ORIGINAL ARTICLE

Impact of hepatitis C virus and direct acting antivirals on kidney recipients: a retrospective study

Mohamed Gendia[1,2], Pietro Lampertico[3,4], Carlo Maria Alfieri[1], Roberta D'Ambrosio[3], Maria Teresa Gandolfo[1], Maria Rosaria Campise[1], Fabrizio Fabrizi[1] & Piergiorgio Messa[1,4]

1 Unit of Nephrology, Dialysis and Renal Transplant, Department of Medicine, Fondazione Ca' Granda IRCCS Ospedale Maggiore Policlinico di Milano, Milan, Italy
2 Nephrology Unit, Internal Medicine Department, Zagazig University, Zagazig, Egypt
3 CRC "A. M.e A. Migliavacca" Center for Liver Disease, Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy
4 Università degli studi di Milano, Milan, Italy

Correspondence
Prof. Piergiorgio Messa MD, Unit of Nephrology, Dialysis and Renal Transplant, Department of Medicine, Fondazione Ca' Granda IRCCS Ospedale Maggiore Policlinico di Milano, Università degli studi di Milano, Via Commenda 15, 20122 Milan, Italy.
Tel.: +390255034552;
fax +390255034550;
e-mail: piergiorgio.messa@unimi.it

ABSTRACT

Hepatitis C virus (HCV) in kidney transplanted patients (KTx-p) carries a high risk for a worse outcome. This retrospective study evaluates the impact of HCV and of the new direct acting antivirals (DAAs) on patient and graft outcomes in KTx patients. Forty (6.5%) of the 616 KTx-p, who received a kidney transplantation (KTx) in our Centre had antibodies against HCV: 13 were positive for HCV RNA and received DAAs (Group A); 11 were HCV RNA positive and did not receive any treatment (Group B; $n = 11$); 16 were negative for HCV RNA (Group C). All Group A patients had HCV RNA negativity after 12 weeks of treatment, and 12 (92.30%) achieved a sustained virological response (SVR). Only two patients, who had proteinuria greater than 500 mg/day showed a worsening of proteinuria after antiviral therapy in Group A. Liver enzyme elevation and death were significantly more frequent in Group B than other groups. Our results support the notion that active HCV infection negatively affects kidney recipients and that DAA have a high safety and efficacy profile after KTx with no significant negative effect on allograft function, particularly in well-functioning renal grafts.

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Key words
direct acting antivirals, graft outcome, hepatitis-C, kidney transplantation

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Introduction

More than 200 million people are infected with Hepatitis C virus (HCV), all over the world [1]. The approximate mortality rate due to hepatitis C virus infection is 500 000 deaths per year [2].

Chronic kidney disease (CKD) patients are at great risk of HCV infection either because of frequent blood transfusions or for exposure to infection during hemodialysis [3]. Consequently, also in kidney transplanted patients (KTx-p), the prevalence of HCV is higher than the general population [4].

Since it has been long known that HCV infection negatively impacts on the graft and patient outcomes after kidney transplantation (KTx) [5,6], enrolling HCV positive patients in the KTx waiting list was a critical issue up

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to a few years ago. In fact, the available interferon (IFN)-based therapy was only partially effective on dialysis patients and even more critical after transplantation, given the high risk of inducing rejection [7,8].

Before the era of direct acting antivirals (DAAs), Kidney-Disease Improving Global Outcomes (KDIGO) recommended treating HCV before KTx and suggested using IFN plus Ribavirin (RBV) in the post-transplant period only in case of fibrosing cholestatic hepatitis or life-threatening vasculitis [9].

Starting from 2014, a notable modification in HCV treatment has been developed following the availability of IFN-free DAA-based regimens. Early clinical trials have presented a high efficacy of DAAs in HCV treatment both in cirrhotic or non-cirrhotic patients [10,11].

Direct acting antivirals have been also shown to have optimal tolerability and efficacy profiles in HCV treatment in liver transplanted patients [12], and in combined liver–kidney transplant recipients as well [13].

