American Journal of Transplantation 2010; 10: 2453–2462
Wiley Periodicals Inc.

doi: 10.1111/j.1600-6143.2010.03280.x

Long-Term Experience With Kidney Transplantation From Hepatitis C-Positive Donors Into Hepatitis C-Positive Recipients

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Kidney transplantation from hepatitis C virus (HCV) antibody positive donors (HCVD+) into HCV antibody positive recipients (HCVR+) is controversial. We implemented this policy in our units in 1990. Herein, we report the long-term safety of this strategy. From March 1990 to March 2007, 162 HCVR+ received a kidney from HCVD+ (group 1) and 306 from HCVD− (group 2) in our units. Mean follow-up was 74.5 months. Five-and 10-year patient survival was 84.8% and 72.7% in group 1 *vs.* 86.6% and 76.5% in group 2 (p = 0.250). Three deaths in group 1 and two in group 2 were liver-disease related. Five- and 10-year graft survival was 58.9% and 34.4% versus 65.5% and 47.6% respectively (p = 0.006) while death-censored graft survival was 69% and 47% versus 72.7% and 58.5% (p = 0.055). Decompensated chronic liver disease was similar: 10.3% versus 6.2%. Cox-regression analysis could not identify the donor's HCV serology as a significant risk factor for death, graft failure and severe liver disease in HCVR+. In conclusion, long-term outcome of HCVR+ transplanted with kidneys from HCVD+ seems good in terms of patient survival, graft survival and liver disease. HCVD+ was not a significant risk factor for mortality, graft failure and liver disease among HCVR+. These data strongly suggest that the use of kidneys from HCVD+ in HCVR+ is a safe long-term strategy that helps to prevent kidney loss.

Key words: Hepatitis C, kidney transplantation, liver disease, organ donation

Abbreviations: ALT, Alanine Aminotransferase; APRD, Adult Polycystic kidney disease; CLD, Chronic Liver Disease; DGF, Delayed Graft Function; HCV, Hepatitis C virus; HCVD+, Hepatitis C virus Antibody Positive Donor; HCVD−, Hepatitis C virus Antibody Negative Donor; HCVR+, Hepatitis C virus Antibody Positive Recipient; IT, induction with antilymphocyte antibodies; KDIGO, Kidney Disease: Improving Global Outcomes; MMF, Mycophenolate Mofetil; NODAT, New Onset of Diabetes After Transplantation; PCR, Polymerase Chain Reaction; PRA, Peak Panel Reactive Antibodies; RNA, Ribonucleic Acid; sCr, Serum Creatinine; UNOS, United Network for Organ Sharing.

Received 07 March 2010, revised 19 July 2010 and accepted for publication 07 August 2010

Introduction

The waiting list for renal transplantation has increased at a higher rate than the number of donors and organs. Even in Spain, with the highest deceased donation rates ever described, approximately 4000 patients were on the waiting list for kidney transplantation last year. However, only about 2200 procedures are performed annually (www.ont.es). Therefore, the use of expanded criteria donors and donors with potentially transmissible diseases has been established as a way to mitigate this global organ shortage.

Because hepatitis C virus (HCV) infection is transmitted through organ transplantation (1–5) there is almost universal consensus on rejecting kidneys from HCV antibody positive donors (HCVD+) for transplantation in HCV antibody negative recipients (6). However, there is still controversy regarding the use of these kidneys for HCV antibody positive recipients (HCVR+), and some countries even have legal and/or technical provisions in force which preclude the use of these organs.

In 1990, our two Spanish centers adopted the policy of using kidneys from HCVD+ in HCVR+. This strategy, approved by the *Nephrology and Transplantation Departments*, was safe in the short term (7). However, it was modified in July 1993, after it was observed that four out of five HCVR+ with a negative HCV RNA before transplantation became HCV RNA positive after receiving a kidney graft from an HCV RNA positive donor, two of them

developing what we defined as biochemical chronic liver disease (CLD) (8). Since then, the use of kidneys from HCVD+ has been limited to recipients with positive HCV ribonucleic acid at the moment of transplantation. This has become a routine policy in our centers, supported by the *Spanish National Transplant Organization*. Our experience has become a landmark reference for international guidelines, including the recently edited by the Kidney Disease: Improving Global outcomes (KDIGO) foundation (9–11). However, there are doubts about its long-term safety (12) and some groups are still reluctant to use HCV antibody positive kidneys. Therefore, in this study, we aimed to assess the long-term results of our strategy for renal transplantation from HCVD+.

