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Transplantation of Renal Allografts From Organ Donors Reactive for HCV Antibodies to HCV-Negative Recipients: Safety and Clinical Outcome

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Introduction: Because of the shortage of available organs for renal transplantation, strategies enabling the safe use of organs from donors with potential chronic infections such as hepatitis C are necessary. The aim of this study was to analyze the outcome of renal transplant donation from hepatitis C virus (HCV)-positive donors.

Methods: Between September 2002 and May 2007, 51 kidneys (34 donors) reactive for HCV antibodies were further evaluated. Six kidneys (5 donors) were transplanted to 6 recipients with known chronic HCV infection. The remaining 29 donors underwent extended virological testing. Nine donors were HCV RNA positive and thus not suitable for HCV-negative patients. Twenty donors (21 kidneys) did not have detectable HCV RNA copies and were transplanted into 21 HCV-negative recipients. Clinical outcomes focusing on safety, allograft function, and *de novo* HCV infection in the recipient were collected.

Results: There were no *de novo* HCV infections detected in recipients who were HCV negative before transplantation. The extended virological donor screening did not have an impact on median cold ischemia time. Five-year graft survival was 75%.

Discussion: Organs from anti-HCV-reactive, nonviremic donors can be transplanted safely to HCV-negative recipients.

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In 1991, Pereira *et al.*[1] demonstrated that hepatitis C virus (HCV) can be transmitted by organ transplantation. The number of organ donors showing antibodies against HCV (HCV-AB) is estimated to be approximately 5% of all potential cadaveric organ donors in Europe and the USA.[2–4] In contrast, the prevalence of HCV is estimated be around 0.5% to 0.7% in the German adult general population (HCV-AB positive).[5–7] For other countries in Western Europe, the number varies and ranges from 0.5% to 2.0%.[8] Taking into account the shortage of organs, loss of organ donors due to false-positive HCV-AB is a relevant problem in transplantation.

Transplanting HCV-positive recipients entails a number of clinical consequences such as limited HCV treatment options after transplantation, limited graft and/or patient survival, and exacerbation of liver disease. Nevertheless, kidney transplantation is currently the preferred treatment option for patients with end-stage renal disease and HCV infection who do not present with liver cirrhosis.[9–14]

Because of ongoing controversy surrounding the consequences of transplanting HCV-positive kidney recipients with HCV-positive organs, most transplantation centers in the Eurotransplant region are not willing to transplant kidneys of HCV-positive donors. The transplantation of HCV-AB-positive organs to

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HCV-AB-negative recipients is performed in few transplantation centers at present. In the past, different policies regarding the use of these organs were established.[1,15–18]

Because of the shortage of organs, strategies for the use of organs from HCV-AB-positive donors need to be developed. New and rapid virological test methods for HCV are enabling strategies that had been impossible in the past considering the time frame of organ procurement and transplantation. Different methodologies are usually applied to assess the HCV status of a donor. Enzyme immunoassays (EIAs) serve as screening tests to assess the presence of anti-HCV antibodies. The specificity of the test result and the presence of anti-HCV antibodies can be confirmed by western blot-based methods. However, the infectivity of a donor cannot be judged entirely on the grounds of antibody serology. The viral load of the donor is crucial to determine the risk of infection and can be assessed by nucleic acid testing (NAT). Thus, the evaluation of HCV-positive donors is complex and multiple test methodologies are needed to assess the infectivity of a donor.

The aim of this study was to analyze the clinical outcome of HCV-negative recipients who were transplanted with renal allografts from nonviremic HCV-AB-reactive donors. Thus, clinical outcome focusing on *de novo* HCV infections, cold ischemia time, allograft function, and safety was assessed.

METHODS

Organ Donors

Between September 2002 and May 2007, 269 kidneys from deceased organ donors were accepted for adult recipients at our transplant center. A total of 51 kidneys from 34 donors were tested positive or borderline positive for HCV-AB in the organ donor screening (ODS). All organs were stored by standard cold storage.

