

Shorter waiting times for hepatitis C virus seropositive recipients of cadaveric renal allografts from hepatitis C virus seropositive donors

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Abstract: Introduction. The purposes of this study were: 1) to analyze the early results of cadaveric renal transplantation from either hepatitis C virus seropositive (HCV +) or hepatitis C virus seronegative (HCV –) donors into HCV + recipients; and 2) to determine whether HCV + patients with end-stage renal disease (ESRD) might benefit from receiving renal allografts from HCV + donors.

Methods. From January 1997 to June 1999, 28 patients with ESRD and HCV infection underwent 29 cadaveric renal transplants. The data were reviewed retrospectively. Nineteen of the renal transplants were performed with allografts obtained from 15 HCV + donors and 10 with allografts obtained from 10 HCV – donors. The median follow-up was 16.2 months, with an average of 15.4 ± 2 months.

Results. Recipients of HCV + renal allografts had shorter waiting times for transplantation. On average, patients who received a kidney from HCV + donors were transplanted 9 ± 3 months after being placed on the transplant list, compared to 29 ± 3 months for patients who received a kidney from a HCV – donor. Shorter waiting times were noted in every blood type group. There were no significant differences in rejection episodes, infectious complications, renal function, liver function, graft survival, or patient survival.

Conclusions. The use of renal allografts from HCV + donors for HCV + recipients shortens the waiting time for these patients, with no short-term differences in renal and liver function, graft loss, or patient survival.

Aloke K Mandal^{a,1}, Edward S Kraus^b, Milagros Samaniego^b, Rudra Rai^c, Susan L Humphreys^a, Lloyd E Ratner^a, Warren R Maley^a and James F Burdick^a

^a Division of Transplant Surgery, Department of Surgery, The Johns Hopkins Hospital, ^b Division of Nephrology, Department of Medicine, The Johns Hopkins Hospital, ^c Division of Gastroenterology, Department of Medicine, The Johns Hopkins Hospital, Baltimore, MD, USA

Corresponding author: James F Burdick, MD, Division of Transplant Surgery, Department of Surgery, The Johns Hopkins Hospital, 600 N. Wolfe St./Harvey 611, Baltimore, MD 21287-8611, USA. Tel.: +1 410 955-6875; Fax: +1 410 614-2079

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Hepatitis C virus (HCV) infection is epidemic among end-stage renal disease (ESRD) patients. In the United States, the prevalence of HCV infection among ESRD patients is 22%, varying between 0 and 50% at dialysis centers with over 40 patients (1–3). When compared to anti-HCV seronegative (HCV –) ESRD patients, anti-HCV seropositive

(HCV +) ESRD patients had increased rates of liver disease, septic complications, graft loss, and mortality (4–9). Despite these observations, however, renal transplantation is the superior form of renal replacement therapy for HCV + ESRD patients (10, 11). Therefore, anti-HCV seropositivity by itself is not a contraindication for renal transplantation.

As the disparity between the number of patients waiting for kidney transplants and the number of cadaveric renal allografts available continues to increase, this critical shortage in organs has re-

¹ Current address: Division of Transplant Surgery, Department of Surgery, Hennepin County Medical Center, 701 Park Avenue South, Minneapolis, MN 554145-2810, USA.

sulted in the decision of many centers to expand the criteria used to define suitable cadaveric organ donors. Because the prevalence of HCV infection may be as high as 8.3% in some cadaveric organ donor pools, one area of such organ donor criteria expansion is the transplantation of kidneys from HCV seropositive donors into ESRD patients with known HCV infection (12–14). Such a policy may increase the donor pool by close to 400 kidneys (12, 14). Two studies have shown that donor HCV serology has no adverse effects on the short-term outcomes of renal transplantation of HCV + recipients (15, 16).

The purposes of this study were: 1) to analyze the early results of cadaveric renal transplantation from either HCV + or HCV – donors into HCV + recipients at The Johns Hopkins Hospital; and 2) to determine whether HCV + patients with ESRD may benefit from receiving allografts from HCV + donors.

