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Hepatitis C-positive Donors in Heart Transplantation

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Hepatitis C virus (HCV) can be transmitted to heart transplant recipients by donor organs. Mid-term results were reported using HCV-positive donors in patients at risk of imminent death (group I, n = 10), or in patients who otherwise would not have been offered heart transplantation (group II, n = 10) because of age (9/10) or associated medical risk (1/10). Medical records pertaining to patients receiving HCV-positive allografts between July 1994 and December 1999 were reviewed. The recipients consisted of 19 males and one female, with a median age of 54 years for group I and 66 for group II. The HCV RNA level, seroconversion of anti-HCV antibody, biochemical liver dysfunction, and causes of death were examined. Older recipients received reduced immunosuppression. Two patients in group II were HCV positive and were also retransplants. The hospital mortality rate was 10% in group I and 20% in group II; both hepatitis C-positive recipients died postoperatively prior to discharge. All predischarge deaths were related to multi-system organ failure (MSOF). All 17 survivors were HCV negative prior to transplant. Of these, 4/17 seroconverted. HCV RNA was detected in two of them. At a median follow-up of 26.4 months, 2/11 current survivors continue to test anti-HCV positive and are RNA negative. Three-year actual survival was 40% for group I and 70% in group II. Transplant coronary artery disease (TCAD) accounted for one postoperative death in group I. Current data show that four out of 11 survivors had developed TCAD at 3-year follow-up, yielding an actual freedom from TCAD rate of 12/17 (70%) at 3-year follow-up. Hepatitis C transmission using a donor heart as the reservoir is moderate (25%). Limited use of such donors is justified in selected patients. The risk for hepatic disease may be reduced by tailoring immunosuppression specifically for such recipients, particularly if they are at low risk of rejection. Further studies are necessary to define a possible association between HCV and TCAD.

Key words: Heart donors, hepatitis C

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Introduction

Data from the United Network of Organ Sharing (UNOS) has revealed several trends in solid organ transplantation over the past decade. The supply of donor hearts was sufficient to meet recipient demand through the early nineties. Over the past decade, there has been a considerable increase in the numbers of patients annually listed for cardiac transplantation, creating an under-supply of available organs. The number of heart transplants performed each year remains in the 2000–2500 range while the number of patients listed nationally at year's end increased from 2690 in 1992 to 4164 in 2000. During the same time period, median waiting times have increased from 28 to 56 days for those beginning and ending status I (urgent) and from 221 days to 502 days for those beginning and ending status II (non-urgent) (1). This has led to increased consideration of HCV-positive donor allografts by many heart transplant centers within the United States and Europe (2).

Controversy exists concerning the use of hepatitis C-positive (HCV) hearts, particularly in HCV-negative recipients (3). Because of the potential risk for transmission of HCV and significant viral replication which can occur with immunosuppression, hearts from hepatitis C-positive donors are not considered standard (4). At the center of this controversy are two groups of potential recipients: those listed as UNOS status I facing imminent death, and those who would otherwise not be listed because of medical comorbidities and/or advancing age (5, 6). This paper reviews the UCLA experience with 20 recipients of cardiac allografts from anti-HCV-positive donors over the last 8 years.

Patients and Methods

Patients were divided into two groups based on listing at time of transplant. Group I consisted of UNOS status I patients (n = 10); group II were patients on the alternate list who would otherwise not have been transplanted (n = 10). Median age was 54 years old (range = 18–62) for group I and 66 years old (range = 26–63) for group II. Nineteen of the 20 patients were male. Median waiting time was 58 days and median hospital stay was 24 days. Primary indications for transplantation included ischemic cardiomyopathy (40%), transplant coronary artery disease (TCAD) (30%), dilated cardiomyopathy (20%), congenital heart failure (5%), and alcoholic cardiomyopathy (5%). Median ischemia time was 190 min. Two of the patients in group II were HCV positive and were also retransplants.

