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Research Article

Direct action antivirals are effective in the total eradication of HCV in renal transplants

Abstract

Introduction: The main objective of our study was to analyze the effectiveness of antiviral treatment (conventional or with direct-acting antivirals (DAA)) for total eradication of Hepatitis C Virus (HCV) in kidney transplant (KT) recipients. DAA are known drugs that are approved by FDA for clinical and pre-clinical investigations. The efficacy was analyzed by testing for the presence of HCV- ribonucleic acid (RNA) in the pellets obtained after ultracentrifugation of follow-up plasma samples and in peripheral blood mononuclear cells (PBMC) from patients with HCV infection who had achieved a sustained virological response (SVR). The safety, and the renal and hepatic repercussions of the antiviral treatment were also evaluated.

Patients and methods: We evaluated 18 adults receiving KT, whose HCV infection had been treated with antiviral therapy. HCV RNA was tested by real-time RT-PCR in PBMC and in 2 ml of plasma after ultracentrifugation.

Results: The predominant HCV genotype was 1b (78.6%), followed by 3a (14.3%) and 2a-2c in 1 patient (7.1%). Of the 18 patients, 13 received treatment post-KT with DAA (8 as first treatment and 5 as retreatment due to relapse). The other 5 patients were responders to INF, INF-RBV and one to DAA pre-KT.

In none of the 14 recipients of KT treated with DAA the presence of HCV RNA was detected neither in PBMC nor in plasma after ultracentrifugation. Viral RNA was also undetectable in the PBMC of the 4 patients with SVR after treatment with IFN (monotherapy or with RBV). However, one of them was positive to HCV RNA in the ultracentrifuged plasma. This patient, male, and diagnosed with HCV genotype 1b, had received INF-PEG monotherapy prior to KT.

During a mean follow-up time of 26.61 ± 6.03 months after antiviral treatment of the patients treated with DAA, we observed a significant increase in protein / creatinine ratio (P = 0.001), although there was no impact on the renal function of the graft. Liver function improved significantly as a decrease in AST and ALT (P = 0.006 and P = 0.011), respectively. The worst evolution of the renal graft of the serie was in the recipient with detectable HCV RNA in the ultracentrifuged plasma, due to infection by polyoma virus after a humoral rejection. Liver function despite having SVR, only persisted altered in this patient.

Conclusions: Although a small series of patients are treated and more studies are required, treatment with DAA is effective for complete eradication of the virus unlike conventional treatments with INF, in which HCV can persist being undetectable with conventional techniques. This persistence seems to affect post-KT evolution.

Introduction

Between 1.8 and 8% of patients receiving Kidney Transplantation (KT) are infected with the Hepatitis C virus (HCV) [1]. Despite the higher risk of complications compared to KT recipients without classical HCV, their survival is greater when compared to that of patients on hemodialysis [2]. Conventional antiviral therapies did not eliminate HCV efficiently and safely. Interferon-α, ribavirin and therapies based on protease inhibitors were the best options [3]. However, interferon α is associated with poor sustained viral response (SVR) (negative viral load after 12 weeks of antiviral treatment termination) (13-43%) and is contraindicated in the post-KT due to the high prevalence of adverse effects (rejection of the renal graft) [4]. Monotherapy with ribavirin was not effective and compared to protease inhibitors, its use was limited in

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post-KT due to interactions with calcineurin inhibitors and severe adverse effects [5].

The direct-acting antivirals (DAAs) have recently been considered safe for the treatment of HCV in post-TR [6-9]. KT recipients who received at least two different classes of DAA achieved SVR at 12 weeks by 90% [10]. A recent review evaluated the efficacy and safety of treatment with DAA in KT recipients with chronic HCV infection: 98.3% of the patients had a SVR, and liver function improved significantly and, nevertheless, there was no deterioration in renal function [11].

It has been proven in patients with HCV and without renal disease that HCV RNA can remain in the liver and in PBMC after SVR has been obtained both by conventional treatments and by treatment with DAA [12-15]. It has also been shown that the presence of HCV RNA after ultracentrifugation of serum samples in patients with SVR can predict the reactivation of HCV [14]. As KT recipients are immunologically compromised, we wanted to assess the efficacy of conventional antiviral treatments and DAA in those with SVR, testing for HCV RNA in PBMC and in the pellets obtained by ultracentrifugation of plasma samples (the combination of these assays allows the identification of more than 80% of patients with a confirmed occult HCV infection in their liver [15]), as well as to review the safety of the hepatic and renal repercussions of antiviral treatment.

Material and methods

We analyzed 18 renal transplant recipients, older than 18 years, whose HCV infection had been treated with antivirals and had SVR, who came to our Nephrology Department for follow-up. An informed consent was obtained and the study was approved by the Ethics Committee for clinical research. Patients who did not reach SVR or had a reactivation of viremia at the time of the study were excluded. HCV treatment of the 18 recipients of KT is shown in figure 1.