Materials and methods

Patients

From January 1997 to June 1999, 28 patients with ESRD and HCV seropositivity, with confirmed HCV infection by HCV RNA detection with polymerase chain reaction (PCR), underwent 29 cadaveric renal transplants. (One of the recipients whose initial allograft from a HCV + donor was lost because of accelerated acute rejection received a second allograft from another HCV + donor 11 months after her initial transplant.) In 19 of the transplants in HCV + recipients, the donor was HCV + (D +/R +), and – in 10 of these cases – the donor was HCV – (D –/R +). In this short-term study, all patients were followed for a minimum of 3 months and a maximum of 33 months. The median follow-up was 16.2 months, with an average of 15.4 ± 2 months (mean \pm SEM).

Table 1. Characteristics of HCV+ recipients of cadaveric renal allografts procured from HCV+ (D+/R+) and from HCV– (D–/R+) donors

Recipient characteristics	D+/R+ (n = 18)	D–/R+ (n = 10)
Age in years (range)	48 \pm 2 (32–61)	44 \pm 2 (33–54)
Male/female (% male)	12/6 (66%)	8/2 (80%)
African Americans (%)	12 (66%)	6 (60%)
Previous transplants (%)	5 (28%)	6 (60%)
Diabetes mellitus (%)	5 (28%)	1 (10%)
Hypertension (%)	6 (33%)	4 (40%)
Anti-CMV+ (%)	15 (83%)	7 (70%)
Time on dialysis in months (range)	88 \pm 36 (7–253)	79 \pm 21 (3–151)
Time on transplant waiting list in months (range)	9 \pm 3 * (0.5–44)	29 \pm 3 (1–53)

* $p < 0.05$, using a two-tailed t-test for unpaired data.

Data collection

Pre-transplant and post-transplant records were reviewed retrospectively in these 28 patients. Pre-transplant records were reviewed for age, sex, race, etiology of renal disease, time on dialysis, mode of dialysis, time on the kidney transplant waiting list, blood group, cytomegalovirus (CMV) serology, and hepatitis B virus (HBV) serology. Post-transplant records were reviewed for immediate graft function, induction and maintenance immunosuppression, rejection episodes, type of anti-rejection therapy used, serum aminotransaminase and bilirubin levels, post-transplant infections, graft survival, and patient survival. Creatinine clearance was estimated using the Cockcroft–Gault equation.

Statistical analysis

When possible, all values are expressed as mean \pm SEM. Statistical analyses used included: two-tailed t-test for unpaired data, comparison of proportions, and analysis of variance (ANOVA). A p -value of less than 0.05 was considered statistically significant.

Results

Recipient and donor characteristics

The recipient characteristics of the patients in the D +/R + and D –/R + groups are noted in Table 1. There were no differences in gender or race. Although not statistically significant, the recipients who received kidneys from HCV + donors were slightly older. In addition, a history of diabetes mellitus was more common among recipients of allografts from HCV + donors. There were more retransplants among the patients who received kidneys from HCV – donors, which also was not statistically different.

Of note, although there was no significant difference in the number of months that patients from either group were on dialysis, recipients in the D +/R + group had shorter waiting times for transplantation. On average, patients who received a kidney from HCV + donors were transplanted 9 ± 3 months after being placed on the transplant list, compared to 29 ± 3 months for patients who received a kidney from a HCV – donor ($p < 0.05$). Shorter waiting times were noted in every blood type group. This effect on waiting times was highlighted by one recipient in the D +/R + who initially was transplanted 3 months after being placed on the list. She then lost her allograft be-

Table 2. Characteristics of HCV+ (D+/R+) and HCV- (D-/R+) donors for HCV+ recipients

Donor characteristics	D+/R+ (n = 15/19)	D-/R+ (n = 10)
Age in years (range)	46 ± 2* (31–56)	35 ± 6 (4–57)
Cold ischemic time in hours (range)	28 ± 2 (11–45)	22 ± 3 (12–37)
Terminal creatinine in mg/dL	0.9 ± 0.0	0.9 ± 0.2
Anti-CMV+ (%)	13 (87%)	5 (50%)
A,B mismatch	3.2 ± 0.2*	2.3 ± 0.3
DR mismatch	1.6 ± 0.2	1.3 ± 0.1

* p < 0.05, using a two-tailed t-test for unpaired data.

cause of accelerated acute rejection and received a second allograft from another HCV + donor less than 1 yr after the initial transplant.

