ORIGINAL ARTICLE

Transplantation of kidneys from hepatitis C-positive donors into hepatitis C virus-infected recipients followed by early initiation of direct acting antiviral therapy: a single-center retrospective study

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SUMMARY

The availability of direct acting antiviral agents (DAA) has transformed the treatment of hepatitis C virus (HCV) infection. The current study is a case series that reports the outcomes from a cohort of twenty-five HCV-infected ESRD patients who received a kidney from an anti-HCV-positive deceased organ donor followed by treatment with DAAs in the early post-transplant period. Time to transplantation and the efficacy of DAA therapy as measured by sustained viral response at 12 weeks were assessed. The median waiting time from original date of activation on the United Network Organ Sharing (UNOS) waiting list until transplantation was 427 days; however, the median time from entering the patient into UNet^{sm} for a HCV-positive offer until transplantation was only 58 days. The 25 patients were started on antiviral treatment early post-transplant (median 125 days) and 24 of 25 (96%) achieved a sustained virologic response at 12 weeks. Tacrolimus dose adjustments were required during antiviral treatment in 13 patients to maintain therapeutic levels. Accepting a kidney from an anti-HCV-positive deceased donor shortened the waiting time for HCV-infected kidney transplant candidates. We recommend that kidneys from anti-HCV-positive donors should be considered for transplant into HCV-infected recipients followed by early post-transplant treatment with DAA agents.

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Key words
chronic kidney disease, direct acting antiviral agents, end-stage renal disease, hepatitis C virus, kidney transplantation

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Introduction

The prevalence of hepatitis C virus (HCV) infection in ESRD patients exceeds that of the general population and correlates with the duration of hemodialysis [1,2]. Furthermore, HCV-infected patients receiving maintenance dialysis have been demonstrated to have an increased mortality when compared to the uninfected population [3]. Previous studies have also demonstrated that HCV infection is the primary cause of liver disease

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postkidney transplantation [4], and has been associated with several extra-hepatic manifestations that likely contribute to the increased morbidity and mortality reported in the HCV-infected kidney transplant recipient [5–7]. The systemic complications of HCV infection include an increased incidence of insulin resistance and diabetes mellitus [7–10], a higher cardiovascular event-rate [3] and an increased risk for injury to the allograft, including *de novo* and recurrent membranoproliferative glomerulonephritis [11,12] and transplant glomerulopathy [13]. Despite these adverse clinical outcomes, kidney transplantation has been unequivocally associated with a long-term survival benefit for the HCV-infected patient when compared to remaining on dialysis [14,15].

The availability of direct-acting antiviral (DAA) agents to treat chronic HCV infection has dramatically changed the way patients with this disease are managed and offers the opportunity for cure in most cases [15–18]. Several pivotal phase three clinical trials conducted in the general population have demonstrated sustained viral response rates (SVR12; undetectable viral load 12 weeks after completing therapy) exceeding 90% for most HCV genotypes [19–21]. Until recently, these trials had excluded patients with CKD from enrollment, mostly due to a lack of reliable pharmacokinetic and safety data in patients with reduced kidney function. Fortunately, data from recently published studies are now demonstrating the safety and efficacy of newer DAAs in the advanced CKD and ESRD population [22–24].

Treatment of the HCV-infected ESRD patient had been limited by the low efficacy and poor tolerability of interferon-based regimens. Similarly, treatment of the kidney transplant recipient infected with HCV was generally not recommended due to the increased risk of allograft dysfunction and rejection accompanying the use of interferon [25]. Historically, many kidneys from anti-HCV-positive deceased donors were discarded as there were no safe and effective antiviral agents to use postkidney transplantation. The ability to treat HCV-infected kidney transplant recipients with DAAs now permits this issue to be readdressed. Transplantation of a kidney from an anti-HCV-positive deceased organ donor into a HCV-infected recipient with early post-transplant DAA treatment is a treatment plan that requires careful study. This strategy offers two potential advantages, firstly by increasing the size of the donor pool and secondly by significantly shortening the wait-list time for those patients accepting a kidney from an anti-HCV-positive donor. The current study reports the results of the first 25 patients treated with this regimen at our center.

