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HCV-positive kidney transplant patients treated with direct-acting antivirals maintain stable medium-term graft function despite persistent reduction in tacrolimus trough levels

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Abstract

Background/aim: Direct-acting antivirals (DAAs) have improved the treatment of HCV-positive kidney transplant recipients (KTRs). However, their medium-term follow-up effects on graft function are conflicting. This study aimed to analyze how the interplay between DAAs, calcineurin inhibitors (CNI), and HCV eradication impacts 12-month kidney graft function.

Methods: This double-center retrospective study with a prospective follow-up enrolled 35 KTRs with HCV treated with DAAs for 12 weeks. We compared three parameters: estimated glomerular filtration rate (eGFR), 24-h proteinuria, and CNI trough levels at three time points: baseline, end of treatment (EOT), and 12 months later.

Results: Kidney allograft function remained stable when comparing baseline and 12-month post-treatment values of eGFR (60.7 *versus* 57.8 ml/min; $p = 0.28$) and 24-h proteinuria (0.3 *versus* 0.2 g/24 h; $p = 0.15$), while tacrolimus (Tac) trough levels underwent a statistically significant decline (6.9 *versus* 5.4 ng/ml; $p = 0.004$). Using an ongoing triple Tac-based maintenance therapy as a conservative measure, a dose escalation of Tac was applied only in seven patients. No variation in CyA and mTOR levels was detected.

Conclusion: DAA therapy is safe and effective in HCV-positive KTRs. It also produces a persistent significant reduction in Tac trough levels that does not influence graft function at 12 months.

Keywords: calcineurin inhibitors, DAAs, HCV infection, immunosuppressive drug minimization, renal function

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Introduction

Hepatitis C virus (HCV) infection affects approximately 1.8–8% of kidney transplant recipients,[1,2] and the infection has a negative impact on both patient and graft survival.[3–8]

Interferon-based antiviral regimens against HCV, the only available antiviral therapy over the last 30 years, did not represent a consistent option in the kidney transplant population due to their low efficacy (18–34%), poor tolerability, and high risk of interferon-induced graft rejection (12.5–51%).[9,10]

In the last years, new oral anti-HCV agents have allowed the possibility of HCV eradication in various difficult-to-treat patients, including kidney transplant recipients (KTRs).[11–14] However,

although direct-acting antivirals (DAAs) are highly effective, they present a substantial risk for relevant drug–drug interactions with immunosuppressants. The calcineurin inhibitor (CNI) tacrolimus (Tac), which is the cornerstone of anti-rejection therapy after transplantation, has a narrow therapeutic index and high inter- and intra-patient variability.[15] Thus, the potential interaction of DAAs with CNI after kidney transplantation is a relevant issue in terms of renal graft protection.[16] HCV represents an additional and multifaceted player in renal graft function due to its complex interactions with the immune system and chronic inflammation mediators consisting of a strong cytokine and chemokine network activation.[17,18]

Currently, the interplay involving DAAs, the pharmacokinetics of immunosuppressive drugs, and the decline in inflammatory cytokine and chemokine production related to HCV inflammation and its impacts on kidney graft function in KTRs are conflicting. Indeed, the dose adjustment of immunosuppressive drugs in this complex scenario represents an important issue for clinicians.

In this study, we aimed to evaluate the impact of DAAs on the medium-term follow-up of renal graft function and immunosuppressant trough levels in a cohort of HCV-positive KTRs who underwent 12 weeks of DAA therapy. In addition, we also evaluated the efficacy in terms of HCV eradication and safety of DAA therapy in patients in this setting.

Materials and methods

This study was a double-center retrospective study with a prospective follow-up analysis of 35 post-kidney transplant patients with chronic HCV infection, treated with DAAs from January 2015 to April 2018 at the Gastroenterology and Nephrology, Dialysis and Transplantation Units of University Hospital, Policlinico of Bari, Italy, and at the Division of Nephrology, Dialysis and Transplantation of Policlinico 'San Martino' Hospital, Genoa, Italy.

The study protocol was in accordance with the Declaration of Helsinki as revised in 2013 and approved by the local Ethics Committee (ethics approval number: 7327, 27 April 2022). Written informed consent was obtained from each patient.

The inclusion criteria were HCV-infected kidney transplant patients who were able to sign informed consent, aged over 18 years, and who had regular follow-up.

