ORIGINAL ARTICLE

Renal transplantation from seropositive hepatitis C virus donors to seronegative recipients in Spain: a prospective study

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The results presented in this paper have not been published previously in whole or part.

Informed consent has been obtained from the subjects before starting the procedures.

Procedures followed were in accordance with the standards of the ethical committee of the Hospital General of Alicante (Approval discharged in 18th of July 2017) and the Spanish Transplant National Organization (ONT).

SUMMARY

Hepatitis C virus (HCV) positive donors are identified in Spain by antibody detection (HCV-Ab) techniques while a HCV nuclear acid-testing (HCV-NAT) is not mandatory. Since it has been shown that HCV-Ab positive HCV-NAT negative donors do not universally transmit the infection, we designed a protocol based on the identification of viremia in HCV-Ab positive donors to start treatment if needed. HCV-Ab-positive donors were identified and we performed HCV-NAT immediately. Donors coinfected with HIV were excluded. Recipients with a low chance to receive a transplant, with no history of liver disease and who were negative for HCV-Ab were selected after informed consent was signed. Kidney recipients from HCV-NAT-positive donors received glecaprevir and pibrentasvir from 6 h before the transplant until 8 weeks after. Recipients from HCV-NAT-negative donors were not treated. Regular monitoring by HCV-NAT was performed to initiate antiviral treatment. We included 11 recipients from six deceased donors Four recipients received grafts from HCV-NAT-positive donors and seven patients received grafts from HCV-NAT-negative donors. None of our recipients exhibited HCV-NAT positivity during the minimum follow-up period of 6 months. Recipients from HCV-NAT-positive donors exhibited sustained virologic response at 12 weeks. One recipient from an HCV-NAT-negative donor lost his graft via a process thought to be unrelated to HCV. The remaining 10 patients had a stable functioning graft at the end of the follow-up period. Our preliminary data suggest that renal transplantation from HCV-Ab- positive donors to HCV-Ab negative recipients is safe when only the recipients of organs from HCV-NAT-positive donors are treated.

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Key words
direct acting antiviral agents, hepatitis C virus, nuclear acid testing, renal transplantation, seronegative recipient, viremia

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Introduction

The transmission of hepatitis C virus (HCV) by organ transplantation, which may result in acute or chronic hepatitis, has been widely reported [1] and raises serious concerns about the convenience of accepting transplantation organs from donors with antibodies against HCV (HCV-Ab). Given the inadequate supply of kidneys for transplantation from deceased donors, a policy to transplant kidneys from HCV-Ab-positive donors to HCV-Ab positive recipients was adopted [2], but the availability of an effective treatment of HCV infection for patients who are on dialysis before transplant has excluded this option [3].

The imbalance between organ supply and demand results in an ethical mandate to improve organ utilization [4]. This mandate includes the broader consideration of organs from HCV-Ab positive donors which are currently discarded at relatively high rates. Transplanting organs from HCV-Ab-positive donors to HCV-Ab-negative recipients may allow patients to receive a transplant much sooner and, thus, reduce the death rate of those on the waiting list [5]. The clinical practice of transplanting a kidney from an infected donor to a noninfected recipient is not new. Cytomegalovirus seronegative patients have routinely received organs from seropositive donors, and treatment for CMV infection is far less effective and much more toxic than HCV therapy [6].

Historically, donor carriers of HCV were identified based on serological testing using enzyme immunoassays (EIAs) or chemiluminescence microparticle immunoassays (CMIAs), which only detect antibodies. Thus, it was impossible to determine whether kidneys from those donors could transmit the infection to a recipient [7]. HCV-Ab-positive donors without viremia typically do not transmit the infection [8–10], but donors who are negative via HCV nucleic-acid-testing (HCV-NAT)with risk factors for recent HCV infection, such as parenteral drug use, have been reported to transmit HCV infection [11,12]. In a large systematic review, pooled HCV incidence across high risk populations from United States and Canada was used to analyze the risk of the window period infection and allowed to estimate that the risk of HCV transmission in very high risk donors such as nonmedical drug intravenous users may be as high as 300 per 10.000 using HCV-Ab testing and 32 per 10.000 using HCV-NAT testing. [13]. Based on the reduced window period by HCV-NAT, in December 2014, the Organ procurement and Transplantation Network (OPTN) updated its policy requiring that all donors should be screened with HCV-NAT in addition to serology [14]. Goldberg *et al.* and Durand *et al.* conducted two successful trials based on kidney transplantation from HCV-infected donors to noninfected recipients who received treatment with direct-acting antiviral agents (DAAs) starting after or before surgery [15,16].