Materials and methods

Subjects

Patients on the deceased donor waiting list who were confirmed to be HCV nucleic acid test (NAT; Roche Cobas Taqscreen MPX v2.0; lower limit of detection 6.8 IU/ml) positive were consented to indicate their willingness to accept a kidney from an anti-HCV-positive donor. Twenty-five consecutive patients were transplanted between May, 2014 and April, 2016 with a kidney from an anti-HCV-positive donor (Table 1). There were three patients with failed renal allografts and one patient with a prior orthotopic liver transplant. Six of the patients were highly sensitized at the time of transplant (calculated panel reacting antibody [cPRA] >40%). All patients had been fully evaluated to determine their suitability for placement on the United Network Organ Sharing (UNOS) waiting list using the standard screening protocols at our center. In addition, each patient had a liver biopsy and hepatology clearance as part of the pretransplant evaluation. The study was approved by the University of Miami Institutional Review Board. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

Of the 25 anti-HCV antibody-positive donors, 19 of 25 were HCV NAT positive at the time of organ retrieval. HCV genotyping was available for each recipient prior to kidney transplant. Genotyping was not available from the donors at the time of organ retrieval. Repeat HCV genotyping was obtained on each of the 25 recipients postkidney transplant prior to beginning DAA therapy to determine the predominant HCV genotype. The mean kidney donor profile index (KDPI) of the donors was 58% [interquartile range (IQR), 41–74].

Immunosuppression

Induction immunosuppression (IS) included three doses of rabbit antithymocyte globulin (Thymoglobulin®; Genzyme, Cambridge, Massachusetts, USA), high-dose solumedrol (500 mg daily for 3 days) and two doses of basiliximab (Simulect®; Novartis, Basel, Switzerland). Maintenance IS included tacrolimus and mycophenolate mofetil; three patients were switched from mycophenolate mofetil to everolimus due to leukopenia. Target

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Table 1. Patient characteristics and immunosuppression.

Patient	Gender	Race	Age, yr	Cause of ESRD	Number of days until transplant*	RRT prior to transplantation	HIV Status	cPRA, %	KDPI, %	Maintenance immunosuppression
1	M	H	47	HTN	9	HD	Negative	0	34	TAC + MYF
2	M	AA	61	DM	245	HD	Negative	34	84	TAC + EVR + P
3	M	AA	62	HTN	88	HD	Positive	57	25	TAC + MYF + P
4	M	AA	61	HTN	27	HD	Negative	0	28	TAC + MYF
5	M	AA	68	HTN	17	HD	Negative	0	45	TAC + MYF
6	M	H	68	DM	71	HD	Negative	0	51	TAC + MYF
7	M	AA	59	GN	180	PD	Negative	39	65	TAC + MYF
8	M	AA	61	UNKN	336	HD	Negative	71	37	TAC + MYF + P
9	M	AA	54	HTN	6	HD	Negative	0	87	TAC + MYF
10	M	AA	62	UNKN	42	HD	Positive	0	41	TAC + EVR + P
11	M	AA	30	UNKN	26	HD	Negative	19	72	TAC + MYF
12	M	H	50	GN	58	HD	Negative	0	75	TAC + MYF + P
13	M	AA	67	HTN	34	HD	Negative	0	53	TAC + MYF
14	F	H	43	GN	367	PD	Negative	90	78	TAC + MYF + P
15	F	AA	63	DM	197	NONE	Negative	98	72	TAC + MYF + P
16	F	AA	67	DM	17	HD	Negative	0	94	TAC + MYF
17	M	AA	35	DM	36	HD	Negative	0	34	TAC + MYF
18	F	AA	65	DM	19	HD	Negative	0	41	TAC + MYF
19	M	AA	67	HTN	311	HD	Negative	77	73	TAC + EVR + P
20	M	H	63	DM	19	HD	Negative	0	41	TAC + MYF
21	M	H	43	UNKN	184	HD	Negative	0	71	TAC + MYF
22	M	AA	57	DM	34	HD	Negative	0	75	TAC + MYF
23	M	AA	56	DM	206	HD	Negative	0	35	TAC + MYF
24	M	H	62	UNKN	85	HD	Negative	0	80	TAC + MYF
25	F	AA	59	HTN	15	HD	Negative	0	64	TAC + MYF