Patients and Methods

General policy for the transplantation of kidneys from HCV antibody positive donors

Pretransplantation: Since March 1990, all dialysis patients with HCV antibody positive have been informed about the possibility of renal transplantation from an HCVD+ at their inclusion on the waiting list. Since July 1993, this option has been limited to patients with positive HCV RNA when placed on the waiting list. A specific informed consent has been obtained from those patients who accept being transplanted from an HCVD+.

Noteworthy, during the last 10 years, the allocation policy in both our centers has varied, taking into account the significant increase in the age of both donors and recipients (13). Hence, the general allocation policy is based on the use of kidneys from old donors into old recipients. Kidneys are allocated into HCVR+ according to these same criteria. The same criteria also apply for kidneys from HCVD+, but these organs are allocated into those HCVR+ who have accepted being transplanted with kidneys from HCVD+ in advance.

Posttransplantation: Pulsatile perfusion is not used for preservation in our series. The long-term care of HCVR+ is performed as previously published (14). In summary, induction with antilymphocyte antibodies (IT) is only used in immunologically high-risk patients, either because of a highly sensitized status or because of a history of previous transplants lost due to immunological reasons. The patients are closely followed up in order to detect HCV-related complications early. Liver ultrasound is performed at least yearly and liver histology is obtained when clinically indicated.

HCV determinations: Anti-HCV antibodies were detected by first generation ELISA during 1990–1994, second generation ELISA between 1994 and 1998 and third generation ELISA from 1998 on. HCV RNA was determined by polymerase chain reaction (PCR), as previously described (8). HCV RNA has been detected in plasma with the Amplicor system, according to the manufacturer's manual (Roche Molecular Diagnostics, Basel, Switzerland).

Methodology for the present analysis

Inclusion and exclusion criteria: Clinical charts of renal transplants from deceased donors performed in patients with HCV antibody positive at transplantation in both our units from March 1990–March 2007 were reviewed retrospectively. For the purpose of this analysis, patients with HBsAg positive at transplantation, those previously treated with Interferon and those who had received a previous or simultaneous nonkidney solid organ transplant were excluded.

Study groups: HCVR+ were distributed according to their donor's HCV serology in two groups: those transplanted with a kidney from an HCVD+ (Group 1) versus those who received their kidney from an HCVD− (Group 2).

Variables collected: Patients were followed up until death, graft loss (transplantectomy, return to chronic dialysis or retransplantation) or last available visit. Information was collected on baseline demographic characteristics of the recipients and their donors, peak panel reactive antibodies (PRA), induction and maintenance immunosuppression at discharge after transplantation, date and cause of death, date and cause of graft loss, delayed graft function (DGF), acute rejection episodes, recipient's HCV RNA before and after transplantation, biochemical liver profile, new onset of diabetes after transplantation (NODAT), serum creatinine (sCr) and 24 h proteinuria at the last available visit and *de novo* or recurrent HCV-related glomerulonephritis.

Definitions

- Highly sensitized patients' were defined as those with a current and/or historical PRA $\geq$ 50%.
- 'Delayed graft function' was defined as the need for dialysis during the first week after transplantation.
- 'Acute rejection' was considered when clinically suspected and/or biopsy proven.
- 'Liver disease' The assessment of posttransplant liver disease was based on alanine aminotransferase (ALT) levels. 'Mild CLD' was defined as the elevation of ALT levels below 2.5 times the upper normal limit. ALT levels increase over 2.5 times the upper normal limit for more than six consecutive months was defined as 'moderate CLD'. An episode of 'acute hepatitis' was considered if ALT levels were 2.5 times greater than the upper normal limit for more than one week but less than six consecutive months. Finally, 'decompensated CLD' was defined as the development of at least one episode of ascites, hepatic encephalopathy and/or gastrointestinal bleeding due to ruptured gastrointestinal varices.
- 'NODAT' was defined as the use of oral antidiabetics and/or insulin at any time after transplantation in patients with no pretransplant diagnosis of diabetes and/or not being treated with antidiabetic medication at the time of transplantation.
- 'HCV-related glomerulonephritis' were diagnosed according to classical histological criteria (15).

Statistical analysis

Quantitative variables were expressed by mean and standard deviation (SD). Qualitative variables were represented as percentages. Statistical comparisons between the groups were performed with the Student's t-test and the χ^2 test for quantitative and qualitative variables, respectively. Nonparametric statistics were used when applicable.

Patient and graft survival were analyzed through the Kaplan–Meier method and the Log-Rank test was used for the statistical comparison between the groups. Cox regression analysis was applied to identify factors related to patient death and graft loss. A logistic regression analysis was used to determine those factors related to the development of decompensated CLD and NODAT. To construct the multivariate models, those variables identified as significant in the univariate analysis and those considered clinically relevant were introduced in the model, including HCV serology of the donor.