Plasma HCV-RNA was analyzed using the COBAS AmpliPrep/COBAS TaqMan HCV Test, v2.0 (Roche Molecular Systems), with a lower limit of quantification (LLOQ) of 15 IU/ml. HCV genotype and subtype were determined using the Versant HCV Genotype INNO-LiPA 2.0 assay (Siemens).

The liver disease stage was evaluated before therapy using a combination of clinical, laboratory, and imaging features, including abdominal ultrasound (US) and liver stiffness measurement by transient elastography (FibroScan; ECHOSENS).

A stiffness of 9.5 kPa was used to rule out advanced fibrosis (F3–F4) and the cutoff of 12.5 kPa to detect cirrhosis.[19]

The choice of appropriate DAA regimen was based on HCV genotype, estimated glomerular filtration rate (eGFR), treatment history, and liver transplant function according to the Italian Association of the Study of the Liver (AISF) guidelines.[20,21] Ribavirin was prescribed according to eGFR value and body weight (1000 mg daily for weight <75 kg and 1200 mg daily for weight >75 kg). A sofosbuvir (SFB)-free regimen was used in KTR with impaired renal transplant function (GFR lower than 30 ml/min per 1.73 m^2).

Sustained viral response (SVR) was defined as undetectable serum HCV-RNA at 12 weeks after treatment (SVR12). Viral relapse was defined as the subsequent reappearance of serum HCV-RNA at any time after having achieved undetectable HCV-RNA at end of treatment (EOT).[22]

In all patients, liver, kidney, viral parameters, and level of immunosuppressive drugs were collected before therapy, every 2 weeks during the first month, and then monthly until the EOT as well as at 12, 24, and 48 weeks after the end of therapy.

Statistical analysis

We assessed the normal distribution of continuous variables using the Shapiro–Wilk test and expressed them as mean and standard deviation

(SD) or median and interquartile range (IQR). We reported categorical variables as percentages. We compared the mean values of eGFR, 24-h proteinuria, and immunosuppressant levels (i.e. mTOR inhibitors, Tac, and Cya) at three time points (baseline, EOT, and 1-year follow-up) using the one-way repeated-measures analysis of variance (ANOVA) with Bonferroni's *post hoc* analysis. If a significant change was found over time in any outcome analysis, we explored the association of relevant demographic, nephrological, and hepatological parameters with the observed outcome variation using univariate linear regression models. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using the SPSS Software. A sample size calculation was not performed for the retrospective nature of the study and for the sample size which is not high.

Results

Clinical baseline characteristics and immunosuppressive/DAA regimens

We evaluated 19 men and 16 women, all Caucasian, with ages ranging from 26 to 71 years (median, 57). Genotype 1b was the predominant HCV subtype ($n = 19$). The median viral load before treatment was 2.0×10^6 IU/ml (range, 1.0×10^6–5.7×10^6 IU/ml).

One patient was HIV-positive. Evidence of past infection with hepatitis B (hepatitis B core antibody positivity) was present in eight patients (22.85%). The median time between the last kidney transplantation and the start of DAA therapy was 96 months (range, 36–192 months). Up to 60% of the patients had hypertension. Twenty-five patients were treatment-naive (71%) and eight had stage disease F3 or F4 by real-time elastography and/or stigmata of advanced liver disease by US without signs of clinical impairment in liver function.

The most commonly used DAA regimens included the following: SFB/ledipasvir ($n = 16$, 46%), SFB/velpatasvir ($n = 6$, 17%), SFB + daclatasvir ($n = 7$, 20%), SFB ($n = 3$, 8%), ritonavir/paritaprevir/ombitasvir + dasabuvir ($n = 2$, 5.71%), and paritaprevir/ombitasvir ($n = 1$, 2.81%). Ribavirin was added in eight of them (23%).

Immunosuppression was based on Tac, Cya, and mTOR inhibitors in 57%, 23%, and 11%, respectively. Mycophenolate mofetil (MMF) was used in 72% of the cases.

Most of the patients were treated with a triple regimen consisting of low-dose steroids in combination with Tac and MMF ($n = 12$) and a double combination of Tac and MMF ($n = 6$); two patients were treated with steroids in combination with azathioprine; one patient was treated with steroids and Tac alone; two patients were treated with steroids plus Tac and everolimus. Cya-based immunosuppression was used in three patients in combination with MMF and in two patients with either MMF or steroids. Therapeutic schemes and patients' baseline characteristics are summarized in Table 1.