We designed a protocol based on the immediate identification of an HCV-Ab-positive donor as viremic (HCV-NAT positive), with a high risk of infection transmission, or nonviremic (HCV-NAT negative) with a very low risk of transmission, to start an early treatment with a DAA, if needed.

Patients and methods

This is a prospective, observational, multicenter study conducted in three renal transplant units in Spain between March and December 2017. We requested that the (Spanish Transplant National Organization) ONT inform us of HCV-Ab- positive donors detected in Spain. The determination of HCV serology in donors is mandatory in Spain, but determination using NAT is not mandatory. We accepted all HCV-Ab-positive donors, who were <70 years of age, except for those admitted into the penitentiary system and/or with active addiction to parenteral drugs. We performed an immediate HCV-NAT test (Xpert® HCV Viral Load assay, Cepheid, CA, USA) to detect HCV-RNA and classify the donor as infective or non- infective. Donors coinfected with HIV were excluded. (Xpert® HIV Viral Load assay).

A subgroup of HCV-Ab-negative recipients from our kidney transplant waiting list was considered for transplantation from HCV-Ab-positive donors. The inclusion criteria included a low chance to receive a renal transplant from a deceased donor within 2 years (especially patients younger than 65 years with blood type O), no clinical history of liver disease and a signed multi-step informed consent form. We enrolled the candidates when they were included on the transplant waiting list. The consent process started when the patient registered on the waiting list and was reinforced when the graft was offered by the ONT. The consent was offered to 54 patients and three of them refused to participate in the study.

According to the HCV-NAT results in the donors, the recipient was managed as follows:

Action Taken 1 (recipient from an HCV-NAT-positive donor): Treatment with 300 mg/24 h glecaprevir and 120 mg/24 h pibrentasvir was administered from 6 h before transplant until 8 weeks after transplantation. HCV-NAT monitoring was performed at 0, 1, 7, 14, 28 and 56 days after transplantation (i.e., the end of treatment) and again at 12, 24 and 52 weeks.

Action Taken 2 (recipient from an HCV-NAT-negative donor): No antiviral treatment. The monitoring of HCV-NAT followed the same above mentioned schedule. Patients with HCV transmission in whom positive HCV-NAT was detected were treated with a DAA.

During the study period, any possible side effect related to DAA treatment was recorded. Follow-up information was recorded for at least 6 months. The regular monitoring of HLA antibodies by Luminex Technology was performed during the follow-up period.

Results

We included 11 recipients who received a kidney transplant from one of six deceased donors. Additionally, during the study period two HCV-Ab-positive donors were not utilized, one with active addiction to parenteral drugs and one without suitable renal transplant candidates. All recipients were hepatitis B virus negative.

Two out of six donors (33.3%) were HCV-NAT positive; one was an untreated donor while the other was receiving DAA treatment at the time of death and exhibited a minimal viral load (100 Ul/ml). Four donors (66.7%) were HCV-NAT negative and three of them have been previously diagnosed of HCV infection and successfully treated with different DAA regimens (Table 1). One HCV-NAT-negative donor had not been treated. The demographic data of the donors and recipients, including donor HCV-infection risk factors, HCV genotype, previous treatments for HCV infection and actions taken at the time of transplant are presented in Table 1. The HCV genotype of donors with positive NAT was determined using blood samples stored at the time of donation whereas the HCV genotype from treated patients was obtained from their clinical records. The HCV genotype was 1a in two donors and 1b in three donors. Genotype 3 was not observed in this set of patients.

The transplant-related variables from our cohort of patients are presented in Table 2. All patients but one were treated with thymoglobulin induction and delayed introduction (serum creatinine under 3 mg/dl) of extended release tacrolimus (Advagraf®) started at 0.1 mg/kbw/day in patients receiving DAAs and at 0.2 mg/kbw/day in patients not receiving DAAs. Two days after tacrolimus initiation trough blood levels were checked and thereafter close monitoring of tacrolimus trough levels was followed. One patient receiving a graft from an HCV-NAT negative donor received induction with basiliximab and tacrolimus was started at the same

Table 1. Demographics from donors and recipients, nuclear acid testing, HCV genotyping, HCV-infection risk factors and recorded treatments.