A p-value <0.05 was considered as statistically significant. SPSS 12.0 was used for the statistical analysis.

Results

From March 1990 to March 2007, 545 kidney transplants from deceased donors were performed in HCVR+. For

Table 1: Baseline clinical and demographic characteristics of donors and kidney recipients in both groups of study

	Total N = 468	Group 1 (HCVD+/HCVR+) N = 162	Group 2 (HCVD−/HCVR+) N = 306	p
Donor age (years)	42.9 (SD = 17.4)	46.5 (SD = 13.6)	41 (SD = 18.9)	0.002
Donor gender (Male)	65.4%	71%	62.6%	0.07
Recipient age (years)	46.6 (SD = 14.3)	50.3 (SD = 13.1)	44.7 (SD = 14.6)	<0.0001
Gender (Male)	56.8%	56.8%	56.9%	0.988
HLA matches	2.3 (SD = 1.2)	1.9 (SD = 1.1)	2.5 (SD = 1.2)	<0.0001
Highly sensitized patients[1]	23.7%	18.9%	26.5%	0.068
Previous transplants	41.7%	42.6%	41.2%	0.943
Dialysis time (years)	6.8 (SD = 5.3)	7.3 (SD = 5.3)	6.5 (SD = 5.4)	0.103
Pretransplant DM[2]	5.1%	5.1%	5.1%	0.997
Pretransplant cardiovascular disease[3]	15.9%	17.5%	15.1%	0.499
Cause of end stage renal disease				0.659
Glomerular (%)	31.25	34	29.7	
Interstitial (%)	24.1	22.8	24.8	
APRD (%)	8.3	10.5	7.2	
Diabetes (%)	4.9	4.9	4.9	
Vascular (nephroangiosclerosis included) (%)	6	5.4	6.2	
Others (%)	11.5	8.6	13.1	
Unknown (%)	13.5	13.6	14	

[1]Historical or current PRA ≥ 50%.
[2]Insulin use.
[3]At least one of the following: ischemic heart disease, peripheral artery disease and cerebrovascular disease. APRD = adult polycystic kidney disease.

this analysis, 77 patients were excluded: 19 because of a concomitant HBsAg positive at transplantation, 49 due to treatment with Interferon before transplantation and nine because of a previous or simultaneous nonkidney solid organ transplant. Out of the 468 HCVR+ included in the analysis, 162 were transplanted from HCVD+ (group 1) and 306 from HCVD− (group 2). Mean follow-up time was 66 (SD = 52.1) and 79 (SD = 60.7) months, respectively (p = 0.018).

Pretransplantation

Table 1 shows the demographic and clinical characteristics of both groups prior to transplantation. Donor and recipient age were significantly higher and HLA matching was significantly lower in group 1 than in group 2. These differences are due to the allocation strategy applied in our units, mainly based on age matching between donors and recipients in the last 10 years. There was a large percentage of highly sensitized patients and previous kidney transplants in both groups, as well as a long time on dialysis therapy.

Posttransplantation

Immunosuppression: Despite the immunosuppressive changes in the long time period covered, no differences were observed between the groups in terms of immunosuppression. Antilymphocyte antibodies for induction were used in 34% of the patients in group 1 versus 36% in group 2 (p = 0.66). Induction with lymphocyte depleting antibodies was performed in 22.2% and 26.7% of patients in groups 1 and 2, respectively (p = 0.286). Furthermore, no differences were observed in terms of immunosuppression at discharge after transplantation: steroids (96.9% vs. 96.7%; p = 0.909), cyclosporine (67.3 vs. 62.5%; p = 0.31), tacrolimus (27.7% vs. 31.8%; p = 0.36), mycophenolate mofetil (MMF) (40.3% vs. 41.5%; p = 0.80), mTOR inhibitors (3.8% vs. 2.7%; p = 0.57) or azathioprine (27% vs. 26.8%; p = 0.95). The combination of steroids, cyclosporine and MMF was the most frequent regimen used. Changes in immunosuppressive treatment during follow-up were not considered in this analysis.

Patient survival: No differences in patient survival (Figure 1A) were observed between the groups (p = 0.250). Five- and 10-year patient survival was 84.8% and 72.7% in group 1 versus 86.6% and 76.5% in group 2. Thirty-three (20.4%) and 53 (17.3%) patients died, respectively (p = 0.41). Cardiovascular and infectious diseases were the most frequent causes of death (Table 2). Remarkably, in our 17-year experience, only three deaths in group 1 and 2 in group 2, respectively, were directly attributed to liver disease.

Cox-regression analysis (Table 3) identified recipient age, evolution toward a decompensated CLD and NODAT as significant risk factors for patient death. Notably, HCV serology of the donor did not significantly increase the risk of death in HCVR+.