The main aims of the present study were: (i) to evaluate the prevalence of HCV infections in our cohort of KTx-p; (ii) to assess the impact of HCV infection on KTx outcomes; (iii) to evaluate the efficacy and safety of DAAs in our treated patients.

Material and methods

Patients

This is a retrospective single center cohort study carried out on the 616 patients who received a KTx between January 2004 and December 2016 at Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan, Italy.

This retrospective protocol was approved by the Ethic Committee of Fondazione IRCCS Policlinico and was conducted according to the ethical principles of the Helsinki Convention.

All patients underwent screening for HCV infection with anti-HCV antibodies, and HCV-RNA was tested in case of positive serology. Patients who had a positivity for HCV-RNA were evaluated for antiviral therapy with DAAs. Not treated patients had been transplanted before 2014, when only IFN therapy was available.

According to anti-HCV and HCV-RNA status, patients were divided into three groups (Fig. 1):

1. the first group included patients with positive HCV-RNA who received DAAs after KTx (Group A; $n = 13$);

2. the second group was represented by HCV-RNA positive patients who did not receive any antiviral treatment after KTx (Group B; $n = 11$). Among Group B, six patients died or experienced graft failure before the era of DAAs, two patients were transferred to other centers and three patients are still waiting for the starting of DAA treatment;

3. the third group included KTx patients with positive serology and negative HCV-RNA (Group C; $n = 16$).

All the patients studied received a kidney from a deceased donor, and only one patient (Group B) received a kidney from a HCV positive donor.

We evaluated the epidemiological and clinical characteristics and outcomes of the three groups and studied the differences between them as far as age, gender, dialysis vintage, occurrence of liver enzyme elevation ≥2 folds UNL, at any time during the follow-up, death percentage and graft loss.

All patients were followed up during KTx according to the current clinical practice in our Department.

Antiviral treatment was based on DAAs availability at the time of evaluation, and was prescribed by the hepatologists according to HCV genotype, liver disease severity, estimated glomerular filtration rate (eGFR), and concomitant medications, according to international recommendations (EASL Recommendations 2016).

Available DAA-based regimens at the time of the study period were: Sofosbuvir (SOF) plus RBV; Daclatasvir (DCV); SOF/Velpatasvir (VEL); SOF/Ledipasvir (LDV).

The used regimens of DAAs were: sofosbuvir 400 mg + ribavirin in weight based and eGFR matching doses (six patients); sofosbuvir 400 mg + Daclatasvir 60 mg (two patients); sofosbuvir 400 mg + velpatasvir 100 mg (one patient) and sofosbuvir 400 mg + ledipasvir 90 mg (four patients).

As reported in the indications, all patients, studied and treated with SOF, had eGFR > 30 ml/min. In only one case (genotype 2), SOF was administered with eGFR < 30 ml/min because of the absence of alternative regimens SOF-free (see results section).

Duration of DAA therapy and timing of HCV-RNA evaluations

Duration of DAA was 3 months in all patients, while one patient underwent SOF plus DCV for 24 weeks. The median duration of DAA therapy was 3 (3–6) months. In all DAAs treated patients quantitative HCV-RNA was tested at the beginning of treatment, monthly during the treatment and at 4, 12, and 24 weeks after the end of treatment (EOT). Sustained viral response (SVR) was defined by persisting HCV negativity after 12 weeks from the end of treatment.