M, male; F, female; H, Hispanic; AA, African–American; C, Caucasian; DM, diabetes mellitus; HTN, hypertension; GN, glomerulonephritis; UNKN, unknown; PKD, polycystic kidney disease; CNI Tox, calcineurin inhibitor toxicity; ESRD, end-stage renal disease; HCV, hepatitis C virus; RRT, renal replacement therapy; HD, hemodialysis; PD, peritoneal dialysis; KDPI, kidney donor profile index; cPRA, calculated panel reactive antibodies at transplant; TAC, tacrolimus; MYF, myfortic; EVR, everolimus; P, prednisone (highly sensitized patients were on prednisone).

*Number of days until transplant after entered into UNet^{sm} to accept a kidney from a HCV-positive donor.

tacrolimus trough levels were 7–9 ng/ml during the first 6 months post-transplant and 6–8 ng/ml for the remainder of the first year. Eight patients were maintained on long-term maintenance steroids because of a history of a failed renal allograft ($n = 3$), HIV infection ($n = 2$) or cPRA >40% at the time of transplantation ($n = 3$).

HCV antiviral therapy

All patients were treated for 12 weeks with various DAA regimens except patient #20 (24 weeks) and patient #22 (8 weeks) (Table 2). The goal was to initiate DAA treatment within the first 3 months post-transplant once kidney function had stabilized and stable IS was achieved; however, challenges obtaining insurance approval delayed initiation of therapy in several patients. The combination of DAAs used included: sofosbuvir 400 mg daily/simeprevir 150 mg daily ($n = 1$), sofosbuvir 400 mg daily/ledipasvir 90 mg daily ($n = 4$), and sofosbuvir 400 mg daily/ledipasvir 90 mg daily/ribavirin (weight based) ($n = 19$) to treat HCV genotype 1; and sofosbuvir 400 mg daily/daclatasvir 60 mg daily for HCV genotype 2b ($n = 1$). The choice of the HCV treatment regimen was partly dependent upon insurance/payor approval and also the discretion of the treating hepatologist. The addition of ribavirin to the sofosbuvir/ledipasvir regimen has been associated with higher SVR rates compared to without ribavirin in the postliver transplant setting [26].

Statistical analysis

Data collected included gender, race, age at the time of transplantation, date of transplantation, date of signing

Table 2. Hepatitis C virus parameters and outcomes post treatment.