Donor							Recipient			
ID	Age (years)	Gender	NAT (UI/ml)	Genotype	Risk factor	Previous HCV tretament	ID	Age (years)	Gender	Action taken
1	40	Female	Negative	1b	NAAPD	Interferon	1	41	Male	1
							2	51	Female	1
2	57	Male	Negative	1b	NAAPD	Interferon	3	58	Male	1
								Transplantation to an HCV-Ab positive NAT negative recipient		
3	66	Male	Negative	1b	NAAPD	Sofosbuvir Ledipasvir (12 weeks)	4	65	Male	1
							5	63	Female	1
4	48	Male	1.800.000	1a	NAAPD	None	6	65	Female	2
							7	58	Female	2
5	51	Male	Negative	ND	None	None	8	62	Male	1
							9	41	Female	1
6	50	Male	100	1a	NAAPD	Sofosbuvir Ledipasvir (6 weeks)	10	49	Female	2
							11	55	Male	2

NAT, nuclear acid testing for hepatitis C virus; NAAPD, non-active addiction to parenteral drugs; action taken 1: HCV-NAT monitoring; action taken 2: treatment with glecaprevir/pibrentasbir.

Table 2. Allograft and recipient characteristics (n=11).

ID	HLA mm	cPRA (%)	CIT	Induction	Maintenance	DGF	Rejection	Follow up (months)	Last eGFR (ml/min/1.73 m^2)
1	3	0	23	Thymoglobulin	TAC+SRL+P	No	No	16	57
2	2	0	19	Basiliximab	TAC+MMF+P	No	No	16	44
3	2	0	19	Thymoglobulin	TAC+SRL+P	No	No	11	45
4	5	0	17	Thymoglobulin	TAC+MMF+P	No	No	7	35
5	3	0	14	Thymoglobulin	TAC+SRL+P	No	No	7	38
6	5	0	11	Thymoglobulin	TAC+SRL+P	No	No	7	66
7	5	0	14	Thymoglobulin	TAC+SRL+P	No	No	7	65
8	3	0	27	Thymoglobulin	TAC+MMF+P	No	No	6	74
9	3	32	17	Thymoglobulin	TAC+SRL+P	Yes	No	6	Dialysis
10	4	71	21	Thymoglobulin	TAC+SRL+P	No	No	6	46
11	3	59	24	Thymoglobulin	TAC+SRL+P	No	No	6	45

CIT, cold ischemia time; cPRA, calculated panel of reactive antibodies by Luminex assay at the time of transplant; DGF, delayed graft function; eGFR, estimated glomerular filtration rate by the CKD-EPI formula at the time of the last follow-up visit; HLA mm, addition of HLA mismatches at the A, B and DR loci; MMF, mycophenolate mofetil; P, prednisone; SRL, sirolimus; TAC, tacrolimus.

day of transplant. Importantly, all HCV-NAT performed in the recipients during the follow-up period showed negative results. One patient suffered from acute necrotizing pancreatitis after transplantation and lost her graft. The remaining 10 patients had a functioning graft at the time of the last follow-up visit (Table 2). The evolution of liver enzymes and renal function during the initial 12 weeks after transplantation is presented in Fig. 1. No adverse events associated with DAA treatment were recorded.

The screening results for donor specific antibodies were negative for all patients enrolled in the study at 12 weeks post-trasnplant.

Discussion

The objective of our protocol is to expand the donor pool by transplanting kidneys retrieved from HCV-Ab-positive donors to HCV-Ab-negative recipients. In Spain in 2016, fifteen kidneys that were suitable for transplantation were discarded due to having come from HCV-Ab-positive donors, which represents 1.6% of all discarded kidneys [17]. Additionally, our protocol aimed to treat only recipients with a high risk of HCV transmission [18].