Six kidneys of 5 donors with a positive HCV-AB test were transplanted to 6 recipients with known chronic HCV infection before extended virological testing. The remaining 29 of 34 donors (donating 45 kidneys) tested positive or borderline for HCV-AB in the initial screening were subject to the extended donor screening.

Extended Donor Screening

The extended donor screening included qualitative or quantitative HCV RNA testing. All testing procedures available at the time of the organs' arrival at our hospital were used for analysis. This included the repetition of an EIA (third generation Bio-Rad, Munich, Germany), replaced by enhanced chemiluminescence microparticle immunoassay (CMIA, Abbott, Wiesbaden, Germany) since August 2004 for HCV-AB. The specificity of reactive results in the HCV-AB immunoassay was further confirmed by an immunoblot (Blot, Mikrogen, Neuried, Germany), polymerase chain reaction (Roche, Basel, Suisse; lower limit of detection 50 IU/ml), or transcription-mediated amplification (Siemens, Munich, Germany; lower limit of detection 10 IU/ml). Whenever possible, all 3 testing procedures were performed simultaneously. According to the results of the enhanced donor screening, the renal allografts were handled as follows:

- Organs from donors that tested reactive in the ODS without any additional testing were declared HCV positive and were only transplanted to recipients with chronic HCV infection.
- Organs from donors that were tested reactive for HCV in the ODS and were confirmed to be positive for HCV RNA in the extended donor screening were only transplanted to recipients with chronic HCV infection.
- Organs from donors that were tested reactive for HCV in the ODS and were negative for HCV RNA in the extended donor screening were transplanted either to recipients with chronic HCV infection or to recipients who were negative for HCV.

Transplant Recipients

Recipients were predefined by the Eurotransplant allocation protocol. If kidneys are rejected by 5 different centers, a different allocation algorithm is applied according to the Eurotransplant protocol. In this case, the organs are allocated according to the rules for extended allocation and rescue allocation. These rules are explicitly explained and defined in chapter 3 of the Eurotransplant manual.[19] Recipients for "Organ rescue allocations" were chosen via interdisciplinary consent with the best medical judgment regarding the risk-benefit profile. In total, 21 patients negative for HCV (HCV group) received renal allografts from donors being reactive for HCV-AB in the ODS but were lacking detectable HCV RNA. The recipients were explicitly informed about the risk to acquire an HCV infection that is estimated to be low. Every recipient gave written informed consent concerning this risk.

Definitions and Statistic Analysis

The waiting time was calculated as the time from first dialysis to transplantation. Also, the time on the transplant list was calculated as the time from being registered by Eurotransplant until the day of transplantation.

These results were compared with the waiting time and time on transplant list of 253 other adult renal recipients who underwent solitary cadaver kidney transplantation at our center during the same period. Data concerning graft function (creatinine, urea), liver function (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase,

bilirubin, international normalized ratio), and screening tests for HCV by CMIA or polymerase chain reaction/transcription-mediated amplification were collected and analyzed retrospectively.

The deceased donor score was calculated for the evaluation of the donor according to Nyberg *et al.*[20]

For the evaluation of quantitative variables, the Mann-Whitney *U* test was used. These data are presented as medians with range. Qualitative variables were compared with the χ^2 and/or Fisher exact test. A P value < 0.05 was considered to be significant.

RESULTS

Extended Donor Screening Findings

Six kidneys of 5 donors with a positive HCV-AB test in the ODS were transplanted to 6 recipients with known chronic HCV infection before extended virological testing. The specimens of the remaining 29 HCV-AB-reactive organ donors underwent extended virological testing for HCV including EIA or CMIA, immunoblot and/or NAT. The test results are given in detail in Figure 1. Briefly, 28 of 29 organ donors were further evaluated with NAT for detectable HCV RNA. Eight donors were positive for HCV RNA. Interestingly, all of these 8 donors were shown to have a positive immunoblot. These viremic donors were considered as potentially infective and in general unsuitable for HCV-negative recipients. The remaining 20 donors (71%) lacked detectable HCV RNA. Thus, these donors were considered suitable for HCV-negative recipients and 21 allografts were transplanted accordingly. In all cases, in which EIA/CMIA showed no reactivity on repetition, HCV RNA was not detectable by NAT (detailed results are shown in Table 1). Specificity, sensitivity, negative and positive predictive values of the immunoblot, and the EIA/CMIA in comparison with NAT are outlined in Table 2.