Patient	HCV genotype pre-KT	HCV genotype post KT	Liver fibrosis stage	Donor HCV NAT	Day DAA started post-transplant	DAA regimen	SVR	Rejection	Change in TAC dose	Creatinine (mg/dl) before DAA	Creatinine (mg/dl) at EOT
1	1a	1a	F 0	Pos	153	SOF/LDV/RBV	Y		None	1.4	1.1
2	1a	1a	F 2	Pos	50	SOF/LDV/RBV	Y		Increase 12.5%	1.3	1.2
3	1a	1a	F 1	Neg	64	SOF/LDV/RBV	Y		Increase 20%	1.1	1.1
4	2b	2b	F 0	Pos	52	SOF/DAC	Y		None	1.5	1.2
5	1a	1a	F 1	Neg	124	SOF/LDV	Y		None	1.7	1.5
6	1a	1a	F 2	Neg	140	SOF/LDV/RBV	Y		Increase 17%	1.4	1
7	1a	1a	F 1	Pos	125	SOF/SIM	Y	ABMR	Increase 67%	1.4	1.4
8	1b	1b	F 0	Pos	126	SOF/LDV/RBV	Y		None	1	0.9
9	1b	1b	F 2	Neg	110	SOF/LDV/RBV	Y		Increase 33%	1.6	1.6
10	1a	1a	F 0	Pos	54	SOF/LDV	Y		Increase 100%	1.6	1.6
11	1b	1b	F 0	Pos	135	SOF/LDV/RBV	Y	ABMR	None	1.7	1.7
12	1a	1a	F 1	Pos	215	SOF/LDV/RBV	Y	ABMR	Increase 17%	1.5	1.7
13	1a	1a	F 2	Pos	113	SOF/LDV/RBV	Y		Increase 12.5%	1	0.9
14	1b	1b	F 0	Pos	150	SOF/LDV/RBV	Y		None	1.2	1.2
15	1b	1b	F 0	Pos	99	SOF/LDV/RBV	Y		None	0.7	0.8
16	1a	1a	F 3	Pos	185	SOF/LDV	Y		Increase 50%	0.8	0.7
17	1a	1a	F 1	Pos	227	SOF/LDV/RBV	Y		None	1.1	0.9
18	1a	1a	F 1	Pos	309	SOF/LDV/RBV	N		None	1.5	1.5
19	1a	1a	F 0	Pos	87	SOF/LDV/RBV	Y	ABMR	Increase 75%	0.9	1.9
20	1a	1a	F 0	Pos	107	SOF/LDV	Y		Decrease 25%	1.1	1.1
21	1b	1b	F 0	Neg	102	SOF/LDV/RBV	Y		None	1.3	1.0
22	1a	1a	F 0	Pos	199	SOF/LDV/RBV	Y		Increase 11%	1.1	1.1
23	1a	1a	F 2	Neg	62	SOF/LDV/RBV	Y		None	1.4	1.5
24	3	1a	F 1	Pos	81	SOF/LDV/RBV	Y		Increase 100%	2	1.4
25	1a	1a	F 0	Pos	171	SOF/LDV/RBV	Y		None	1.1	1.0

KT, kidney transplant; NAT, nucleic acid testing; Pos, positive; Neg, negative; DAA, direct acting antiviral; HCV, hepatitis C virus; SOF, sofosbuvir; LDV, ledipasvir; DAC, daclatasvir; RBV, ribavirin; SIM, simeprevir; VEL, velpatasvir; SVR, sustained virologic response; ABMR, antibody-mediated rejection; TAC, tacrolimus; EOT, end of treatment with DAAs; F, METAVIR fibrosis stage (see Ref. [27]) on most recent pretransplant liver biopsy.

Public Health Service high risk donor consent form (coincides with the date of transplant), original listing date on the UNOS transplant list, date patient was listed in UNet^{sm} to accept an offer from a HCV-positive donor, induction and maintenance immunosuppression, cause of ESRD, liver histology from pretransplant biopsy and HCV genotype of the recipient. HCV genotyping was performed on all recipients post-transplant to determine whether the pretransplant genotype persisted, co-infection with two genotypes was now evident or a new, previously not identified dominant genotype was present. The mean, median, and standard deviation were calculated for continuous variables.

Results

Twenty-five HCV-infected patients were transplanted with a kidney from an anti-HCV antibody-positive donor (Table 1). They were predominantly male (n = 20, 80%) and African American (n = 18, 72%). The mean age was 58 $\pm$ 10.7 years at the time of transplant. Two patients were co-infected with HIV and on antiretroviral therapy (Patient #3 on dolutegravir, emtricitabine, tenofovir; patient #10 on emtricitabine, tenofovir, etravirine). No recipients were hepatitis B surface antigen positive. Three patients had previously failed HCV treatment with an interferon-based regimen. The median METAVIR fibrosis stage from pretransplant liver biopsy was 1.0 (score range 0-four, with four representing cirrhosis) and there were no cirrhotics [27]. Genotype 1a infection predominated (n = 17) with genotype 1b (n = 6), genotype 2b (n = 1), and genotype 3 (n = 1) also present in the cohort. After being activated on the UNOS list the median waiting time to transplantation was 427 days (IQR 226–771). However, the median waiting time to transplant after entering the patient into UNet^{sm} to accept an offer from a HCV-positive donor was only 58 days (IQR 26–184). The difference in these two results reflects that many of the patients had been already listed prior to being entered into UNet^{sm} for a HCV donor offer. The median time to transplant after liver biopsy was 746 days (IQR 370–1079). Treatment with DAA therapy was started postkidney transplantation after a median of 125 days (IQR 100–169). The most frequently prescribed DAA regimen was the combination of sofosbuvir 400 mg/ledipasvir 90 mg and ribavirin (weight based) given daily for 12 weeks (n = 19). The median length of follow-up post-transplant was 13 months (IQR, 6–21).