In terms of donor characteristics, 15 donors provided 19 renal allografts in the D + /R + group, and 10 donors provided 10 allografts in the D - /R + group. A history of intravenous drug use was not elicited in either group; nevertheless, a history of cocaine snorting or selling of drugs was, significantly, more prevalent among the HCV + donors (p < 0.05). A history of alcohol abuse was noted in one donor in each group. Other aspects of the donors are listed in Table 3. The HCV - donors were significantly younger. There was a higher rate of anti-CMV seropositivity in the HCV + donors, which was not statistically significant. The cold ischemic times and terminal serum creatinine of the donors were similar in either groups. In terms of human leucocyte antigen (HLA)-matching, there was a significantly higher degree of HLA-A and HLA-B mismatching in the D + /R + group (Table 2).

Post-transplant results

The results after transplantation are summarized in Table 3. Immunosuppression protocols were similar in both groups. One patient in each group received cyclosporine. The remainder of the patients received tacrolimus. In addition, all patients initially were on prednisone and mycophenolate mofetil. Despite the aforementioned differences in HLA mismatching, there was no difference in rejection between the D + /R + and D - /R + group. Among the D + /R + group, 8 (42%) patients had eight episodes of rejection. Among the D - /R + group, 5 (50%) patients had seven episodes of rejection, with one patient experiencing three episodes of rejection. Steroids alone were used for the treatment of most of these rejection episodes. Two patients in each group required antilymphocytic antibody for the treatment of rejection.

In terms of renal function, the calculated creatinine clearance at various time points up to the first year after transplantation was similar in both groups (Fig. 1). At 12 months, the calculated creatinine clearance was 67 ± 8 mL/min in the D + /R + group and 78 ± 8 mL/min in the D - /R + group. Immediate allograft function was noted in 13 (68%) patients in the D + /R + group, and in 8 (80%) in the D - /R + group. This difference in immediate function was not statistically significant. In the D + /R + patients who required dialysis after transplantation, the average duration of dialysis was 20 ± 6 d, with a range between 5 and 33 d. The number of patients who developed proteinuria was similar in each group (Table 3).

Liver dysfunction was defined as an elevation of serum alanine aminotransferase (ALT) levels greater than twice normal levels. Acute liver dysfunction was noted in 3 (16%) of the D + /R + patients and in 1 (10%) of the D - /R + patients (Table 3). Chronic liver dysfunction, which was defined as persistent elevations of ALT for at least 3 months, was noted in 2 (11%) of the D + /R + recipients and in 1 (10%) of the D - /R + recipients (Table 3). The trend in serum ALT is depicted in Fig. 2. A peak in ALT levels was noted in both groups 1 month after transplantation, with a higher mean ALT level noted in the D + /R + group. The mean ALT levels then returned to normal ranges (0–40 IU/L). Nevertheless, from 6 months to 1 yr after transplantation, the ALT was higher in the D + /R + group than in the D - /R + group. Because of the wide variability, there was no statistical difference in the aminotransferase levels between the groups at any given time.

Graft and patient survival were similar in both groups (Table 3). There were two deaths in the study, one in each group. The two deaths were from overwhelming Gram-negative sepsis 2 wk after transplantation in the D + /R + group and from sudden cardiac death 9 months after transplantation in the D - /R + group. An autopsy on the patient in the D + /R + group demonstrated severe liver disease that was not appreciated in his preoperative evaluation. He was transplanted within 2 wk of being placed on the transplant list. In terms of graft loss, accelerated acute rejection and chronic allograft nephropathy caused the losses in the D + /R + group. In the D - /R + group, the causes of the three graft losses included: accelerated acute rejection, primary nonfunction, and chronic allograft nephropathy. In terms of infectious complications, other than the death from sepsis, there were no differences in CMV infection or other infections between the two groups.