Analysis of Demographic Data

The study population of HCV-negative recipients showed no significant differences in waiting time. Interestingly, the mean cold ischemia time was not significantly

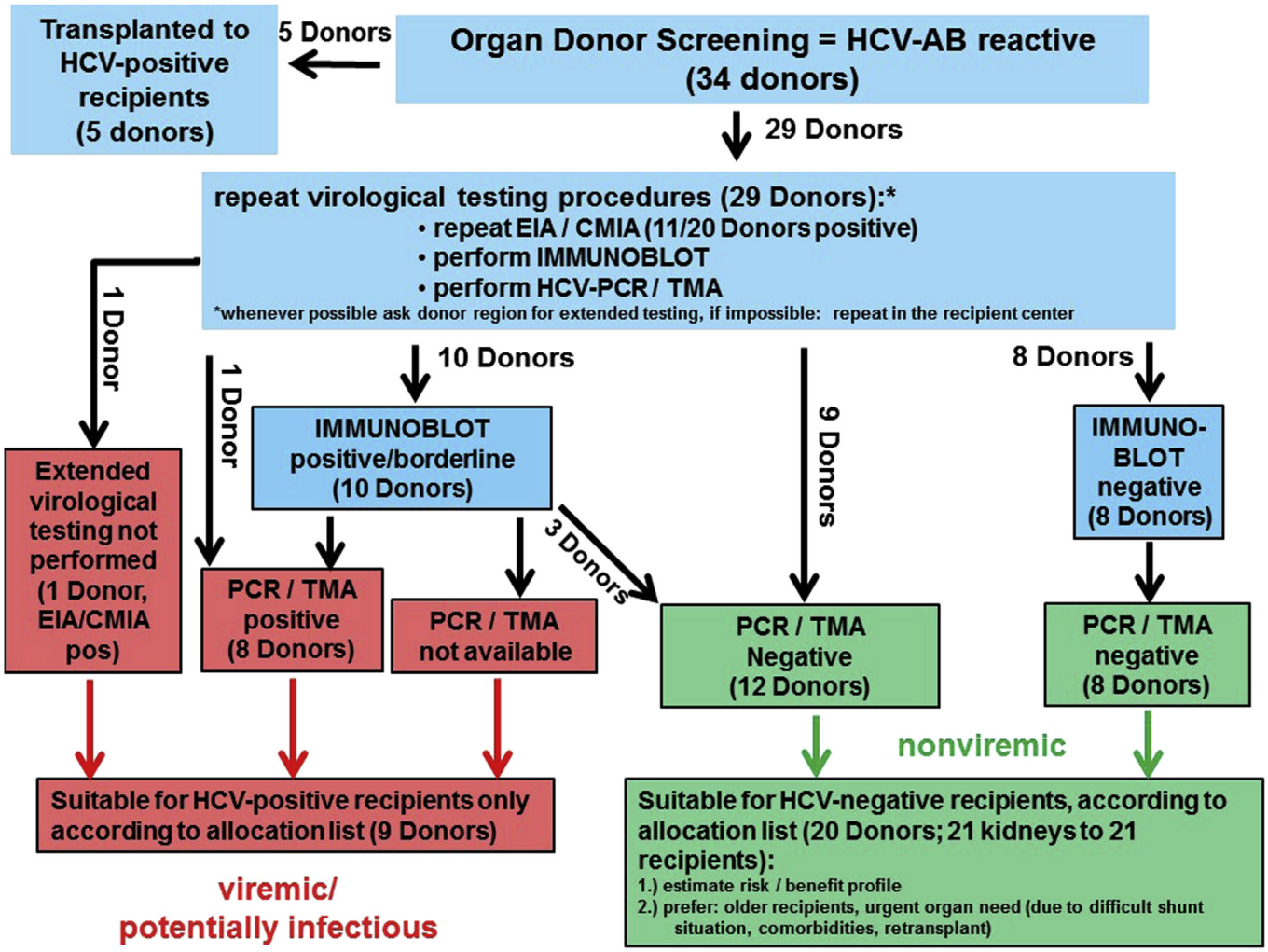

Figure 1. Test results of the extended donor screening. CMIA, chemiluminescence microparticle immunoassay; EIA, enzyme immunoassay; HCV, hepatitis C virus; PCR, polymerase chain reaction; TMA, transcription-mediated amplification.

Table 1. Results of the extended organ donor screening

Donor no.	Immunoblot	EIA/CMIA	PCR/TMA	b-DNA (IU/ml)	Genotype	Location of test
1						Not tested
2						Not tested
3	Negative	Negative	Negative			Donor region
4						Not tested
5		Negative	Negative			Recipient center
6			Negative			Recipient center
7			Negative			Recipient center
8	Positive	Positive	Positive	490,000	2b	Recipient center
9	Positive	Positive	Positive	27,000	1b	Recipient center
10		Positive				Donor region
11	Negative	Positive	Negative			Recipient center
12						Not tested
13						Not tested
14	Negative	Negative	Negative			Recipient center
15	Positive	Positive	Positive	297,700	1b	Recipient center
16	Positive	Positive	Positive	587,700	1b	Recipient center
17	Negative	Positive	Negative			Recipient center
18	Negative	Negative	Negative			Recipient center
19	Negative	Negative	Negative			Recipient center
20		Negative	Negative			Recipient center
21	Negative		Negative			Recipient center
22			Negative			Donor region
23	Positive	Positive	Positive	2,265,000		Recipient center
24	Doubtful		Negative			Recipient center
25	Doubtful		Negative			Donor region
26	Positive	Positive	Positive	<615	n.a.	Recipient center