Twenty-four patients completed the prescribed course of DAA therapy and achieved a SVR12. One patient was noncompliant with antiviral therapy and was entered as a treatment failure. Patient #20 was initially treated with a suboptimal antiviral regimen and experienced relapse; however, a SVR was obtained when retreatment with a dual DAA combination was prescribed. The overall SVR12 was 96% on an intention to treat (ITT) basis and 100% in patients who completed treatment as per-protocol analysis. Ribavirin administration did not have an additional impact on SVR in this cohort.

Hepatitis C virus genotype testing in the 25 patients post-transplant identified one case (patient #24, Table 2) in which a new genotype was identified that differed from the patients original pretransplant genotype. This genotype was now dominant with no evidence of the recipients' original genotype. This patient had received a kidney from a HCV NAT-positive donor. In all other cases, the pretransplant genotype remained unchanged when tested post-transplant.

Seven of 19 patients receiving ribavirin required dose reduction and two others discontinued the medication due to worsening anemia. There was a greater than 2-g decrease in hemoglobin in seven of the nine patients that required ribavirin dose adjustment. Sofosbuvir was discontinued due to side effects in one patient but then restarted at a lower dose with successful completion of treatment. Another patient treated with sofosbuvir/ledipasvir required discontinuation of ledipasvir and replacement with daclatasvir due to gastrointestinal symptoms.

An adjustment of the tacrolimus dose was necessary during the course of the DAA therapy in 13 patients to maintain therapeutic levels, with 12 of 13 requiring a dose increase (changes were made at the discretion of the treating transplant nephrologist and there was a 43% mean increase of the total tacrolimus dose) (Table 2). Four patients developed biopsy-proven antibody-mediated rejection (ABMR) while receiving DAA treatment and none of the four patients had DSA present at the time of transplantation. Of note, three of these patients had experienced a significant decrease in tacrolimus trough levels during DAA therapy in the weeks prior to the rejection event. One of these patients developed *de novo* donor-specific antibodies and two were highly sensitized (Table 3). Kidney function was assessed at the end of treatment with DAAs and of the 24 patients who completed DAA therapy with SVR12 (including the patient that relapsed and was retreated), 7 had an improvement in function (defined as a decrease of the serum creatinine >0.2 mg/dl), 14 had no change and four patients had worsening kidney function associated with ABMR. However, in three of four

Table 3. Patient with allograft rejection.

Patient	Kidney biopsy	C4D	Antirejection medications	*De novo* DSA	Tacrolimus levels prior to rejection
7	AMR type II + BTCR	Positive	Thymoglobulin, steroids, plasmapheresis, IV immunoglobulin, bortezomib, rituximab	Positive	Below therapeutic
11	AMR type II + TCR IA	Positive	Thymoglobulin, steroids, plasmapheresis, IV immunoglobulin, bortezomib, rituximab	Negative	Below therapeutic
12	AMR type II	Positive	Plasmapheresis, IV immunoglobulin, bortezomib, rituximab	Negative	Therapeutic
19	AMR type II	Positive	Plasmapheresis, IV immunoglobulin, bortezomib, rituximab	Negative	Below therapeutic

C4D, results of C4D staining on biopsy; AMR, antibody-medicated rejection; BTCR, borderline changes T cell-mediated rejection; TCR, T cell-medicated rejection; DSA, donor-specific antibodies at time of rejection.

patients with ABMR the serum creatinine eventually returned to baseline levels.

Discussion

This single-center case series reports the results from 25 HCV-infected patients who had been transplanted with a kidney from an anti-HCV-positive donor and were started on DAA therapy early post-transplant. Our experience indicates that this strategy is a safe and effective approach to the management of the noncirrhotic HCV-infected kidney transplant candidate. Of note, these patients achieved SVR rates of 96% per ITT analysis and 100% per-protocol. They benefited from a substantially shortened time on the UNOS wait-list compared to the 4–7 years or more that is usually expected at our center. A strategy of utilizing HCV-positive donor organs also has the potential to increase the currently limited deceased donor pool. Although there was one case in which superinfection with donor HCV was suggested from genotype data, this patient obtained a SVR with DAA treatment.