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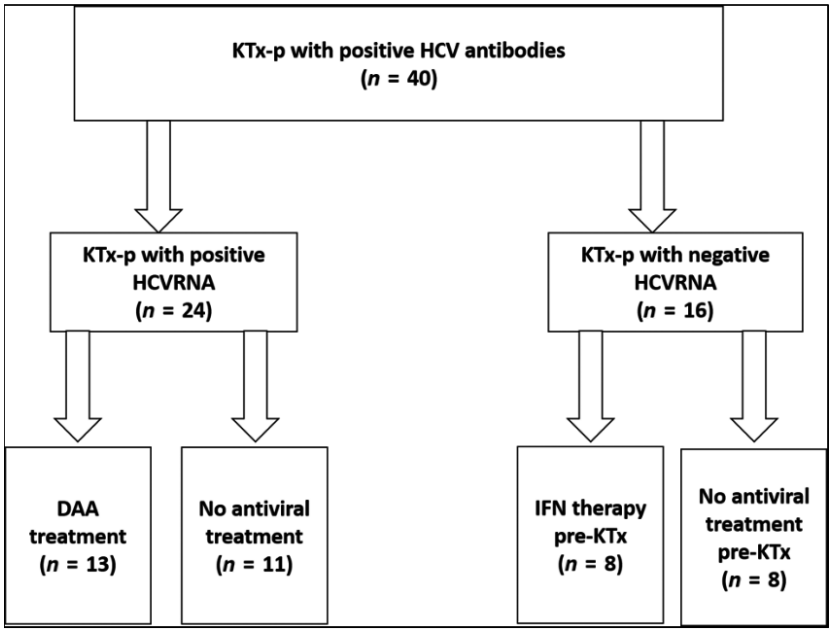

Figure 1 graphical representation of the studied HCV positive cohort. DAA, direct acting antivirals; KTx-p, kidney transplanted patents; KTx, kidney transplantation.

Renal assessment

All biochemical analyses were performed in the same laboratory at our Institution. Jaffè method was used to dose serum creatinine and eGFR was estimated with CKD-EPI formula. Proteinuria was determined by immunoturbidimetric method.

Liver assessment

Quantitative measurement of HCV was tested using Abbott Real Time HCV Kit, while HCV antibody was investigated with ANTI-HCV-G2 Elecsys E 2G Roche. AST and ALT were assessed using AST-PM Cobas C701 Roche and ALT-PM COBAS C701 Roche, respectively. In addition, ALB-2 COBAS C701 Roche and BIT-T-DPD Cobas C701 Roche were used in measurement of serum albumin and blood bilirubin, respectively; whereas, complete blood picture was evaluated by means of Sysmex XN Ditta Dasit.

Fib-4 index, calculated by the formula proposed by Sterling *et al.*, has been used to estimate the extent of liver fibrosis [14].

Time points of biochemical evaluations

Estimated GFR, proteinuria, liver functions and haematological parameters were evaluated within 1 month of completing antiviral treatment and the results were compared to values of those parameters at baseline.

Outcome definitions

All patients were followed up for a mean time of 4.5 [3.0–9.8] years.

The principal renal outcomes considered were: graft loss: need of restart dialysis, and death during the follow-up time.

Statistical analysis

Baseline characteristics of all subjects were described with each variable being expressed as mean ± SD or median (range), according to the normal or not normal distribution, respectively. Chi square test was used to calculate the difference between categorical variables. One-way ANOVA–test and Kruskal–Wallis test were used to check differences between continuous variables of the three included groups. Paired samples *t*-test was used in comparing the post-DAA values to the pre-treatment measurements.

Log-rank analysis with an inverse Kaplan Meier has been performed in survival statistical analysis. A *P*-value < 0.05 was considered to be statistically significant.

Statistical analysis was performed using Statview® and SPSS® version 21.

Results

Hepatitis C virus positive serology was detected in 40 (6.5%) of the overall cohort, with only 24 patients having

also positive HCV-RNA. Thirteen of the HCV-RNA positive patients received anti-HCV treatment with DAAs, while the remaining 11 did not receive any treatment.

The main general characteristics of the three groups of HCV positive KTx-p are described in Table 1. No difference among the three groups was found as far as, age, gender, pre-KTx dialysis duration, or diabetes, before and after KTx, were concerned. Interestingly, 69% and 90% of the patients of group A and group B respectively were transplanted before 2014.