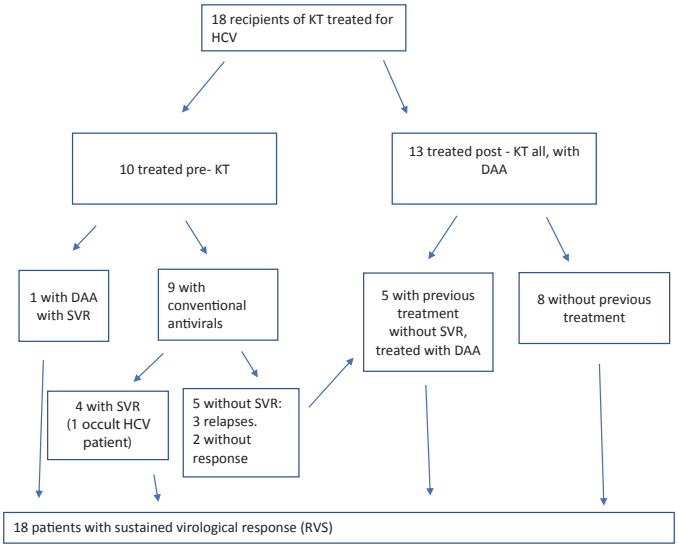

Figure 1: HCV treatment of the 18 recipients of kidney transplantation (KT).

Different parameters were collected in relation to the cause of renal failure, the type of dialysis received, the number of previous transplants, the HCV genotype and the antiviral treatments received, as well as the time of antiviral treatment (dialysis or with functioning KT), whose data are shown in table 1.

In those KT recipients treated post-KT, hepatic and renal function were analyzed before and after treatment with DAA, as well as the number of renal graft rejections, interactions and complications of antiviral treatment.

Methods

Plasma and PBMCs were isolated from anticoagulated blood by density gradient centrifugation (Biocoll, Biochrom, Berlin, Germany). Plasma samples were stored at -30ºC and the PBMCs at -30°C in RNAlater solution (Ambion, Austin, TX) until detection of HCV-RNA.

Two milliliters of plasma were ultracentrifuged over a 10% sucrose cushion for 17 h at 100,000 x g and 4°C to concentrate HCV particles [16]. The pellet was dissolved in 250 µl of TE buffer (Tris-HCl 10 mM, EDTA 10 mM; pH 7.5) and RNA was isolated with the Trizol LS Reagent (Invitrogen, Carlsbad, CA). After precipitation, the RNA pellet was dissolved in 10 µl of nucleases-free water. Total RNA was isolated from PBMCs using the SV Total RNA Isolation System (Promega, Madison, WI). After isopropanol precipitation, RNA pellet was dissolved in 10 of µl nucleases-free water and its concentration was measured by spectrophotometry.

Detection of the 5 'non-coding region of HCV-RNA was performed by real-time reverse transcription (RT)-PCR with fluorescence resonance energy transfer probes. Two microliters of total RNA isolated from 2 mL of ultracentrifuged plasma, or 0.5 µg of total RNA from PBMCs was retrotranscribed and amplified in a singletube reaction containing RNA reaction mix (LightCycler Master Hybprobe, Roche, and Mannheim, Germany). Primers, probes and conditions of this RT-PCR reaction have been previously reported [17]. For avoiding contaminations, the guidelines of Kwok and Higuchi [18], were strictly observed and negative controls and blanks were coprepared with the samples and accompanied them through the entire PCR process. As positive controls, HCV RNA–positive plasma and PBMCs from patients with chronic HCV infection were used.

Statistics

The categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. The continuous variables were calculated using Student's t-test for paired data, and significance using the U-tests of Mann-Whitney and Wilcoxon. All this using the SPSS program version 20.0

Results

The characteristics of the KT patients, treated with DAA, and the treatments used are listed in table 2. The most used regimen was sofosbuvir / ledipasvir and the initial FG in all

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Table 1: Clinical data of the 18 patients.

Years (mean ± SD)	55.4 ± 9.09
Male (n; %)	13; 72.2
Renal kidney disease (n; %)	
Glomerular	10; 55.6
Hereditary	4; 22.7
Others	4; 22.7
Type of dialysis (n; %)	
Hemodialysis	10; 55.6
Peritoneal dialysis	2; 11.1
Both	5; 27.7
None	1; 5.6
Genotype HCV (n; %)	
1b	11; 78.6
2a-2c	1; 7.1
3	2; 14.3
N/A	4; 22.7
Moment of the antiviral treatment (n; %)	
Post-kidney transplantation	13; 72.23
Antiviral treatment (n; %)	18; 100
INF o INF -PEG	3; 16.7
INF-RBV	1; 5.6
DAA (first treatment)	9; 50
Second treatments with DAA, due to HCV relapse	5; 27.7
Time from antiviral treatment to analysis occult HCV (months) (mean ± SD)	26.63 ± 6.03
Time from Kidney Transplantation (months) (mean ± SD)	146.66 ± 110.10

Table 2: Characteristics of the 14 patients treated with direct-acting antivirals.