Graft outcome: No differences were observed regarding the incidence of DGF (54.4% vs. 48.8%; p = 0.26) and acute rejection (42.1% vs. 37.2%; p = 0.57). Among recipients with a functioning graft in the last assessment,

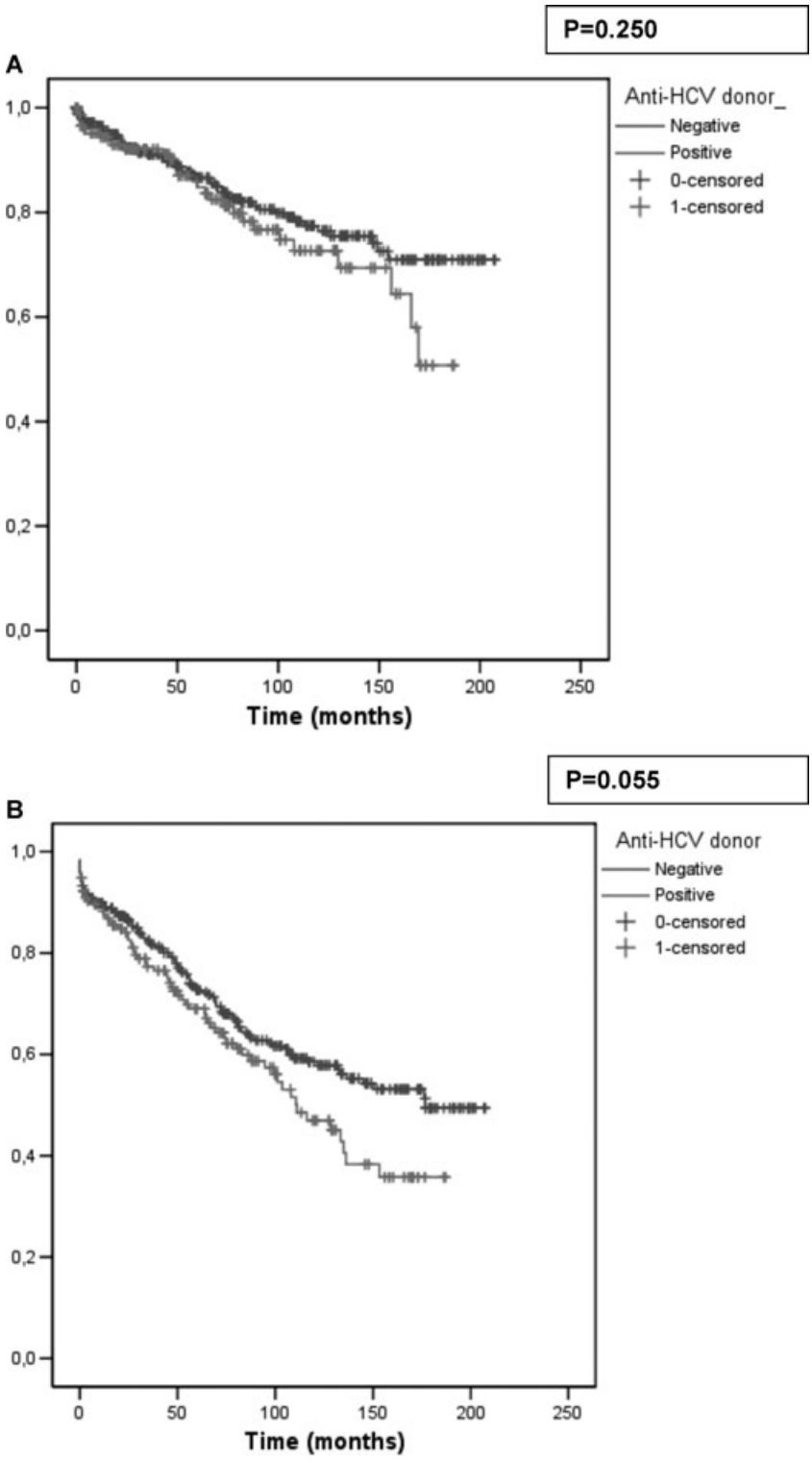

Figure 1: Patient survival (A), death-censored graft survival (B) and non-censored for death graft survival (C) (Kaplan–Meier method) after kidney transplantation of HCVR+, according to HCV serology of their donors.

sCr and 24 h proteinuria were also similar: 1.83 (SD = 0.8) versus 1.75 (SD = 1) mg/dL (p = 0.15) and 0.93 (SD = 1.3) versus 0.72 (SD = 1.1) g/day (p = 0.25), in groups 1 and 2, respectively.