Renal allograft function

Renal allograft function remained stable during therapy with DAA (Table 2). All patients exhibited stable eGFR rates between baseline and after 12 months of follow-up (eGFR: 60.7 *versus* 57.8 ml/min; $p = 0.28$) as well as stable 24-h proteinuria values (0.3 g/24 h *versus* 0.2 g/24 h; $p = 0.15$). No significant impairment in renal allograft function was observed during 12 weeks of treatment or during the post-treatment follow-up period, and no documented episodes of allograft rejection were recorded either during antiviral therapy or at 12 months of evaluation.

Virological outcomes and adverse events

The sustained virological response at 12 weeks was 97.14%. All patients in stage F0/F1/F2 achieved SVR, whereas one of eight patients in stage F3/F4 did not. This patient was a 66-year-old man, genotype 3a, treatment-experienced, with positivity for hepatitis B core antibody and HIV affected by advanced liver disease. He received a kidney transplant for end-stage renal disease (ESRD) due to cryoglobulinemic nephropathy and was treated with a combination of SFB plus daclatasvir.

The DAA therapy was well tolerated in all patients except one who required discontinuation. This patient was a 30-year-old woman, treatment-naive, genotype 1b, who received a kidney transplant for ESRD due to post-streptococcal

Table 1. Baseline characteristics of 35 HCV-positive kidney transplant recipients treated with a 12-week course of direct-acting antivirals.

Characteristic	Patients ($n=35$)
Sex, *n* (%)	
Female	16 (46)
Male	19 (54)
Age, median (IQR), years	57 (52–62)
Number of kidney transplantations, *n* (%)	
1	24 (69)
2	9 (25)
3	2 (6)
Etiology of renal disease, *n* (%)	
Hereditary disease	10 (29)
Glomerulonephritis	9 (25)
Other[a]	6 (17)
Unknown	10 (29)
Chronic kidney disease stage, *n* (%)	
1–2	14 (40)
3–4[b]	21 (60)
HCV-RNA levels, median (IQR), IU/ml	2.0×10^6 (1.0×10^6–5.7×10^6)
Liver and metabolic parameters	
Aspartate aminotransferase, mean ± SD	37.2 ± 25.4
Alanine aminotransferase, mean ± SD	34.3 ± 29.3
Gamma-glutamyl transferase, mean ± SD	56.1 ± 39.2
Total bilirubin, median (IQR), mg/dl	0.61 (0.41–0.92)
Glycaemia, median (IQR), mg/dl	98 (85–120)
Total cholesterol, median (IQR), mg/dl	155 (137–196)
Triglycerides, median (IQR), mg/dl	120 (88–155)
Hemoglobin, mean ± SD, g/dl, mean (SD)	12.9 ± 1.9
Platelet count, median (IQR), per mm^3	180 (158–235)
HCV genotype[c]	
1-1A	5 (14)
1B	19 (54)
2-2A/2C	5 (14)
3-3A	3 (9)
4-4C/4D	3 (9)
Liver stiffness, *n* (%)	
F0–F2	23 (66)
F3–F4	12 (34)
History of previous antiviral treatment, *n* (%)	
Naïve	25 (71)
Experienced	10 (29)
DAA regimen, *n* (%)	
Sofosbuvir/Ledipasvir	16 (46)
Sofosbuvir/Velpatasvir	6 (17)
Sofosbuvir	3 (8)
Sofosbuvir + Daclatasvir	7 (20)
Ombitasvir/Paritaprevir/Ritonavir ± Dasabuvir	3 (9)
Ribavirin administration, *n* (%)	8 (23)
SVR achievement, *n* (%)	34 (97)
Time from transplantation to DAA start, median (IQR), months	96 (36–192)
Immunosuppressive schedule *n* (%)	
Tacrolimus	20 (57)
Tacrolimus + Mycophenolate mofetil + steroids	12 (60)
Tacrolimus + Mycophenolate mofetil	6 (30)
Tacrolimus + Everolimus + steroids	1 (5)
Tacrolimus + Steroids	1 (5)
Cyclosporine	8 (23)
mTOR inhibitors	4(11)
Others	3 (9)

DAA, direct-acting antivirals; IQR, interquartile range; SD, standard deviation; SVR, sustained viral response.
[a]Including diabetes mellitus (2 patients), cryoglobulinemia (2 patients), amyloidosis (1 patient), and lupus nephritis (1 patient).
[b]Including 20 patients in stage 3 and 1 patient in stage 4.
[c]Genotype 1 (1 patient), 1A (4 patients), 2 (2 patients), 2A/2C (3 patients), 3 (2 patients), 3A (1 patient), 4 (2 patients), 4C/4D (1 patient).