Number Years	Years	Sex	HCV genotype	Immunosupression	Direct-acting antiviral
1	59	F	1b	CyA + MMF	Sofosbuvir / ledipasvir
2	51	M	1b	Tacro + MMF + Pred	Sofosbuvir / ledipasvir, previous INF
3	55	M	1b	MMF + Pred	Sofosbuvir / ledipasvir
4	65	F	1b	Tacro + MMF + Pred	Elbasvir / grazoprevir
5	68	M	2a-2c	Tacro + Sirol	Sofosbuvir / ledipasvir, previous INF
6	61	F	1b	Tacro + MMF + Pred	Sofosbuvir / ledipasvir
7	61	F	3a	MMF + CyA	Sofosbuvir / daclastavir
8	44	M	1b	CyA + Pred	Sofosbuvir / ledipasvir
9	46	M	1b	CyA + MMF + Pred	Sofosbuvir / ledipasvir
10	42	M	N /A	MMF	Sofosbuvir / ledipasvir, previous INF
11	56	M	1b	MMF + Tacro	Sofosbuvir / ledipasvir, previous INF wiyhout SVR
12	63	M	N /A	Tacro + MMF + Pred	Sofosbuvir / ledipasvir
13	52	M	N / A	Tacro + MMF + Pred	Sofosbuvir / ledipasvir
14	74	M	1b	Tacro + MMF + Pred	Ombitasvir / Paritaprevir /Ritonavir/ Dasabuvir, previous INF without SVR

the recipients were > 30 ml / min. There were no adverse effects during antiviral treatment that required hospitalization or discontinuation of therapy. All patients treated post-KT received the therapy after 6 months post KT, with stable renal function and levels of calcineurin inhibitors and low doses of steroids (in the case of being with these treatments).

In none of the 14 recipients of KT treated with DAA, the presence of HCV RNA was detected neither in PBMC nor in plasma after ultracentrifugation. Viral RNA was also not detected in the PBMCs of the 4 patients with SVR after treatment with IFN (monotherapy or with RBV). However, one of them was positive to HCV RNA in the pellet obtained by plasma ultracentrifugation. This patient, male, and diagnosed with HCV genotype 1b, had received INF-PEG monotherapy prior to KT, and during the subsequent follow-up of 103 months the presence of HCV-RNA in serum was not detected by conventional technique. Graft and patient survival were 100% at the end of follow-up.

In the 14 patients treated with DAA, liver function improved significantly when comparing basal and post-treatment levels of AST and ALT (P = 0.006 and P = 0.011, respectively.

Of the patients included in the study, 17 had previously received dialysis (hemodialysis in 55.6%, peritoneal dialysis in 11.1% and both in 27.8%), and the remaining patient was transplanted from a pre-dialysis live donor. 10 patients (55.6%) had their first KT, 7 the second (38.9%) and 1 patient had received his third KT (5.6%). Regarding antiviral treatment, 9 patients were previously treated with KT; 1 with DAA (in which no relapse is targeted), 7 with INF-α, and in one case, with INF- and RBV. Of these, 3 had SVR, another 3 suffered a reactivation after finishing the treatment and 2 did not respond, with the efficacy of pre-KT treatment with conventional antivirals of 50%. The 5 patients who did not respond to pre-KT or relapsed pre-KT were treated post-KT with DAA and another 8 who had not received pre-KT treatment. In total 14 patients were treated with DAA (13 post KT and one pre KT). All patients completed the treatment with DAA and were followed for a minimum of 12 months after antiviral treatment with a mean follow-up time of 26.61 ± 6.03 months.

No significant differences were observed in the renal function of the graft before and after treatment with DAA (in the 13 patients treated after KT). The protein / creatinine index increased significantly after treatment, but was not associated with ledipasvir / sofosbuvir treatment, the genotype, or the underlying type of kidney disease, significantly. The results on liver and kidney function can be found in table 3.

Regarding the evolution of the patient with occult HCV, a nephropathy due to the polyoma virus after the diagnosis and treatment of a humoral rejection, was diagnosed. The kidney function of this patient's graft had not been considered for renal evaluation since it was previously treated with KT with INF-PEG. Its renal function and the evolution of the renal graft was the worst in the serie, despite the fact that he had a follow-up time of 103 months, which was lower than the mean of the serie. Finally, his liver function did not improve significantly, unlike the rest of the patients.