27	Positive	Positive	Positive	10,600	n.a.	Recipient center
28		Negative	Negative			Recipient center
29		Negative	Negative			Recipient center
30			Positive	3,780,000	1a	Donor region
31	Positive	Positive	Negative			Recipient center
32	Negative	Negative	Negative			Donor region
33			Negative			Donor region
34			Negative			Donor region

CMIA, chemiluminescence microparticle immunoassay; EIA, enzyme immunoassay; PCR, polymerase chain reaction; TMA, transcription-mediated amplification.

different from the controls despite extended virological testing including NAT. The donor age was significantly younger compared with the controls (Table 3).

Deceased Donor Score Findings and Transplant Outcome

The analysis of the deceased donor score shows that 17 of 21 kidneys (81%) were classified as category A or B. There were 2 graft losses in the first year after transplantation. Of 19 recipients, 16 (84%) had a serum creatinine below 2 mg/dl after 1 year (Table 4). Five-year allograft survival was 75%. No patient developed HCV as shown by repeated negative HCV-AB tests during an observation period of at least 43 months after transplantation. There was a minimum time lag of 18 months between transplantation and the tests performed. In all but 4 patients, results from post-transplant HCV NAT were available. None of the patients tested had detectable HCV RNA viral load.

DISCUSSION

Our study demonstrates that renal allografts of HCV-AB-reactive, nonviremic donors can be used safely for HCV-negative recipients. Furthermore, we showed that cold ischemia time is not significantly influenced by extended virological testing. Moreover, renal allograft survival was excellent with 75% at 5 years.