Definition of terms

Non-standard donor: A marginal donor is defined as any donor who does not meet standard criteria. UCLA has a set of guidelines for marginal heart donors (Table 1) to expand the donor pool. In general, such donor hearts are offered to recipients who face imminent death without transplantation (status I). If the donor organ remains unused, it may be then offered to an alternate recipient, who would otherwise not be listed for transplant. For example, from 1992 to 2000, UCLA accepted 260 marginal donor hearts. Of these, 197 went to regularly listed patients and 63 were allocated to an alternate recipient.

Table 1: UCLA marginal donor criteria

Risk factor	Definition
Cardiac	
Coronary artery disease (5%)	Any coronary artery stenosis evident on coronary angiogram or greater than mild calcified plaque
Age > 45, coronary angiogram not available (2%)	Normal function on echocardiogram
LVH by ECG criteria (2%)	Abnormal on ECG in V_5 and V_6
LVH by echocardiogram (15%)	Posterior wall thickness ≥ 14 mm
Low LVEF (9%)	< 50% on echocardiogram
High-dose inotropic requirement (1%)	1 inotrope at maximal dose or 2 inotropes at greater than 1/2 maximal dose (Dopamine and Dobutamine maximal dose = 20 μg/kg/min)
Suspected myocardial contusion	Significant anterior blunt chest injury with RV or septal wall motion
econdary to chest trauma (21%)	abnormality on echo, complemented by elevated CPK-MB
Recent cardiac arrest (15%)	Organ retrieved less than 24 h post cardiac arrest
Non-cardiac	
Older age (17%)	Age greater than 55 years
Hepatitis B positive (1%)	IgG core antibody positive; IgM unknown
Hepatitis C positive (11%)	Positive anti-HCV

LVH: left ventricular hypertrophy; LVEF: left ventricular ejection fraction; ECG: electrocardiogram; RV: right ventricle; CPK-MB: creatinine phosphokinase MB fraction.

Alternate recipient: In 1992, the UCLA heart transplant program created a second adult recipient list for heart failure patients who felt well enough to tolerate surgery. In these patients, long-term prognosis was less certain, due to associated medical risk. Such patients were felt to have an acceptable medium-term outlook. This category of patients has become increasingly important, since at that time the UCLA heart transplant program had set a recipient age limit of 65 years. An opportunity was created for patients who would typically not be transplanted because of previous age restriction or other relative medical exclusion criteria to receive hearts that would otherwise not be used.

Nine patients in group II were listed as alternates because of age; the other patient was so listed because of renal insufficiency, transplant coronary artery disease, and obesity, despite being aged 42 years.

Donor hepatitis C profile

When an organ procurement agency is notified that there is a potential organ donor, the establishment of hepatitis C status is part of the screening criteria. If the result of the HCV antibody is positive by second-generation enzyme-linked immunosorbent assay (ELISA) testing, the heart may still be considered. This is only if the donor has not had a recent or ongoing clinical history of liver dysfunction and if serum markers of hepatic function are within normal limits.

Organ preservation and surgical technique

Thyroid (T4) hormone infusion is started several hours prior to retrieval at 0.4 μg/cc. Flush-cooling was with University of Wisconsin (UW) solution. Reperfusion was accomplished with leukocyte-depleted, aspartate/glutamate-enriched, warm blood cardioplegia (Buckberg Solution) for 3–4 min, followed by leukocyte-depleted blood for 5–10 min. Bicaval anastomosis was used for the right atrium.

Immunosuppression

The UCLA heart transplant program has not used induction therapy to complement triple-drug regimens. An initial steroid bolus of intravenous methylprednisolone (7 mg/kg) is given at the time of reperfusion and upon separation from cardiopulmonary bypass. Methylprednisolone is given at a dose of 125 mg every 12 h for 3 doses following initial bolus administration at the time of transplant, switching to oral prednisone at 1 mg/kg/day and tapered to 0.1 mg/kg/day over 3 months. For those patients with few rejection episodes, complete steroid taper is attempted and achievable in 80% of selected recipients by 6 months. Oral cyclosporine-A is administered on postoperative day 1, and adjusted to achieve maintenance serum blood levels of 250 ng/mL. Azathioprine is given at a dosage of 2 mg/kg/day over the initial 3-month period. In patients who develop severe, or repeated episodes of rejection, Cyclosporine is changed to tacrolimus and azathioprine to mycophenolate mofetil (MMF). More recently, MMF has been used part of the initial postoperative triple-drug immunosuppressive regimen. In older recipients without evidence of rejection, MMF or azathioprine is given at reduced (half) dose after 3–4 weeks postoperatively.