Five- and 10-year death-censored graft survival was 69% and 47% in group 1 versus 72.7% and 58.5% in group 2 (p = 0.055) (Figure 1B). Five- and 10-year noncensored for death graft survival was 58.9% and 34.4% in group 1

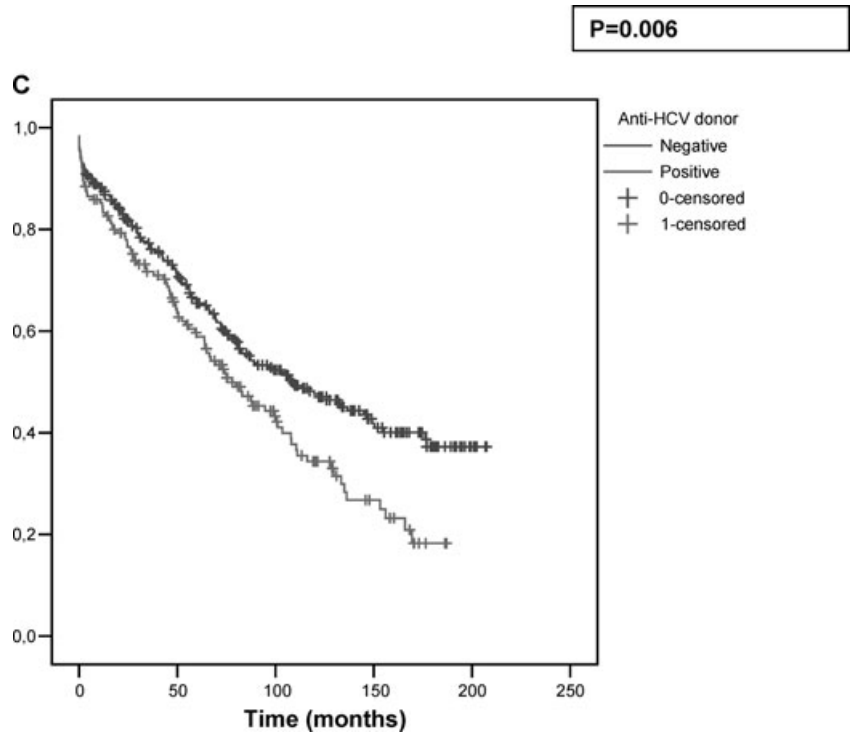

Figure 1: Continued.

versus 65.5% and 47.6% in group 2 (p = 0.006) (Figure 1C). Causes of death-censored graft loss are shown in Table 2, without differences between the groups.

Cox-regression analysis (Table 4) identified donor age, recipient's highly sensitized status, DGF and acute rejection as significant risk factors for death-censored graft loss. In the multivariate analysis, HCV serology of the donor was not a significant risk factor for death-censored graft loss among HCVR+. Similar results were obtained in the multivariate analysis for factors related to noncensored for death graft survival (data not shown).

Table 2: Number and causes of patient death and graft loss in HCVR+, according to HCV serology of their donors

	Total N = 468	Group 1 (HCVD+/HCVR+) N = 162	Group 2 (HCVD-/HCVR+) N = 306	p
Number of graft losses	180 (38.5%)	68 (42%)	112 (37%)	0.525
Causes of graft loss				
Chronic allograft nephropathy	105 (58.4%)	42 (61.8%)	63 (56.3%)	0.387
Acute rejection	23 (12.8%)	10 (14.7%)	13 (11.6%)	
Posttransplant glomerulonephritis	17 (9.4%)	5 (7.4%)	12 (10.8%)	
Primary nonfunction	15 (8.3%)	6 (8.8%)	9 (8%)	
Surgical/urological complications	7 (3.9%)	3 (4.4%)	4 (3.6%)	
Vascular complications	7 (3.9%)	1 (1.5%)	6 (5.4%)	
Other	4 (2.2%)	1 (1.5%)	3 (2.7%)	
Unknown	2 (1.1%)	0	2 (1.7%)	
Number of patient deaths	86 (18.4%)	33 (20.4%)	53 (17.3%)	0.409
Causes of patient death				
Cardiovascular	24 (28%)	12 (36.4%)	12 (22.6%)	0.580
Infection	27 (31%)	10 (30.3%)	17 (32.1%)	
Tumor	11 (12.8%)	3 (9.1%)	8 (15.1%)	
Liver disease	5 (5.8%)	3 (9.1%)	2 (3.8%)	
Traumatism	4 (4.7%)	1 (3%)	3 (5.7%)	
Other	13 (15%)	3 (9.1%)	10 (18.9%)	
Unknown	2 (2.5%)	1 (3%)	1 (1.9%)	

Table 3: Univariate analysis and Cox-regression analysis to identify factors associated to patient death among HCVR+