De novo infection of recipients with HCV is a relevant issue in organ transplantation. Reports of

Table 2. Validation of tests compared with nucleic acid testing

	Immunoblot	EIA/CMIA
Positive predictive value	87.5% (7/8)[a] 70% (7/10)[b]	70% (7/10)
Negative predictive value	100% (8/8)	100% (9/9)
Sensitivity	100% (7/7)	100% (7/7)
Specificity	88.8% (8/9)[a] 72.4 (8/11)[b]	75% (9/12)

CMIA, chemiluminescence microparticle immunoassay; EIA, enzyme immunoassay.
[a]If doubtful is interpreted as negative.
[b]If doubtful is interpreted as reactive.

Table 3. Analysis of demographic data

Subject	Controls	HCV-negative recipients	*P* value
Patients	n = 253	n = 21	
Time on waiting list (mo)	72. (2.24–182.12)	65 (19.79–101.87)	0.45
Time on transplant list (mo)	45 (0.49–128.50)	44 (4.17–97.3)	0.57
Cold ischemic time	16 h 31 min (4 h 25 min–32 h)	18 h 58 min (10 h 30 min–24 h 44 min)	0.06
Donor age	53 (15–86)	41.5 (14–71)	<0.001

HCV, hepatitis C virus.

unintended *de novo* viral infection with HCV or HIV raised a debate about high-risk donors and NAT.[21–23] The estimated number of organ donors being reactive for HCV-AB is different from findings of other cross-sectional studies;[2–8] this discrepancy can be explained by the increased sensitivity and specificity of the serological tests for HCV available. Reactivity for HCV-AB needs further interpretation and confirmation; it can imply acute seroconversion in HCV infection, chronic infection, persisting reactivity after eliminated HCV infection, or a false-positive test.[24] Thus, different strategies exist to identify donors with very low risk of infectivity. The results of the extended donor screening in this analysis underline the complexity to characterize the infectivity of a donor at the time of organ donation. It is useful to repeat the serological testing for detection of HCV antibodies and to confirm the previous result with immunoblot. In our study, 9 of 20 donors failed to show HCV-AB in the repeated EIA/CMIA, whereas 11 were repeatedly positive. Of these 11 cases, 10 were assayed again in an immunoblot and the presence of HCV antibodies was confirmed in 8 cases. However, serological assays indicate recent or past HCV infection but do not reflect current infectivity. Viremia indicates infectivity of the donor, and transplantation of these organs leads to *de novo* HCV infection or superinfection in the case of genotype mismatch in a recipient.[25–28] Therefore, it is necessary to perform NAT in every case in which a reactive HCV-AB result has been obtained.[15] When NAT for HCV RNA was used for the extended virological screening, 20 of 28 (71%) anti-HCV-reactive donors were negative for HCV-RNA and were predicted to transmit HCV infection with a very low probability.[1,29] Thus, 21 renal allografts of these 20 donors were transplanted to HCV-negative recipients. The expected result from transplanting an anti-HCV-reactive but HCV-RNA-negative organ to a recipient without HCV infection was the lack of *de novo* HCV infection as has been described before by Aeder *et al*.[30] Indeed, in our series of HCV-negative recipients, no *de novo* HCV infection occurred. Interestingly, the quality of the 21 allografts was judged as category A or B based on the deceased donor score. Moreover, 5-year graft survival was excellent with 75%. Previous studies showed increased mortality of patients receiving renal allografts from donors with positive anti-HCV antibodies as compared with recipients of HCV-negative organs.[31–34] However, in these studies, donors could not be stratified according to viral load. Nevertheless, recipients of HCV-positive organs still showed an advantage in survival compared with matched patients remaining on the waiting list.[31–34] Thus, excluding all HCV-reactive donors without further evaluation of viremia may lead to loss of significant numbers of renal allografts suitable for HCV-negative recipients.