Table 3. Characteristics of patients after transplantation

	D+/R+ (n = 19)	D-/R+ (n = 10)
Number of patients rejecting (%)	8 (42%)	5 (50%)
Rejection episodes	8	7
Rejection episodes per patient	1.0	1.4
Patients with proteinuria	5 (26%)	3 (30%)
Liver dysfunction		
Acute (%)	3 (16%)	1 (10%)
Chronic (%)	2 (11%)	1 (10%)
Graft loss excluding death (%)	2 (11%)	3 (30%)
Death (%)	2 (11%)	1 (10%)

Discussion

This study demonstrates that, in the early period, transplantation of kidneys from HCV + cadaveric donors into HCV + recipients did not effect overall patient survival, graft survival, liver function, or rejection episodes when compared to HCV + recipients of kidneys from HCV – cadaveric donors. These results are in agreement with other recent reports (15, 16). In addition, our study demonstrates a potential benefit in the transplantation of cadaveric renal allografts from HCV + donors for HCV + recipients; specifically, the use of these organs shortens the time on the transplant waiting list for this group of ESRD patients.

HCV infection at the time of referral for renal transplantation is associated with an increased risk of death, regardless of which renal replacement strategy is used (10, 11). As with other patient groups, within 6 months after transplantation, mortality is greater among those patients who are transplanted than those who are not. However, after that initial period, renal transplantation is associated with increased survival. Therefore, shortening the waiting time for ESRD patients with HCV infection appears to be beneficial. In our study, the waiting time for HCV + ESRD patients who received a kidney from a HCV + donor was one-third of the time for those who received a kidney from a HCV – donor.

Despite this potential advantage, the use of organs from this donor pool is surrounded by controversy. It is well known that HCV infection can be transmitted by organ transplantation (17). Moreover, HCV infection is the major cause of post-transplant liver disease (18). Since T-cells are important in lysing cells infected by virus and produce cytokines that inhibit viral replication, there is considerable concern that immunosuppression may favor the development of chronic infection that, in turn, would lead to chronic hepatitis

and then cirrhosis. Once infected, post-transplant patients cannot undergo interferon-alpha-based treatment of their HCV infection because of the increased incidence of rejection (7, 19).

In the initial report on using renal allografts from HCV + donors in HCV + recipients, Morales and colleagues (15) noted that 4 out of 5 HCV + recipients who were HCV-RNA negative by PCR testing became HCV-RNA positive after receiving a kidney from a HCV-RNA positive recipient. Moreover, half of these patients then developed chronic liver disease. Therefore, renal allografts from HCV + donors should only be used for recipients whose HCV infection is confirmed by detection of HCV-RNA by PCR testing.

There are at least six genotypic variations of HCV and over 30 subtypes. The different genotypes of HCV also differ in their virulence and have differing susceptibilities to current modes of treatment (20). Moreover, antibodies against HCV are not neutralizing and do not provide protective immunity (21). Therefore, transplantation from a HCV + donor into a HCV + recipient may result in superinfection, persistence of the pre-transplant strain, or a chronic mixed infection. Although current studies do not demonstrate any adverse effects in the early post-transplant period, increased or accelerated liver damage may occur in superinfected individuals (22).

This study did not demonstrate any difference in liver dysfunction between the two groups when reviewing serum ALT levels. The serum ALT level, however, is a poor predictor of HCV-associated liver disease (1). Also, all current studies suffer from a lack of long-term data. HCV infection has a chronic and indolent course with the appearance