Recipient hepatitis C profile

Initial evaluation includes routine liver blood tests as well as a full hepatitis serology panel. Diagnostic modalities of hepatitis C have since evolved from first-generation to third-generation serological assays, along with the development of polymerase chain reaction (PCR) and viral genotyping techniques. The most widely available initial screening assay for identification of hepatitis C virus (HCV) is the second-generation enzyme-linked immunosorbent assay test (Abbott Laboratories HCV EIA 2.0), which detects antibodies to HCV (anti-HCV). More recently the third-generation assay has been introduced, which has improved advantages over its predecessor assays, reaching an increased sensitivity of 97%.

In immunosuppressed individuals, however, HCV has been shown to develop and progress in the absence of detectable antibodies to hepatitis C virus. Reverse transcription PCR tests for the presence of HCV RNA, have the added advantage of measuring viral load. This test, performed using the Amplicor system (Roche Molecular Systems) provides a much more sensitive and specific means of detecting infection. Utilization of this technique enables detection of as few as 100 viral copies/mL. More invasive evaluation with percutaneous or transjugular liver biopsy is used to identify histologic changes such as bridging fibrosis or cirrhosis as a complement to serological and molecular testing.

Post-transplantation treatment

Immunosuppression for older recipients of hearts from anti-HCV positive donors was selectively tailored. All patients received low-dose azathioprine, an analog purine base, because MMF was felt to be more toxic due to the specificity of its mechanism of action. MMF is a selective blocker of lymphocyte proliferative responses that inhibits de novo nucleotide synthesis. Cyclosporine and steroids were weaned to lower levels over 1–2 months if there was no evidence of rejection.

Results

Clinical data

Since 1991, 20 recipients have been transplanted using anti-HCV-positive hearts. The median recipient age was 58 years old, with a median donor age of 41 years. These patients had a median waiting time of 58 days and a median hospital stay of 24 days. Two groups were identified, based on the listing at time of transplantation. Group I (n = 10) were listed as status I, and group II (n = 10) were listed as alternates. Two of the recipients in group II were HCV positive at the time of transplant (Table 2).

Table 2: Hepatitis seroconversion data

Pt no.	Status	Follow-up	HCV status
Group I			
1	I	50.5	
2	I	14.0	
3	I	11.6	
4	I	7.8	Seroconversion
5	I	13.4	
6	I	22.3	Anti-HCV positive
7	I	0.2	
8	I	6.8	
9	I	111.8	
10	I	9.4	
Group II			
11	A	33.5	
12	A	37.7	Seroconversion
13	A	53.5	
14	A	22.3	Anti-HCV positive, elevated LFTs
15	A	43.0	
16	A	44.0	
17	A	18.7	
18	A	23.4	
19	A	2.0	Pre-tx positivity
20	A	1.7	Pre-tx positivity

LFTs: liver function tests.

Overall survival

Eleven of the 20 recipients transplanted are currently alive. Sixty-day survival was 90% for group I and 80% for group II (p = NS). One-year survival for group I patients was 50% compared to 80% for group II (Table 3). To date, six patients in group I have died and three of the patients in group II have died. None of the survivors were HCV positive preoperatively. Two have subsequently tested anti-HCV positive and RNA negative. One of the patients who tested anti-HCV positive postoperatively has elevated liver function tests.

Hepatitis C-free survival

Sixty-day survival: Two patients were HCV positive before transplantation. The first patient had a moderate rise in liver function tests during the initial month following transplant. He suffered a cerebrovascular accident and expired 2 months postoperatively. The second patient had persistent severe hepatitis with deteriorating liver function tests after transplantation and died of multiple system organ failure (MSOF) within 8 weeks of his transplant. One other patient, who was status I and HCV negative at the time of transplant, died in the early postoperative period of multi-system organ failure.