In the case of HCV positive donors, the procedures in the USA are different from those in Spain, given that the number of donors who died by means of drug-over-dose increased from 1.1% to 13.4% between 2000 and 2017 [19]. In the USA there are many young HCV-positive donors due to the outbreak of drug-overdose deaths [20]. In total, 50% of these individuals are infected with HCV and only 1/3 are aware of their diagnosis [21]. Given the growing incidence and high risk of HCV infection, these overdose victims are likely to be one of the main sources of HCV viremic donors in the next decade [22]. A comparison of serology and NAT results using OPTN data from 2015 to 2016, suggests that only 1/3 of this potential donor pool is likely to be HCV-NAT negative [23]. Thus, the need to stablish an active policy for the use of organs from HCV-positive donors is necessary [24].

Most HCV-Ab-positive donors in Spain have been previously diagnosed with HCV infection and properly treated. The possibility of being an HCV-infected donor is lower than that reported in the USA In our study, four out of six donors were HCV-NAT negative (cases 1, 2, 3 and 5) given that three were previously treated with a DAA after their diagnosis.

We did not observe any case of transmission from our donors to our recipients. None of our recipients exhibited positive HCV-NAT during the follow-up

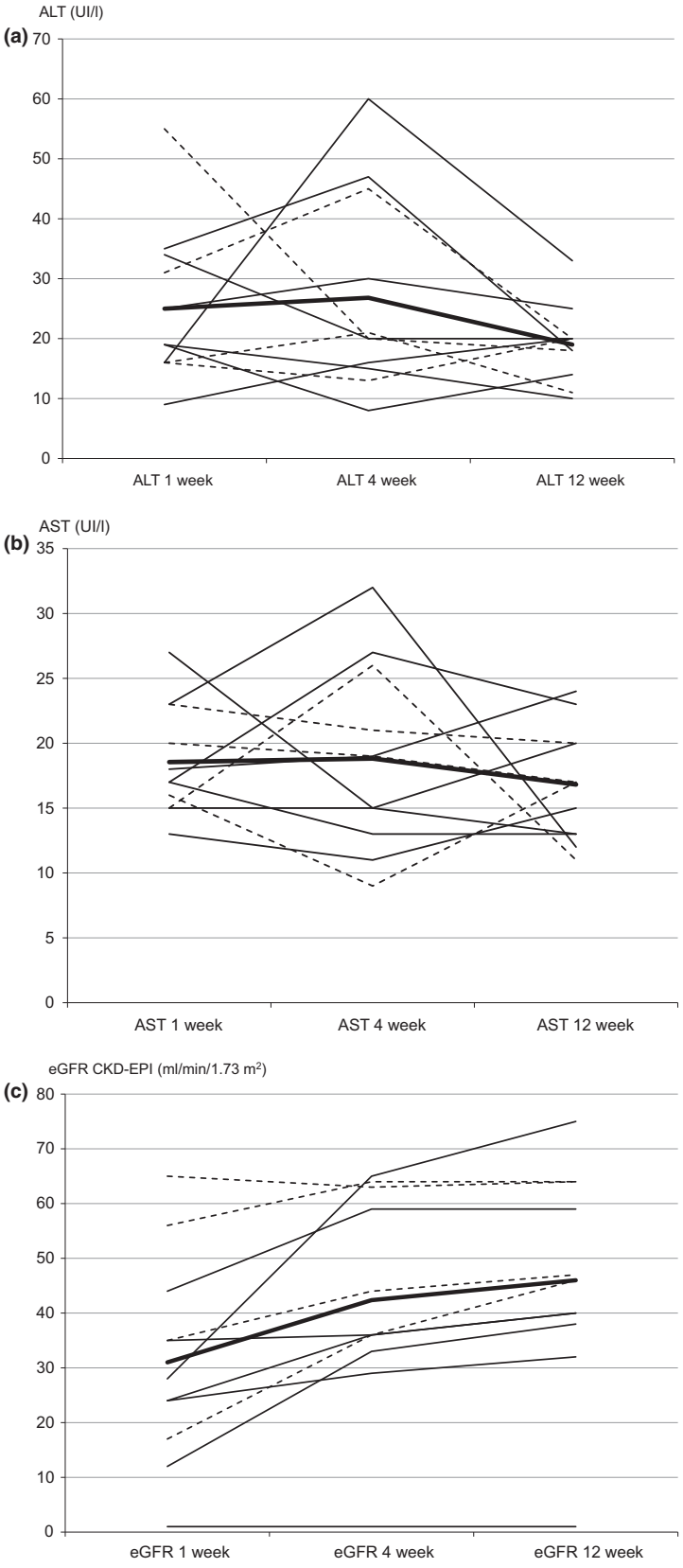

Figure 1 Evolution of liver enzymes ALT (1a) and AST (1b) and the evolution of estimated glomerular filtration rate using the CKD-EPI formula (1c) during the initial 12 weeks after transplantation. In all figures the thick black line represents the mean for all transplant recipients, The thin black continuous lines represent individual values for recipients from HCV-NAT-negative donors and the thin black dotted lines represent individual values for recipients from HCV-NAT-positive donors. ALT and AST normal levels in our labs were < 40 UI/l.

period due to either the lack of transmitted viremia or control with DAA treatment. We have taken advantage of two new DAAs, glecaprevir and pibrentasvir which are pan-genotypic and can be used in recipients with renal disease [25]. Goldberg *et al.* and Durand *et al.* had to consider different strategies according to HCV genotype in their protocols [15,16] whereas the use of pan-genotypic regimens obviates the need for HCV genotyping at the time of transplant. The OPTN *Ad Hoc* Disease Transmission Advisory Committee (DATC) stated that HCV transmission from HCV-Ab-positive, HCV-NAT-negative donors had not yet been described [18]. Subsequent to that conference, DATC has been aware of a small number of cases involving recipient HCV acquisition from donors who were HCV-Ab positive, but HCV-NAT negative [26]. These cases are currently under investigation but this fact reinforces that new well-documented studies are necessary.