Hepatitis C virus genotypes in the 24 HCV-RNA positive patients are shown in Table 2. The most common genotype was genotype 1b which was present in 13 (54%) patients. Fib-4 index resulted 1.56 ± 1.13 in the HCV-RNA positive patients, without significant differences between group A and group B ($P = 0.34$).

Of the 16 patients who were anti-HCV positive and HCV-RNA negative, eight were treated with pegylated-IFN and RBV before KTx, while the others did not receive any antiviral treatment. Neither IFN-treated nor untreated patients showed HCV-RNA positivity post-transplantation.

Thirteen HCV-RNA positive patients received DAAs post-transplantation: SOF plus RBV in 6 (46%), SOF + DCV in 2 (15%), SOF/VEL in 1 (8%) and SOF/LDV in 4 (31%) patients. The median time of DAA initiation was 61 (12–168) months after KTx.

All patients treated with DAAs had a virological response at EOT, independently of treatment duration.

One of the DAAs treated patients, who had eGFR of 26 ml/min and proteinuria >1500 mg/day before treatment and was submitted to a graft biopsy (membranoproliferative HCV-related GN), was treated with a half dose of SOF and minimal dose (200 mg) of RBV. However, he subsequently developed a further increase of proteinuria (up to 3500 mg/day) and a deterioration of renal function (eGFR 19 ml/min). This patient, though he became HCV-RNA negative at 12 weeks of treatment initiation, developed HCV relapse 2 weeks after completing the antiviral therapy. He was then treated with a half dose of SOF plus DCV 60 mg for 3 months, achieving a time-limited HCV negativity followed by a second relapse after the end of treatment which was associated with a progressive deterioration of renal function and eventually, followed by graft loss. After 1 year, the patient received a second KTx and at the present time he is on therapy with SOF 400 mg + VEL 100 mg + RBV 1000 mg. This treatment is planned to go on for 24 weeks (present renal function: eGFR 60 ml/min; proteinuria 0.06 mg/day).

During DAAs treatment, an increased tacrolimus dose was reported in only one patient treated with SOF/LDV, whereas no other changes in immunosuppressant doses were recorded during other antiviral therapies. Among patients in the group A, no significant differences were observed in eGFR and proteinuria values when comparing variables at baseline levels and after 1 month from the EOT (Table 3).

However, two of these patients experienced a certain degree of KTx function worsening after treatment. The first patient, who had 600 mg/day proteinuria before treatment, showed almost doubling of proteinuria (from around 600 to 1000 mg/day) 3 months after SOF/LDV.

Table 1. General characteristics of the three groups of KTx patients with serologic positivity for HCV [mean ± SD; median (range)] and their distribution between pre-2014 and post-2014 era.

	Total $n = 40$	Group (A) $n = 13$	Group (B) $n = 11$	Group (C) $n = 16$	P
General characteristics					
Age (Years) (mean ± SD)	48.58 ± 9.17	47.0 ± 8.18	51.0 ± 10.0	48.4 ± 9.11	0.58
Males	21 (52.5%)	7 (53.84%)	6 (54.54%)	8 (50.00%)	0.77
Females	19 (47.5%)	6 (46.16%)	5 (45.46%)	8 (50.00%)	
Dialysis vintage (Years)					
Median (range)	8 (0–37)	8 (0–37)	9 (0–31)	7 (0–21)	0.81
Diabetes Mellitus					
Non diabetic	33 (82.5%)	11 (84.61%)	8 (72.72%)	14 (87.50%)	0.39
Diabetic pre-Tx	2 (5%)	1 (7.69%)	0 (0.0%)	1 (6.25%)	
Diabetic post-Tx	5 (12.5%)	1 (7.69%)	3 (27.28%)	1 (6.25%)	
KTx era					
Pre-2014	28 (70%)	9 (69.23%)	10 (90.90%)	9 (56.25%)	**<0.0001**
Post-2014	12 (30%)	4 (30.77%)	1 (09.10%)	7 (43.75%)	

Bold values indicate statistical significant results ($P < 0.05$).