Table 2. Analysis of outcome variation from baseline to 1-year follow-up.

Outcome	Number of patients	Baseline Mean (SD)	End of treatment Mean (SD)	1-year follow-up Mean (SD)	*p* value
eGFR, ml/min	35	60.7 (19.5)	57.9 (19.4)	57.8 (15.9)	0.28
Uric acid, mg/dl	35	6.1 (1.3)	6.2 (1.2)	6.0 (0.9)	0.72
24-h proteinuria, g/24 h	30	0.3 (0.1)	–	0.2 (0.1)	0.15
Immunosuppressant levels, ng/ml					
Tacrolimus	20	6.9 (2.1)	5.6 (1.5)	5.5 (1.3)	0.004[a]
Cyclosporine	7	289.9 (251.6)	261.1 (214.4)	255.3 (238.6)	0.66
mTOR inhibitors	4	6.9 (1.9)	5.7 (1.4)	4.9 (0.9)	0.13

eGFR, estimated glomerular filtration rate; SD, standard deviation.
[a]Bonferroni's *post hoc* analysis identified a significant variation only in the comparison between baseline and 1-year follow-up values ($p = 0.01$).

glomerulonephritis. After 2 months of ombitasvir-paritaprevir-ritonavir + dasabuvir, she experienced a hypotensive shock after accidental coadministration with barnidipine, which increases the concentration of calcium channel blockers, inhibiting CYP3A4 by ritonavir.[22] Nevertheless, she went on to achieve SVR.

Two of the 35 patients reported asthenia, and the appearance of anti-mitochondrial antibodies at a 1:160 title was observed in one patient without any clinical symptom. Only two patients developed donor-specific antibodies without impact on renal function. No patients experienced a virological relapse.

Finally, no acute rejection episodes were observed in the population during the 12-month follow-up period.

Clinical outcomes and immunosuppression levels

We compared the mean values of three outcomes (eGFR, 24-h proteinuria, and immunosuppressive levels) at three time points: baseline, EOT, and 1-year follow-up. ANOVA showed a statistically significant decline only in Tac levels (6.9 *versus* 5.5 ng/ml, respectively; $p = 0.004$) (Table 2). In detail, in Bonferroni's *post hoc* analysis, the significant decline in Tac levels was confirmed only between baseline and 1-year follow-up ($p = 0.01$). Among the 20 patients on Tac therapy, a conservative measure approach in the dose escalation of immunosuppression was adopted based on an ongoing triple-combined regimen. Only seven patients (30%), belonging to the double-therapy group, were found, according to a multidisciplinary discussion between hepatologists and nephrologists, to need a dose escalation of the daily dosage of Tac to maintain adequate trough levels.

The effects of each categorical and continuous variable analyzed one at a time on the change in mean Tac levels are outlined in Table 3. In detail, sex was statistically associated with a significant reduction in mean Tac levels from baseline through to the end of observation (p values for Tac levels <0.05).

The effect of each categorical and continuous variable analyzed on the change of Cya and mTOR inhibitor levels was not performed as only seven and four patients, respectively, took these regimens. However, no significant changes in Cya or mTOR levels were detected, as shown in Table 2.

Discussion

Here, we present the results of the medium-term follow-up effect of HCV eradication on HCV kidney transplant recipient's graft function following 12 weeks of DAA therapy. The most important finding of this study is that DAA therapy is associated with medium-term follow-up preservation of

Table 3. Univariate analysis of the association of demographic, nephrological, and hepatological parameters with variation in tacrolimus levels (from baseline to 1-year follow-up).

Variable	Number of patients ($n = 20$)	Change in tacrolimus levels[a] (mean ± SD), ng/ml	*p* value
Sex			0.03
Female	9	−2.3 ± 0.9	
Male	11	−0.6 ± 2.2	
Age, years			0.07
⩽50	5	−2.7 ± 0.9	
>50	15	−1.0 ± 0.5	
Number of kidney transplantations			0.57
1	10	−1.1 ± 2.0	
2–3	10	−1.6 ± 1.8	
Chronic kidney disease stage			0.96
1–2	9	−1.4 ± 0.6	
3–4	11	−1.4 ± 0.6	
Liver stiffness			0.82
F0-F2	13	−1.3 ± 1.9	
F3–F4	7	−1.5 ± 2.0	
History of previous antiviral treatment			0.58
Naïve	13	−1.6 ± 2.0	
Experienced	7	−1.1 ± 1.8	
DAA regimen[b]			0.73
Sofosbuvir/Ledipasvir	9	−1.3 ± 2.2	
Sofosbuvir/Velpatasvir	5	-1.0 ± 1.8	
Sofosbuvir + Daclatasvir	4	−2.0 ± 1.3	
Ribavirin administration			0.89
Yes	5	−1.5 ± 2.4	
No	15	−1.3 ± 1.8	
Time from transplantation to DAA start, months			0.54
⩽24	6	−1.8 ± 2.0	