Table 4. Deceased donor score findings and renal allograft outcome

	HCV-negative recipients
Graft loss	2
Patient loss	0
DDS category	
A	6
B	11
C	3
D	1
Creatinine (1 yr)	
<1.5 mg/dl	11
>1.5–<2 mg/dl	5
>2–<2.5 mg/dl	1
>2.5 mg/dl	2

DDS, deceased donor score; HCV, hepatitis C virus.

Extended virological testing was performed in most of the cases at the recipient center and did not significantly influence the median cold ischemia time. Modern point-of-care systems for detection of HCV-RNA have a low turnaround time of the test results and are no limiting factor in the transplantation procedure; usually modern NAT assays take no longer than 6 hours. However, these assays need a certain expertise and should be performed by trained specialists. Thus, specialized personnel needs to be available on request to perform these assays. Therefore, it is possible to perform sophisticated, additional testing to obtain information on infectivity of HCV-reactive donors within the time frame of organ procurement and transplantation.

Importantly, ODS showing reactivity for HCV-AB screening must be interpreted as current HCV infection if there is no further screening for viremia available. Transplantation of these organs is only safe

for HCV-infected patients after careful consideration.[1,27,35–37] The KDIGO guidelines for hepatitis in chronic kidney disease state that "…kidney donors are best screened for HCV infection using NAT, which is the optimal way to distinguish between donors who may or may not be potentially infectious…."[9,14] Although the KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of HCV infection in chronic kidney disease and the resulting European Renal Best Practice statement suggest "…that transplantation of kidneys from donors infected with HCV should be restricted to recipients with positive HCV RNA results…," it is also acknowledged in the very same document that "…not all anti-HCV-positive donors are viremic, so discarding kidneys from EIA-positive donors will result in the loss of kidney that could otherwise be used…."[9] The grade of recommendation is weak because it results from a consensus-based recommendation. The statement of the American Society of Transplant surgeons is even more reserved concerning HCV-positive organ donors.[38] The National Kidney Foundation suggested in their commentary to the KDIGO guideline that a registry should track clinical outcomes of HCV-positive recipients transplanted with kidneys of HCV-infected donors.[39] Currently, there is no registry for this entity of patients and long-term data are rare. Therefore, accurate and long-term follow-up of patients receiving kidneys from HCV-reactive donors—as performed at our center—is needed urgently. We have to emphasize that our series started long before the current guidelines were published. Recently, novel antiviral drugs have become available that induce a sustained virological response—that is, absence of viremia—in patients with chronic HCV infection.[40] In future, these drugs may allow prevention or treatment of HCV infection in recipients receiving renal allografts of viremic donors. Therefore, viremic donors with chronic HCV infection might be a potential source of donors in the future.[41,42] In addition, the number of HCV-positive, nonviremic donors may increase as a result of the new therapeutic strategies. Thus, the application of NAT for organ donor testing will increase and might become routine. The risk of HCV transmission is—if this strategy is applied more widely—low but not zero. Accordingly, a recent case series reported transmission of HCV from 3 organ donors with negative NAT.[43] However, all donors could be classified as "high-risk donors" retrospectively. This case series demonstrates that careful stratification of donors according to risk behavior for HCV infection such as nonmedical drug injection will become more important.[43,44] Our study has some limitations. It is a retrospective, noncontrolled study, and as a single center trial, it carries a bias risk. On the other hand, our study is one of the largest case series on this topic. The presented data indicate clearly that HCV-AB-positive organs can be transplanted if extended virological testing is implemented. Even if this approach improves the organ shortage only slightly, it is an opportunity.

In conclusion, these data confirm that transplantation of renal allografts from nonviremic HCV-AB-reactive donors to HCV-negative recipients is safe. HCV-AB-reactive organs should not be denied for transplantation in general; as has been demonstrated in our series, organ quality and graft survival are not inferior. Thus, transplantation of HCV-AB-reactive renal allografts to HCV-negative recipients should be considered after extended virological testing, and comprehensive informed consent needs to be obtained from the recipient.

DISCLOSURE

All the authors declared no competing interests.

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