SD, standard deviation.

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Table 2. HCV-RNA title and HCV genotypes in HCV-RNA KTx patients.

	Total *n* = 24	Group (A) *n* = 13	Group (B) *n* = 11
HCV-RNA			
Median (5–95‰) (IU/L)	1 709 400 (44 933–32 654 148)	1 802 869 (44.933–22 010 106)	923 000 (103 721–32 654 148)
Fib-4 Index (mean ± SD)	1.56 ± 1.13	1.78 ± 0.95	1.35 ± 1.26
Genotypes			
1a	4 (16.66%)	2	2
1b	13 (54.16%)	7	6
2a/2c	5 (20.83%)	4	1
3a	1 (4.16%)	0	1
4	1 (4.16%)	0	1

However, he was successfully treated with the addition of an angiotensin receptor blocker (no graft biopsy was performed). The second one was the previously described patient with membranoproliferative HCV-related GN whose proteinuria increased from 1500 to 3500 mg/day 3 months after SOF + RBV. None of the patients treated showed significant variations in eGFR values during the treatment.

As far as haematologic parameters are concerned, DAA-treated patients did not show any significant variation in platelets ($t = 1.11$ & $P = 0.28$), blood hemoglobin was not significantly decreased after RBV-free therapies ($t = 0.31$ & $P = 0.76$) differently from the six patients treated with RBV-containing regimens ($t = 2.68$ & $P = 0.04$; Table 3).

Of note, there was a normalization in SGPT, SGOT, and bilirubin after DAAs completion when compared to the baseline assessments ($t = 3.83$, $P = 0.002$ & $T = 3.68$, $P = 0.003$ & $t = 3.05$, $P = 0.009$, respectively; Table 4). Post-treatment serum albumin values were not significantly different from those shown at baseline ($t = 1.74$ & $P = 0.10$).

The occurrence of liver enzyme elevation by more than two folds the normal range was more frequent in Group B as compared with the Groups A and C (Table 4, $\chi^2 = 6.00$ & $P = 0.04$).

Similarly, death percentage was significantly higher in untreated patients compared to the other groups (Table 4, $\chi^2 = 8.15$ & $P = 0.016$). In the Group B, two of the four deaths were due to hepatic decompensation

Table 3. Comparison of renal, liver and hematological parameters pre versus post-DAAs therapy in group A patients.

Parameter *N* = 13	Pre-antivirals	Post-antivirals	Mean difference	CI	*P*
eGFR (ml/min), mean ± SD	63.53 ± 28.76	61.6 ± 28.05	2.07	−20.92; 25.07	0.21
Proteinuria (g/d), Median (range)	0.182 (0.05–1.5)	0.13 (0.04–3.5)	−0.125	−0.71; 0.46	0.45
S. albumin (g/dl), mean ± SD	4.10 ± 0.42	4.26 ± 0.26	−0.166	−0.45; 0.12	0.10
SGPT (u/l), mean ± SD	44.38 ± 27.69	13.61 ± 3.84	30.76	14.76; 46.77	**0.002**
SGOT (u/l), mean ± SD	42.38 ± 25.77	17.07 ± 4.68	25.30	10.31; 40.30	**0.003**
Blood bilirubin (mg/dl), mean ± SD	0.70 ± 0.33	0.55 ± 0.29	0.149	−0.10; 0.40	**0.009**
Hemoglobin with ribavirin therapy (g/dl) *n* = 6, mean ± SD	13.46 ± 2.00	11.63 ± 1.58	1.83	−0.49; 4.15	**0.04**
Hemoglobin in ribavirin free therapy (g/dl) *n* = 7, mean ± SD	12.81 ± 1.26	12.70 ± 1.73	0.114	−1.65; 1.88	0.76
Platelets, mean ± SD	189 846 ± 60 934	201 769 ± 58 533	−11 923.07	−60 289.10; 36 442.95	0.28

Bold values indicate statistical significant results ($P < 0.05$).