	Univariate	Cox regression			
	p	p	OR	CI 95%	
Donor gender	0.15	–	–	–	–
Donor age[1]	<0.001	–	–	–	–
Donor HCV serology	0.41	0.22	0.709	0.412	1.223
Recipient gender	0.79	–	–	–	–
Recipient age	<0.001	<0.001	1.075	1.049	1.102
Cause of ESRD	0.21	–	–	–	–
Previous transplants	0.009	0.16	1.495	0.854	2.819
Dialysis time	0.94	–	–	–	–
Pretransplant diabetes mellitus	0.036	–	–	–	–
Pretransplant cardiovascular disease	0.002	0.05	1.850	0.997	3.432
Induction therapy	0.025	0.37	0.746	0.395	1.470
Cyclosporine	0.032	0.41	1.313	0.685	2.517
Mycophenolate mofetil	0.031	0.51	1.274	0.621	2.613
Moderate chronic liver disease after transplantation	0.72	–	–	–	–
Decompensated liver disease after transplantation	0.10	0.003	2.883	1.447	5.746
NODAT	0.015	0.032	1.826	1.054	3.162

[1]Since there was a correlation between donor and recipient age, only the latter was included in the multivariate analysis, as it was considered clinically more relevant for patient death.

Outcome of the liver disease: As expected, HCV RNA positive at transplantation was significantly more frequent in recipients transplanted from HCVD+ (Table 5). The frequency of HCV RNA positive after transplantation remained being significantly higher in group 1 than in group 2.

Regarding posttransplantation ALT levels (Table 5), more patients exhibited mild CLD and fewer patients presented normal ALT levels in group 1 than in group 2. However, no significant differences were found regarding the percentage of patients with moderate or decompensated CLD. Only three patients in group 2 were diagnosed of hepatocarcinoma.

Patients who developed decompensated CLD showed a significantly more frequent HCV RNA positive before transplantation (96.2% vs. 78.7%; $p = 0.03$) and more frequently developed moderate CLD (43.8% vs. 8.9%; $p < 0.001$) than those who did not develop advanced liver disease. In the multivariate analysis (Table 6), moderate CLD was the only independent risk factor for the development of decompensated CLD. Once again, HCV serology of the donor did not influence the evolution to a decompensated CLD.

Other HCV-related posttransplant complications: NODAT was more frequent in group 1 (21.1% vs. 12.4%; $p = 0.03$). However, when adjusting by recipient age, donor

Table 4: Univariate and Cox-regression analysis to identify factors associated to death-censored graft loss among HCVR+

	Univariate	Cox regression			
	p	p	OR	CI 95%	
Donor gender	0.11	–	–	–	–
Donor age	0.005	<0.001	1.022	1.012	1.032
Donor HCV serology	0.26	0.18	1.248	0.902	1.726
Recipient gender	0.234	–	–	–	–
Recipient age	0.43	–	–	–	–
Cause of ESRD	0.27	–	–	–	–
Previous transplants	0.99	–	–	–	–
Highly sensitized status	0.007	<0.001	1.912	1.367	2.674
HLA matching	0.90	–	–	–	–
Dialysis time	0.10	–	–	–	–
Pretransplant diabetes mellitus	0.15	–	–	–	–
Acute rejection	<0.001	<0.001	1.778	1.304	2.425
Delayed graft function	<0.001	0.03	1.417	1.031	1.949
Cyclosporine	<0.001	0.48	1.145	0.785	1.671
Mycophenolate mofetil	<0.001	0.51	1.142	0.769	1.695
NODAT	0.28	–	–	–	–

Table 5: HCV RNA in HCVR+ before and after transplantation. Posttransplant clinical outcome of liver disease for HCVR+, according to HCV serology of their donors

	Total N = 468	Group 1 (HCVD+/HCVR+) N = 162	Group 2 (HCVD−/HCVR+) N = 306	p
Pretransplantation				
HCV RNA positive	258 / 322 (80.1%)	147/152 (97%)	111/170 (65.3%)	<0.001
Posttransplantation				
HCV RNA positive	284 / 348 (81.6%)	132/140 (94.3%)	152/208 (73.1%)	<0.001
Normal ALT levels	46.3%	35.8%	52%	0.001
Mild chronic liver disease	41.7%	49%	37.7%	0.02
Moderate chronic liver disease	12%	15.2%	10.3%	0.14
Acute hepatitis	13.2%	16.1%	11.6%	0.19
Decompensated liver disease	7.4%	9.8%	6.2%	0.17
Hepatocarcinoma	3	0	3	

HCV serology was not an independent risk factor for NODAT (logistic regression analysis). Furthermore, treatment with cyclosporine compared to tacrolimus behaved as a protective factor for NODAT. HCV-related glomerulonephritis was similar in both groups: 6.8% versus 7.2%, respectively (p = 0.87).