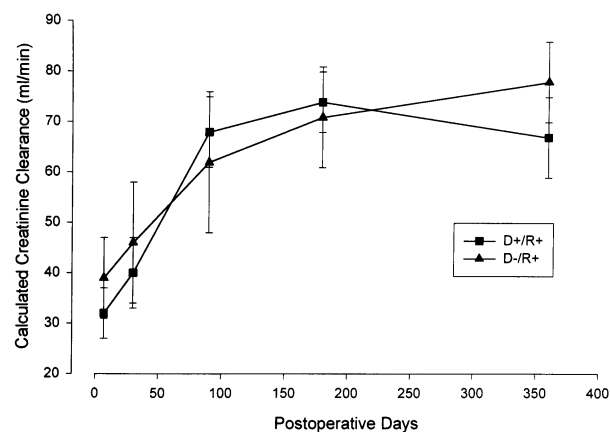


Fig. 1. Change in creatinine clearance over the first year after transplantation. Mean values are expressed as closed squares (D + /R +) or as closed triangles (D – /R +). Error bars depict standard error of the mean.

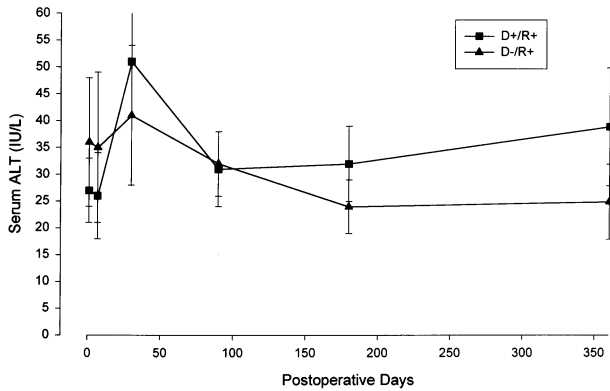


Fig. 2. Change in serum alanine aminotransferase (ALT) levels over the first year after transplantation. Mean values are expressed as closed squares (D + /R +) or as closed triangles (D - /R +). Error bars depict standard error of the mean.

of chronic hepatitis within 10 yr of infection, cirrhosis within 20 yr, and hepatocellular carcinoma within 30 yr. Nevertheless, early cirrhosis and bridging fibrosis may be seen as early as 2 yr after infection. Unfortunately, only liver biopsy can determine the severity of liver injury (23). This point is underscored by the one mortality noted in the D + /R + group in this study. This patient had been placed on the kidney transplant list 2 wk before his transplantation. A liver biopsy was not performed because no evidence of liver disease could be elicited by history, physical examination, or laboratory tests. The extent of the patient's liver disease was appreciated only at the time of autopsy. Therefore, a liver biopsy on all ESRD patients with HCV infection who are considered for renal transplantation should be performed. Moreover, only serial post-transplant biopsies with long-term follow-ups will provide information on the effect of using HCV + donors in the setting of renal transplantation for HCV + recipients.

Moreover, in addition to its effect on the liver, HCV also is associated with kidney diseases such as proteinuria and glomerulonephritis (18, 24). Because of this association, HCV + renal transplant recipients should be carefully followed for proteinuria. In our study short-term study, there was no difference in the incidence of proteinuria.

The advocacy of using HCV + donors for HCV + recipients has been spurred by the ongoing cadaveric organ shortage. As mentioned, close to 400 additional renal allografts may be available with such a policy (12, 14). Additionally, there may be newer treatment options for these patients. For example, one study has shown that pulsatile perfusion may clear the virus from the infected allograft (25). While current therapy is interferon-alpha-

based and may increase the risk of rejection, there are newer drugs on the horizon, such as protease and helicase inhibitors, that may be used in the future in the post-transplant period. Finally, since cardiovascular mortality remains more common than death from liver disease in HCV + ESRD patients on dialysis, getting these patients off of dialysis should be the primary goal.

While renal transplantation is the superior mode of renal replacement therapy for HCV + ESRD patients, this group of ESRD patients is predisposed to infectious complications, liver disease, graft loss, and mortality. Therefore, the pre-transplant evaluation and post-transplant care of these patients has to be tailored for their HCV infection (4–11). The utility of HCV-RNA detection by PCR and pre-transplant liver biopsies has already been mentioned. Immunosuppression should be tailored in order to avoid infectious complications. Careful follow-up should detect the presence of proteinuria. Finally, only long-term studies with serial liver biopsies will provide information on the course of transplanting HCV + renal allografts into ESRD patients with HCV infection.

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