CI, confidence interval; eGFR, estimated glomerular filtration rate; SD, standard deviation; SGPT, serum glutamic pyruvic transaminase; SGOT, serum glutamic oxaloacetic transaminase.

Table 4. Liver enzyme status, outcomes and follow-up duration of studied patients.

	Group (A) n = 13	Group (B) n = 11	Group (C) n = 16	P
Liver enzymes				
Normal	8 (61.53%)	2 (18.18%)	11(68.75%)	**0.04**
Elevated	5 (38.47%)	9 (81.82%)	5 (31.25%)	
Outcomes				
Still under monitoring	12 (92.31%)	3 (27.27%)	9 (56.25%)	
Return to dialysis	1 (7.69%)	2 (18.18%)	4 (25%)	0.47
Transfer to other centre	0 (0.0%)	2 (18.18%)	2 (12.50%)	
Death	0 (0.0%)	4 (36.36%)	1(6.25%)	**0.016**
Post-KTx follow-up period				
Mean ± SD (years)	7.42 ± 3.7	4.9 ± 4.1	4.25 ± 3.53	0.08

Bold values indicate statistical significant results ($P < 0.05$).

SD, standard deviation.

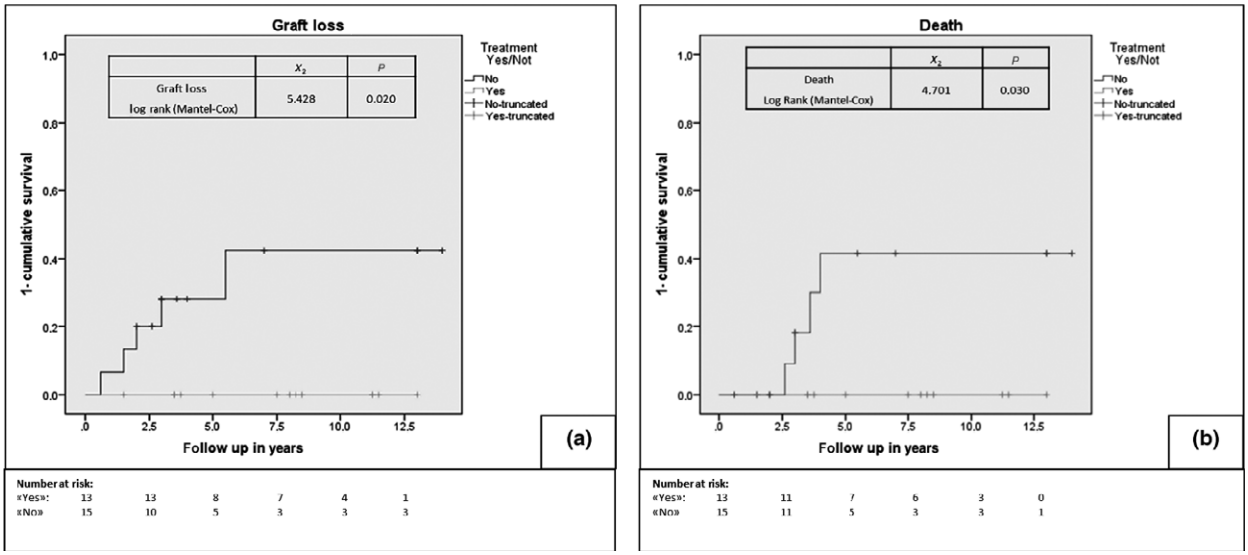

Figure 2 Survival analysis for graft loss (a) and death (b) according to HCV treatment (Yes vs. Not).

(Fib-4 = 5.53) and hepatocellular carcinoma (Fib-4 = 0.75), and the other two patients died of other neoplasms: cancer urinary bladder (Fib-4 = 1.73) and mesothelioma (Fib-4 = 1.89).