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Table 3: Hepatic and renal parameters according to pre and post antiviral treatment.

	pre-treatment	post- treatment	p
AST (UI/l) (mean ± SD)	44 ± 35.9	18.86 ± 8.7	0.006
ALT (UI/l) (mean ± SD)	46.6 ± 45.36	18.86 ± 8.70	0.011
GGT (UI/l) (mean ± SD)	54.53 ± 51.91	42.8 ± 58.26	0.422
Total bilirrubin (mg/dl) (mean ± SD)	0.64 ± 0.22	0.57 ± 0.24	0.463
Creatinine (mg/dl) (mean ± SD)	1.39 ± 0.29	1.42 ± 0.62	0.278
CKD-EPI (ml/min/1,73 m2) (mean ± SD)	55.96 ± 16.97	57.53 ± 19.24	0.388
urine protein/creatinine ratio (mg/g) (mean ± SD)	63.25 ± 13.48	327.5 ± 41.50	0.001

Discussion

The main finding in this study is the safety of knowing that occult HCV infection is negative in patients treated with DAA, even if they are kidney transplants and, therefore, immunosuppressed.

Only in a male diagnosed with HCV genotype 1b, treated prior to KT with INF-PEG monotherapy, HCV RNA was detected in the ultracentrifuged plasma. In the 14 KT receptors treated with DAA, HCV RNA was not detected in any case in PBMC or in plasma after ultracentrifugation.

Effectiveness

All patients treated with DAA (1 pre-KT and 13 post-KT) completed the prescribed treatment. 100% of the patients treated with DAA had a SVR, and in no case was HCV RNA detected by RT-PCR in PBMC or in plasma after ultracentrifugation, during a follow-up period of 26.61 ± 6.04 months.

Safety and tolerance of AAD treatment

Liver function improved significantly after treatment with DAA, measured by the detection of AST and ALT, where both decreased after treatment. No significant differences were observed in renal function of the graft before and after treatment with DAA. These findings have also been found in a recent review [11]. However, a worsening of the protein / creatinine index was observed shortly after the therapy, in 4 patients who had received post-KT DAA, (28.5%). The survival of the graft and the patient was 100%, so our data are very similar to those of Lubetzky et al (20). In this series, 31 patients were analyzed, treated with new DAA, post-KT of which 6 presented a worsening of proteinuria (19.3%) and in which there was a tendency to be treated with ledipasvir / sofosbuvir, in comparison with the control group (0.36 ± 0.72 g / g, P = 0.06). Of the 6 patients, in two cases they showed a worsening of renal function [16].

In our series in only one patient, baseline proteinuria was positive and at the end of follow-up in 4 patients it was positive, unlike the work of Lubetzky et al., [19,20], in which no patient developed de novo proteinuria. Among these patients, 1 patient was treated with sirolimus for a lymphoma, and another had been diagnosed with a monoclonal gammopathy of uncertain significance in the past and had a severe von Willebrand disease, so that a renal biopsy could not be performed to rule out monoclonal gammopathy of renal significance. Neither a renal biopsy was performed in another recipient with new onset proteinuria in a patient with mental retardation, who became intermittent with antiproteinuric drugs. All patients with a positive protein / creatinine index were receiving antiproteinurics and a patient had been biopsied and diagnosed with humoral rejection after receiving antiviral treatment with DAA. In our small series, the increase in protein / creatinine index was not associated with the treatment with ledipasvir / sofosbuvir, the HCV genotype or the type of renal disease, in a significant way. Other studies have also described the appearance of proteinuria in patients treated with DAAs, which include 5 patients with focal and segmental glomerulonephritis development and another case with development of glomerulonephritis mediated by lupus-like immune complexes [19-23].

Podocyte direct damage, immune reconstitution and interaction with concomitant immunosuppressive medication have been suggested as hypotheses [20].

We therefore recommend monitoring urine analysis before, during and after treatment with antiviral drugs, and if proteinuria develops, refer the patient to the nephrologist. Although proteinuria is a marker of kidney damage, its small amount may not represent as much damage.

Regarding our patient with occult HCV infection the persistence of alteration in transaminases reinforces the hypothesis of silent liver damage, since this did not occur in the rest of the patients in the series. However, he did not suffer reactivation of his hepatitis C and neither does this seem to directly affect his post-KT evolution during the observation time.

The detection of the virus by this technique is still a marker of the evolution of the patient and there is a need for more research data that could guide the need or not to receive additional treatments.

In conclusion, although a small series of patients is treated, and more studies are required, treatment with DAA is effective with complete eradication of the virus, unlike conventional treatments, with INF, in which HCV can persist, being undetectable with conventional techniques and this persistence seems to affect post-KT evolution.

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