Numerous reports have demonstrated inferior patient and graft survival in anti-HCV antibody-positive kidney recipients when compared to HCV-negative patients [28]. In contrast, conflicting results have been reported following transplantation of a kidney from an anti-HCV antibody-positive donor into an HCV-infected recipient. In a study using information from the USRDS database, Abbott *et al.* [29] reported inferior outcomes with increased risk of mortality in HCV-positive patients who had received a kidney from a HCV-positive donor compared to recipients of a kidney from a negative donor. In contrast, Morales *et al.* [30] did not observe an increase in mortality or graft failure or more aggressive liver disease in a cohort of 162 HCV-positive patients who had been transplanted with a kidney from a HCV-positive donor. Of note, both of these studies were from the pre-DAA era and did not have nucleic acid testing available to confirm viremia in either the donor or recipient. The current report is focused on early viral outcomes and longer follow-up with larger numbers of patients will be necessary to obtain meaningful patient and graft survival results.

Prior to the availability of DAA agents, the treatment of HCV infection in the postkidney transplant patient was challenging due to an increased risk of allograft dysfunction accompanying the use of interferon-based regimens [31–33]. Gallegos-Orozco *et al.* [34] reported decreased waiting time on the transplant list and a SVR_{12} rate of 100% in a small group of patients treated with DAAs post-transplant. Recently, Sawinski *et al.* reported the outcomes in a case series of 16 kidney and four simultaneous liver–kidney recipients who received DAAs post-transplant. The medications were well tolerated, and a SVR of 100% was achieved without an adverse impact on allograft function [35]. In a case series of 25 patients, Kamar *et al.* [36] obtained a 100% SVR using a sofosbuvir-based regimen and more recently Lubetzky *et al.* [37] reported SVR_{12} rates of 97% in 30 of 31 patients that received DAA therapy. Of note, only 6 of 20 patients in Sawinski's series were initiated on DAA less than one-year post-transplant (with a median post-transplant interval to treatment of approximately 888 days and all of the patients in Kamar's study were well beyond 1-year post-transplant. In Lubetzky's study the patients were treated 6 months after kidney transplantation. In contrast, the current report includes patients in whom DAAs were initiated within the first 6 months at a median of 125 days

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post-transplant (IQR 100–169). There are currently no data regarding the potential benefits of early versus late DAA therapy after transplant. Nevertheless, it seems intuitively best to attempt to eradicate the virus early post-transplant before the HCV-associated adverse impacts of glucose intolerance and immune-complex injury to the allograft are able to become clinically evident [38].

Although the number of patients on ribavirin is small, there was no additional impact on SVR in this cohort, unlike the results observed in liver transplant recipients [39]. Of note, ribavirin was associated with higher rates of adverse effects, specifically progressive anemia, compared to patients who did not receive ribavirin. Based on the available literature [35] and our experience, we would suggest that antiviral treatment using a combination of two DAA agents without ribavirin is sufficient for the HCV-infected kidney transplant recipient and that the addition of ribavirin increases the risk of adverse events and might potentially impact patient adherence to treatment. Early initiation of DAA therapy while the patient was still receiving higher doses of immunosuppression did not adversely impact SVR rates.

The effectiveness and safety of sofosbuvir in patients with a creatinine clearance <30 ml/min has not been established [40]. Bhamidimarri *et al.* [41] reported no significant adverse events with high rates of SVR12 in an open-label treatment study of patients with advanced CKD and ESRD using simeprevir and dose-adjusted sofosbuvir. However, Saxena *et al.* [42] reported increased rates of anemia and diminished kidney function in their "real-world" study of CKD patients receiving a sofosbuvir-based DAA regimen. In the current study, there were no significant changes in kidney function using a sofosbuvir-based regimen; however, the patients were post-transplant with a well-functioning allograft and creatinine clearance above 30 ml/min. Until further studies with larger numbers of patients are available, it is recommended that sofosbuvir be used with caution in kidney recipients with a creatinine clearance <30 ml/min.