(Continued)

Table 3. (Continued)

Variable	Number of patients ($n = 20$)	Change in tacrolimus levels[a] (mean ± SD), ng/ml	p value
>24	14	−1.2 ± 1.9	
Immunosuppresant regimen			0.24
TAC + MMF or everolimus + Steroids	13	−1.0 ± 1.6	
TAC + MMF or steroids	7	−2.0 ± 2.3	
Tacrolimus dose increase during treatment			0.42
Yes	7	−0.9 ± 2.0	
No	13	−1.6 ± 1.9	

DAA, direct-acting antiviral agent; MMF, mycophenolate mofetil; SD, standard deviation; TAC, tacrolimus.
'SVR achievement' was not evaluated since only 1 out of 20 patients did not achieve SVR.
[a]Values were calculated as: (1-year follow-up value) – (baseline value).
[b]One single patient treated with sofosbuvir and one single patient treated with ombitasvir/paritaprevir/ritonavir were not included in the analysis.

renal graft function in KTRs despite significantly lower Tac trough levels that persisted even 1 year from the end of antiviral therapy. This finding adds to the previous knowledge and novel information about the interplay between CNI-associated nephrotoxicity and the likely effect of HCV eradication on CNI metabolism showing, accordingly, a guidance for managing maintenance immunosoppression.[23]

The possibility of eradicating HCV in these patients has been controversial for many years as interferon- and ribavirin-based regimens resulted largely, but not applicable, in renal transplantation due to poor tolerance and interferon's immune-modulating effects which were deemed to be possibly related to an increased risk of organ rejection.[1,24] In 2014, the advent of DAAs represented a new and effective treatment option also for renal transplant patients affected by HCV infection in view of their safety and high efficacy.[25]

Although DAAs are highly effective, their potential interactions with immunosuppressive drugs are a relevant issue in terms of renal graft protection.[16] Moreover, Tac, the pivotal immunosuppressive drug post-transplantation, has a narrow therapeutic index and high inter- and intra-patient variability. Up to now, the results on medium-term effects of DAAs on kidney graft function and immunosuppressive drug pharmacokinetics in KTRs are limited and conflicting. Indeed, data on the medium-term follow-up effect of DAAs in HCV-positive patients who have undergone renal transplantation are fragmentary and refer to the different lengths of follow-up. In their multicenter, phase II clinical trial, Colombo *et al.*[26] evaluated the treatment of 114 kidney graft recipients, with predominantly genotype 1 infection, randomly assigned to receive ledipasvir: SFB for 12 or 24 weeks. Overall, there was no significant difference between the two therapeutic regimens in terms of SVR, while renal function remained stable in most patients after a very short follow-up period of 4 weeks. Sawinski *et al.*[27] identified 20 kidney recipients treated with DAAs. Their most commonly used regimen was SFB in combination with simeprevir, which has competitive interactions with CNI.[28,29] After 3-month post-treatment follow-up, they observed a significant impact on Tac levels [median Tac level, 5.9 ng/ml (interquartile range (IQR), 5.1–6.7) *versus* 4.5 ng/ml (IQR, 3.2–4.9, respectively; $p = 0.006$] without significant impairment in serum creatinine or proteinuria.[29]

A similar effect was observed in the study of Kamar *et al.*[30] in which 25 KTRs with chronic HCV infection were treated with an SFB-based