Discussion

This is the first study that has shown the long-term experience of transplantation with kidneys from HCVD+ into HCVR+, 97% of them with HCV RNA positive. In our series, HCVR+ transplanted from HCVD+ exhibited an adequate long-term outcome in terms of patient survival, graft survival and liver disease.

We adopted this practice in 1990 (8) and demonstrated the short-term safety of this approach along with other center-based experiences (16–21). This strategy has also been associated with a reduction in time on the waiting list (17–19). As the long-term safety of this strategy is still unknown due to lack of data (9), we have analyzed it in the present study.

Notably, mortality was not increased using kidneys from HCVD+ and donor HCV serology was not an independent risk factor for death among HCVR+. Causes of death were similar to those observed in the HCV antibody negative kidney transplant population in Spain (13). Liver disease-related deaths were rather scarce in this high-risk population for liver failure. This lack of difference in patient survival differs from that found in the United Network for Organ Sharing (UNOS) data (22–24). Comorbidity of recipients transplanted from these donors and epidemiological differences between the populations might be the reasons behind this observation in the UNOS study. In any case, the authors have proven that transplantation of HCVR+ with kidneys from HCVD+ is related to better survival than remaining on the waiting list and they consider that this is an acceptable strategy as long as adequate information is offered to the potential recipient (25). Furthermore, the most frequent therapy in our patients included MMF, which has been associated with better patient survival in HCVR+ (26).

A trend was found toward lower death-censored graft survival in recipients transplanted from HCVD+, and noncensored for death graft survival was significantly worse in this group. However, HCV serology of the donor was not an independent risk factor for graft loss in the multivariate analysis and the differences in donor and recipient age between the groups may explain much of the difference

Table 6: Univariate and logistic regression analysis to identify factors related to the development of a decompensated liver disease among HCVR+

	Univariate	Logistic regression			
	p	p	OR	CI 95%	
HCV serology of the donor	0.17	0.92	1.048	0.429	2.560
Recipient gender	0.13	–	–	–	–
Recipient age	0.23	–	–	–	–
Dialysis time	0.71	–	–	–	–
Previous transplants	0.24	–	–	–	–
Highly sensitized status	0.46	–	–	–	–
Pretransplant HCV RNA positive	0.03	0.15	4.483	0.576	34.879
Induction therapy	0.64	–	–	–	–
Cyclosporine	0.43	–	–	–	–
Mycophenolate mofetil	0.80	–	–	–	–
Acute rejection	0.21	–	–	–	–
Moderate chronic liver disease	<0.001	<0.001	9.462	3.887	23.030

observed in this outcome variable. However, the lower graft survival in HCVR+ transplanted with kidneys from HCVD+, although not statistically significant, was also apparent in the multivariate analysis. This might be due to the higher frequency of pretransplant HCV RNA positive in this group in which this viremic state may have had a deleterious effect on the outcome of the kidney graft. In this way, Mahmoud et al. have described a higher frequency of chronic allograft nephropathy among HCV RNA positive recipients (27). The high incidence of acute rejection in both groups might partially be justified by the high frequency of highly sensitized patients and retransplantations, something otherwise similar to what has been described in other series of HCVR+ (28).

One of the most important concerns regarding the use of kidneys from HCVD+ was whether this strategy could increase the frequency of progressive liver disease and liver failure. However, our results showed a similar outcome in this regard in both groups, which might be considered one of the most relevant data of our study. Close follow-up of patients with careful monitoring for early detection of posttransplant liver complications might have been decisive. Lack of correlation between biochemical and histological behavior of the liver disease among HCVR+ has been described. However, and in our experience, patients with biochemical moderate CLD have more frequently progressed to a situation of liver decompensation, an observation that points out the relevance of ALT as a clinical marker of HCV-related liver disease in HCVR+. Biochemically liver disease seemed to be worse, although not significant, among HCVR+ transplanted from HCVD+. Differences between both groups in this regard could be somehow expected due to the procedure for selecting patients to be transplanted with an HCVD+, that is, the presence of positive HCV RNA at transplantation and hence an active viral infection. On the contrary, no differences were observed in the incidence of decompensated CLD between the groups. Because liver disease had not been histologically monitored, comparisons regarding the histological evolution of the liver disease could not be performed.

We corroborate a higher incidence of NODAT in recipients transplanted from HCVD+. However, when adjusted by recipient age, HCV serology of the donor was not a significant risk factor for NODAT. Different baseline demographic profile of kidney recipients in the United States compared to Europe could explain the difference with the UNOS data (24). In our study, NODAT behaved as an independent risk factor for death in HCVR+ and its incidence was lower when patients received cyclosporine-based immunosuppression. However, this treatment did not lead to benefits in terms of patient and graft survival. Whether these benefits might become apparent with a longer follow-up or in larger series has yet to be demonstrated.