Prior studies have observed significant alterations in calcineurin inhibitor (CNI) pharmacokinetics accompanying the clearance of hepatitis C viremia that required dosing adjustments to maintain adequate immunosuppression [35,36]. The results of the current study are consistent with these observations and emphasize the importance of intensified patient follow-up after initiating DAA treatment. The mechanism of this altered CNI pharmacokinetics is not established; however one possibility is that there is an improvement in hepatic function accompanying clearance of the virus, resulting in a change in CNI metabolism [35,43–45]. Although not likely to be causative of the change in tacrolimus levels noted in the current study, there are important drug–drug interactions (DDIs) between currently approved DAAs and some of the IS agents commonly prescribed after kidney transplantation that must be taken into account when a decision to treat HCV is made for the postkidney transplant patient. Taken together, although it appears that DAAs can be used safely and effectively in the kidney transplant recipient [34–36,46], careful monitoring of CNI dosing and consideration of potential DDIs are an important component of the management of the patient during this period.

In the current study, patients accepting a kidney from a HCV-positive donor benefited from a significantly shortened waiting time on the UNOS list. Whereas the average waiting time for a deceased donor kidney at our center is 4–6 years, patients being transplanted with a kidney from an anti-HCV-positive donor had a median wait time of only 58 days (IQR 26–184) after being entered into UNet^{sm} for a HCV-positive donor. This advantage has been reported from other centers as well [35,47–49]. In the study by Sawinski *et al.* [35], the nine patients who received a kidney from a HCV-positive donor were reported to have a reduction in their wait-times, although not specified. We would recommend considering this strategy for the HCV-infected kidney transplant candidate that does not have a living donor and has less than METAVIR stage 4 liver fibrosis on pretransplant evaluation. Patients with early or established cirrhosis must be evaluated on a case-by-case basis to determine whether kidney-alone transplant is advisable and whether antiviral therapy should be offered pretransplant [50].

Our study has several limitations. It is a retrospective analysis with a small sample size, thus its applicability to larger numbers of patient with longer lengths of follow-up remains to be determined. Furthermore, most of the patients were from ethnic minorities and the patients were treatment naïve and without cirrhosis on pretransplant liver biopsy so the results may not be generalizable to these other patient groups. Furthermore, most of the patients were genotype 1a and 1b as would be expected in a study on a North American population. Whether our findings would be applicable to other patient populations must be determined by larger prospective studies. Finally, we did not have genotype data on the donors, thus it was not possible to determine with certainty whether superinfection with the

donor genotype occurred at the time of transplantation. Regardless, our preliminary experience represents real world data that offers important caveats and raises important questions that could be better answered in larger, prospective studies.

In conclusion, the current report demonstrates the safety, efficacy and benefits of a program that encompasses HCV positive-to-positive (HCV D+/R+) kidney transplantation followed by early initiation of DAA therapy post-transplant. Taking into account the known survival advantage associated with kidney transplantation and the possibility of substantially shortening dialysis vintage or moving directly into preemptive transplantation, additional studies with larger numbers of patients using this clinical strategy is warranted. Importantly, it will be necessary to determine whether the SVR remains durable in the long-term immunosuppressed patient and whether other adverse outcomes associated with HCV infection, such as post-transplant diabetes mellitus and immune-complex glomerular injury to the allograft, are favorably impacted.

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Conflict of interest

Dr. Roth is on a Scientific Advisory Board for Merck Co. Dr. Bhamidimarri reports Scientific Advisory Board membership for Gilead, Abbvie, Salix, and Bristol-Myers-Squibb. Educator for Alexion. Research support from Gilead, Abbvie, Vital Therapies, Ocera, and Biotest. Dr. Martin reports being an investigator and consultant for Abbvie, Merck, Gilead and Janssen. Drs. Kupin, Guerra, Mattiazzi, Chen, Ciancio, Burke, Ladino and Pedraza have no disclosures to report.

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