regimen obtaining a rapid virological response without significant adverse events during a 12-week follow-up. In this case, no significant change in eGFR was observed although patients experienced a significant decrease in Tac levels during treatment with the doses of Tac left unchanged during and after therapy. Opposite results were reported when the impact of DAAs on graft function and immunosuppressive drug pharmacokinetics was analyzed in HCV KTRs after a longer follow-up. Fernández-Ruiz *et al.*[31] showed that eGFR, while remaining stable during antiviral therapy, significantly decreased at 12 months of follow-up (57.3 ± 22.7 ml/min *versus* 52.9 ± 21.1 ml/min; p value for trend >0.001). Moreover, a significant decrease in Tac trough levels was found during the first month of treatment. However, differently in our study, up to 80% of their patients received a Tac dose escalation during DAA therapy, leading to a significantly higher 12-month Tac trough level in comparison with EOT (7.8 ± 2.1 ng/ml *versus* 6.7 ± 2.0 ng/ml; $p = 0.002$). This finding could in part explain the impairment of kidney function during the 12-month follow-up in their patients considering that, besides immunological mechanisms, CNI nephrotoxicity is considered among the main mechanisms in the gradual reduction of eGFR in KTRs over years.[32] Differently, in our study, using the ongoing triple Tac maintenance therapy as a conservative measure ($n = 13$), Tac daily doses were not increased, and in view of the stable eGFR level and their favorable immunological previous history, only strict monitoring was planned. Only 6 of 20 patients on a double immunosuppression treatment were deemed suitable for a dose escalation of Tac. Of note, no difference was found between Tac trough levels at the third time point between these 6 patients and the remaining 13 patients on the triple regimen. All patients had been managed according to a strict time follow-up following discussion between hepatologists and nephrologists. When we analyze the effect of demographic, nephrological, and hepatological parameters on the variation in Tac levels from baseline to 1-year follow-up, the only predictive factor associated with the reduction in Tac trough level was female sex ($p = 0.03$). No variation in CyA and mTOR trough levels was detected.

When dealing with the changes in CNI trough levels during DAA therapy, different explanations, arising from studies on both kidney and liver transplantation settings,[27,33] have been described: (1) the already discussed altered pharmacokinetics, namely, drug–drug interaction and (2) the improvement in Tac metabolism related to liver function improvement as well as (3) the influence of the concomitant use of second-line immunosuppressive drugs or other drugs, in accordance with the comorbidity of the patients. An interesting finding in our study is based on the association between Tac variation and age, which is according to the age influences on the pharmacokinetics of tacrolimus already reported in both pediatrics and adult organ transplant settings.[34]

As regards the improvement in liver function, in our study, even if eight patients were found to have mild/moderate liver fibrosis, none of them had biochemical or clinical signs of liver dysfunction. An alternative possible explanation to our results comes from the upregulation of cytochrome CYP3A4 following HCV eradication.[29] CYP3A4 is downregulated by proinflammatory cytokines [interleukin 1, interleukin-6, tumor necrosis factor alpha (TNFα) and transforming growth factor beta (TGFβ)] which are part of the typical inflammatory milieu during chronic HCV hepatitis. The eradication of the infection would increase the enzymatic activity of CYP3A4 and consequently decrease the Tac trough level at 12 months. Interestingly, the lower disposal of CNI did not translate into the risk of acute rejection in our patients. Thus, the unintended consequence of our study is that Tac trough level reduction observed in HCV KTRs treated with DAAs can be considered as a kind of CNI minimization strategy adopted to improve renal function and reduce the risk of graft loss in the medium-term follow-up after kidney transplantation.[35]

Our study is limited by the small sample size, its retrospective nature, and the lack of an immunological follow-up by donor-specific antibody dosing and/or graft biopsy during a medium-term follow-up. Thus, results need to be confirmed by further prospective well-designed immunological study.

Conclusion

In conclusion, according to the previous observations, this study confirms the effectiveness of DAAs in the treatment of HCV KTRs. As a significant novelty, during 12 months post-treatment, renal function was maintained despite the persistent lower Tac trough levels. The latter result

comes from the interplay between DAAs, CNI, and HCV eradication, adding new arguments to immunosuppression minimization strategies in KTRs.

Declarations

Ethics approval and consent to participate

The study protocol was in accordance with the Declaration of Helsinki as revised in 2013 and approved by the local Ethics Committee (ethics approval number: 7327, 27/04/2022). Written informed consent was obtained from each patient.

Consent for publication

Not applicable.

Author contributions

Maria Rendina: Conceptualization; Project administration.

Ernesto Paoletti: Investigation.

Nunzia Labarile: Writing – original draft.

Antonella Marra: Writing – original draft.

Andrea Iannone: Formal analysis; Methodology.

Antonino Castellaneta: Data curation.

Elisabetta Bussalino: Data curation.

Maura Ravera: Data curation.

Antonio Schena: Supervision.

Nicola M. Castellaneta: Data curation.

Michele Barone: Writing – review & editing.

Simona Simone: Visualization.

Loreto Gesualdo: Validation.

Alfredo Di Leo: Validation.

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