The evaluation of the outcome of HCVR+ according to the immunosuppression used was not the main aim of our study. However, besides the previously mentioned benefits of cyclosporine-based treatment in terms of NODAT, the univariate comparisons and the different multivariate models constructed did not show a significant impact of any immunosuppressive agent at discharge after transplantation on patient and graft survival and outcome of liver disease. Induction with antilymphocyte antibodies in our study and with lymphocyte depleting antibodies (29) also did not affect the posttransplant outcome of HCVR+.

Our study has proven that HCVR+ might be safely transplanted from HCVD+, preventing organ loss. For instance, during 1998–2008, there were 2777 and 310 HCVD+ in the United States and Spain, respectively (UNOS and ONT data upon request). This means that up to 505 and 56 kidneys from HCVD+ would be saved per year, respectively, in both countries if this strategy was applied. This finding implies that there would be an additional high number of available kidneys for the next years that could be used in patients with HCV infection, especially in countries with a high prevalence of HCV infection among kidney patients. Another potential advantage of this strategy is the reduction of time on the waiting list (17–19). Furthermore, according to these experiences in kidney transplantation, livers from HCVD+ have been transplanted into HCVR+ with good results (30).

Our study has several limitations. (1) Because we do not have information on HCV RNA of HCVD+, we are unaware of how many donors were viremic at the time of donation. The practice of testing donors with Nucleic Acid Testing (NAT) has only been recently suggested (9) while the policy of testing with ELISA has been supported by European guidelines since 2000. On the other hand, since we did not routinely test HCV genotype in donors and recipients we were unable to show, in the case of HCVD+, if superinfection with another HCV genotype could have occurred (31,32), but mixed infection has not been associated with an increased mortality (33). However, the possibilities of superinfection in our study might be limited because genotype 1b is the most frequent in our area. Testing and matching HCV genotypes in donors and recipients should be the next step (9) although there are obvious time constraints. (2) HCV RNA was also not available for all patients included in the study because of its retrospective nature and limited availability of NAT in the earliest years. For those in whom HCV RNA was available, it was more frequently positive among recipients transplanted from HCVD+, as expected. Although this could somehow limit the comparability between the groups, we decided to include HCV RNA negative cases in the analysis as well, since some of these patients become HCV RNA positive after transplantation, even when transplanted from HCVD−. This would mean that the viremic state is hard to detect in some patients with a very low viral load at transplantation. (3) Because

liver biopsies were not routinely performed in our patients, whether the histological outcome of HCV-related liver disease is different (stable or progressive liver fibrosis) (34), in HCVR+ transplanted from HCVD+ versus HCVD− still remains to be answered.

In conclusion, the long-term outcome of HCVR+ transplanted with kidneys from HCVD+ seems good in terms of patient and graft survival and clinical evolution of liver disease. The safety of this approach might be enhanced by limiting the use of these organs to recipients who are HCV RNA+ before transplantation and ideally by matching donors and recipients according to HCV genotype. With this limitation, our results strongly suggest that the use of kidneys from HCVD+ into HCVR+ is a safe strategy in the long term and a useful way of avoiding kidney loss at a time of dramatic organ shortage. Prospective studies with detailed information on NAT and HCV genotypes both in donors and recipients are mandatory in order to confirm these relevant clinical findings.

Acknowledgment

Jose M Morales, Josep M Campistol, Amado Andrés, Federico Oppenheimer and Manuel Praga conceived and developed the policy of using kidneys from HCV antibodies positive donors into HCV antibodies positive recipients. Gregorio Castellano and Miguel Bruguera have been advisors for the liver disease evaluation and Antonio Fuertes for the HCV determinations of donors and recipients. Beatriz Domínguez-Gil and Nuria Esforzado have been in charge of data collection and statistical analysis for the present study. All authors have participated in the preparation of the manuscript, especially Beatriz Dominguez-Gil and Jose M Morales. Part of this study was presented at the 2008 American Transplant Congress (Toronto) and the XXII International Congress of the Transplantation Society (Sidney). The authors would like to thank the Organización Nacional de Trasplantes (ONT) (Spain) and all the regional and hospital transplant coordinators for their continuous collaboration in the application of this strategy. We thank Dr. Elisabeth Coll (ONT) for her help in the statistical analysis as well as Dr Brian Pereira and Dr. Andrew Levey (Tufts University, Boston, USA) for their collaboration and support to this project in the first years of the 1990s.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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