There was no significant difference between the three groups as regards graft failure and return to dialysis (Table 4, $\chi^2 = 1.49$ & $P = 0.47$) or in follow-up duration (Table 4, F = 2.6 & $P = 0.08$).

A sub-analysis performed considering only the KTx-p treated during the first year of KTx ($n = 4$) didn't show significant differences with respect to the overall cohort analysis. Those four patients received 3 months of DAAs treatment and initiated their DAA therapy in the 12th month of KTx.

In spite of the relative small number of patients in the study and the few events observed, the effect of the HCV treatment in influencing graft loss and death was also evaluated by means of survival analysis.

In the long term follow-up, the treatment demonstrated to have an impact both on graft loss and on death occurrence (log-rank test, Fig. 2a–b).

Discussion

This retrospective single center study was performed to evaluate the prevalence of hepatitis C virus infection among renal transplant recipients and to study the impact of hepatitis C virus and of the new

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treatment options (DAAs) on both patients and graft outcomes.

The percentage of HCV positive serology among recipients of a KTx in our center was in line with the most recent studies which report a prevalence from 1.8% to 8% of KTx cohorts [1,15–17].

In the present study we analyzed the outcomes of our HCV KTx-p. We divided our cohort into three different groups, according to the presence or not of HCV-RNA positivity and on receiving or not DAAs treatment after KTx.

There were no significant differences between patients included in the three groups regarding their main clinical features, i.e. age, sex, or dialysis vintage before KTx. Notably, the group of patients with active HCV infection, who did not receive DAAs treatment, showed a significantly higher prevalence of elevated liver enzymes – by more than two folds of normal range – throughout the post-transplant follow-up than the other two groups, with group C showing the lowest occurrence of biochemical liver function worsening, as expected.

This result underlines the active negative effect of HCV replication in untreated patients. This is particularly true for immunocompromised patients who are also prone to a higher risk of progression toward hepatic decompensation, if not treated [18]. This represents the rationale for anti-HCV treatment in KTx-p.

A half of transplanted patients, who were positive only for HCV antibodies, had been treated with peg IFN and RBV before transplantation, while the other half had not received any antiviral treatment. None of these patients developed positivity for HCV-RNA after KTx. This last result could in part be explained by the consideration that this group includes the patients who successfully responded to the old treatment schedules or those who spontaneously cleared the virus without any treatment, representing those with the most favorable characteristics for the treatment with IFN (HCV genotype and fibrosis status).

As already mentioned, in the group B two of the four deaths were due to hepatic decompensation and hepatocellular carcinoma. It could be argued that the ongoing HCV infection, in these immunosuppressed patients, could have played a relevant synergistic causal role.

All 13 patients who received DAAs therapy achieved an EOT response (i.e. HCV-RNA negative at the EOT), with 12 (92%) of them finally achieving a SVR**.** Indeed, the only patient who experienced a relapse, as already described, was treated with modified treatment schedule with reduced doses of SOF while on dialysis.

Our results on patients treated with SOF-based regimens are in line with those reported in other series. Lubetzky *et al.* [19], detected 100% HCV negativity after 12 weeks of DAAs in 31 KTx-p [genotype 1 ($n = 28$), genotype 2 ($n = 2$) genotype 3 ($n = 1$)] and found a sustained viral response in 97% of treated patients at 24 weeks.

Kamar *et al.* and Sawniski *et al.* reported 100% SVR12 in 25 [genotype 1a ($n = 4$), genotype 1b ($n = 15$), genotype 2 ($n = 2$), genotype 3 ($n = 1$), genotype 4 ($n = 3$)] and 20 [genotype 1a ($n = 6$), genotype 1b ($n = 6$), genotype 1a/1b ($n = 1$), genotype 1 ($n = 4$), genotype 2b ($n = 2$), genotype 2a/2c ($n = 1$)] KTx-p [20,21], while Lin *et al.* revealed that SVR12 was found in 91% of 24 kidney recipients [genotype 1a ($n = 14$), genotype 1b ($n = 4$), genotype 1 ($n = 3$), genotype 2 ($n = 3$)], which was inferior to that expected from registration trials and reported in studies conducted on similar patient populations. This discrepancy was attributed to the heterogeneous characteristics of the patients included and to the higher prevalence of patients with cirrhotic decompensated liver disease (21%) [22].

