirals (DAAs), there was almost no therapeutic option for chronic hepatitis C (CHC) in kidney transplant (KT) recipients
- Since 2014, interferon-free and ribavirin-free oral DAA combinations given for a few weeks can achieve very high cure rates, with excellent tolerability and safety profile
- Currently, DAA combinations represent the standard therapeutic option for the treatment of all CHC subgroups, including KT recipients

What the new findings are:

- In our study of KT recipients with CHC, DAAs showed a satisfactory safety profile and were usually well-tolerated
- Our findings confirmed that DAAs are highly effective in KT recipients
- A sofosbuvir-containing regimen had an overall neutral renal safety profile in this group of patients

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