The American Consensus Conference supports the trials on progress in this topic. At present, 24 USA hospitals are included in the national program and a total of 66 renal transplants from viremic donors have already been performed, according to data recently reported by Goldberg in the 28th European Congress of Clinical Microbiology and Infectious Disease. Our protocol identified that noninfectious donors are not susceptible to the transmission of infection, thereby avoiding expensive treatment in most of the recipients. Recently, a Markov model was used to demonstrate that the use of kidneys from deceased donors with HCV infection is likely to lead to improved clinical outcomes at a reduced cost for HCV-negative transplant candidates [27]. The estimation of this effect with our reduced sample size is out of the scope of this study.

Less information is available from studies conducted in European countries. In the European transplant records between 2002 and 2007, 29 HCV-Ab positive donors were carefully evaluated with different tests to detect antibodies against HCV and with HCV-NAT. Twenty (69%) of these donors were nonviremic and were employed to transplant to 21 HCV-negative recipients given the very low risk of transmission [28]. During the follow-up period, no *de novo* HCV infections were detected in recipients who were HCV negative before transplantation and the clinical outcome at 10 years did not differ from that of patients receiving kidneys from HCV-negative donors. Thus, the transplantation of renal allografts from nonviremic HCV-Ab positive donors to HCV-negative recipients is safe. After extended virologic testing these organs should not be denied for transplantation but close monitoring of patients after receipt of grafts from HCV-Ab positive donors should be mandatory. As far as we know, no experiences with HCV-NAT positive donors have been reported in Europe. Our strategy of treating recipients from organs obtained from HCV-NAT positive donors should be closely monitored by appropriate protocols in order to identify the characteristics of individuals in whom therapeutic failures might occur despite DAA treatment [29]. The role of national organ procurement organizations in this area has not been defined but they should be involved in order to ensure patients' safety.

Despite the small sample size of our study, we demonstrated that renal transplants from HCV-Ab-positive donors into HCV- seronegative recipients using DAA prophylaxis for only the recipients of grafts from HCV-NAT-positive donors seems to be safe and cost effective. This strategy should be studied further in carefully monitored clinical trials. If confirmed in larger studies, this approach will expand the organ donor pool and reduce the time on the waiting list for renal transplant candidates without HCV infection.

Authorship

Each author has participated sufficiently in the work to take public responsibility for the content. This participation includes: (i) Analysis and interpretation of data, (ii) Drafting the article and revising it, (iii) Providing intellectual content of critical importance to the work described, (iv) Final approval of the version to be published.

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Conflict of interest

None declared.

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