Therefore, our results are in line with those previously reported in other studies, and strongly reinforce the suggestion of high efficacy of DAAs in KTx-p with chronic HCV infection.

In addition, the best patient and graft outcomes were observed in group A as compared with the other two groups. In fact, we did not observe any significant deterioration of renal function after completing the treatment course in the whole group, with the exception of the patient with MPGN who showed a deterioration of GFR and a worsening of proteinuria after DAAs.

It is worth mentioning that, no significant changes in proteinuria were observed in group A after DAAs treatment, apart the two patients mentioned above.

The same safety profile was also reported by other authors. Sawiniski *et al.* declared that there was no significant deterioration of GFR of all DAAs treated patients and reported that evaluation of proteinuria in 14 patients revealed no significant changes in proteinuria following anti-HCV completion. In agreement, Suarez Benjumea *et al.*, demonstrated that DAAs did not affect graft function or proteinuria; however, no details about pre-treatment proteinuria were provided by both studies.

In line with our results, Lin *et al.* reported a slight progression of proteinuria after DAAs therapy in two patients with pre-treatment proteinuria of 1.9 and 9 g/day. Both patients showed collapsing glomerulopathy on graft biopsy performed after treatment. Given the significant proteinuria before receiving the antiviral therapy, the authors suggested that the collapsing features could be related to the basal graft condition and not to DAA treatment.

Following the same line, Lubetzky *et al.* [18] found that worsening of proteinuria, after DAAs therapy, was significant only in the six patients who started DAAs therapy with proteinuria greater than 500 mg/g; however, there was no clear evidence of a nephrotoxic effect of DAAs.

We believe that the impact of DAAs on protein loss in urine, in KTx with gross proteinuria, should be carefully evaluated in depth larger studies using variable regimens with monitoring of renal pathology changes after DAAs therapy.

Our study revealed that changes in immunosuppressants during DAAs therapy were infrequent, since an increase in tacrolimus dose was necessary in one patient, only. Sawiniski *et al.* needed tacrolimus dose adjustment in nearly half of DAAs treated patients [20]. They justified this finding by not only the drug-drug interaction with simepravir, that was frequently used in their cohort, but also by improved liver function and drug metabolism after DAA therapy.

As expected, our results reported an improvement in liver function tests after viral eradication. This is in line with other published studies [20,21] and with the findings of Beinhardt *et al.*, [23] who evaluated DAA not only in 8 KTx-p, but also in seven combined liver-kidney transplants and 10 dialysis patients.

Overall, in spite of the relatively small sample size of this study and the unavailability of fibroscan evaluations, our results reinforce the belief about the high efficacy and safety of direct acting antivirals used after renal transplantation.

Conclusions

Given the high risk of liver disease progression and increased mortality in KTx-p with active HCV infection, HCV treatment is highly recommended in patients affected by CKD, either pre- or post-transplantation.

The use of DAAs in KTx-p has displayed excellent safety and efficacy profiles with no negative effects on allograft function; however, larger studies should be performed on KTx-p with a special consideration for patients with GFR less than 30 ml/min and/or proteinuria more than 500 mg/day. In this sense, the use of "pangenomic" DDAs with SOF-free combination, available from the end of 2016, could represent a good option for those patients [24].

Authorship

MG and PM: study concept and design. MG and CMA: acquisition of data. MG and CMA Statistical analysis. MG, CMA, and PM: analysis and interpretation of data. MG, CMA, MTG, MRC, FF, and PM: drafting of the manuscript. PL and RD: critical revision of the manuscript.

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Conflicts of Interest

The authors have declared no conflicts of interest.

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