Greater than 60-day survival: All late survivors (n = 17) were seronegative for HCV preoperatively. Four of the 17 HCV-negative recipients (24%) seroconverted to positive, as evidenced by development of a positive antibody test. Two of these patients tested negative using an HCV-RNA test; one did not show signs of liver dysfunction; the other patient continues to show elevated liver function tests (LFTs). They are both currently alive. The other two patients were HCV RNA positive and had persistent liver enzyme test elevation. One patient died from infection within 1 year of transplant and the other from pulmonary embolism more than 1 year post transplant (Figure 1).

Of the 13 patients who did not seroconvert, nine had a transient rise in liver enzymes but the levels returned to normal; four of the nine have died of MSOF, infection, and other causes at greater than 6 months of follow-up. Four of the 13 patients did not have liver enzyme abnormalities and are currently well.

Rejection and transplant coronary artery disease

Five patients had one or more episodes of rejection. Overall, the average number of rejection episodes International Society for Heart and Lung Transplantation (ISHLT) grade 3A or higher was 0.44 per patient. Of the 11 survivors, four have

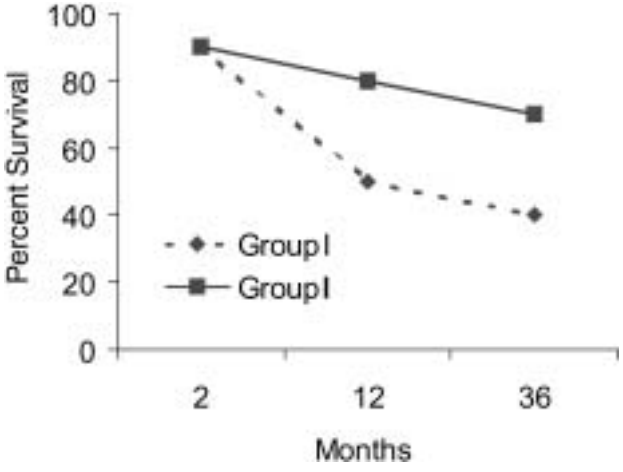

Figure 1: Actual patient survival by group.

Table 3: Death at less than 1 year

Pt no.	Recipient age	Sex	Diagnosis	Survival (months)	Cause of death	Recipient risk	Donor risk
Group I							
1	63.02	female	Ischemic	11.8	TCAD	Age > 62, IABP, CMV mismatch, high-dose inotrope	
2	57.40	male	TCAD	7.8	Infection	Retransplant, CMV mismatch, inotropes, 3 previous cardiotomies, preop ventilator, preop SCr 3.2	Echo LVH
3	57.58	male	Ischemic	0.2	MSOF	Inotropes, preop TBili 3.8	
4	62.62	male	Ischemic	6.9	MSOF	Age > 62, inotropes, PRA's	
5	52.95	male	Ischemic	9.6	Infection	VAD, inotropes, 2 previous cardiotomies, preop ventilator	Ischemia > 4 h, Echo LVH
Group II							
6	38.41	male	TCAD	2.0	CVA	Retransplant, BMI > 30 kg/m^2, HCV +	Ischemia > 4 h, Echo LVH
7	51.26	male	TCAD	1.7	MSOF	Retransplant, 5 previous cardiotomies, preop SCr 4.3, HCV +	Echo LVH

TCAD: transplant coronary artery disease; MSOF: multi-system organ failure; IABP: intra aortic ballooa pump; CMV: cytomegalovirus; Tbili: total bilirubin; SCr: serum creatinine; PRA: panel reactive antibodies; CVA: cerebrovascular accident; BMI: body mass index.

TCAD. One other patient among the 17 late survivors died of TCAD at 1 year. Actual freedom from TCAD is 60% at a median follow-up of 20 months.

Discussion

Transmission of hepatitis C virus by organ transplantation has been demonstrated previously by Periera et al. (3) The use of hepatitis C-positive donor hearts is not standard. While the incidence of clinically significant liver disease as a consequence of the use of HCV-infected cardiac allografts is unknown, a previous study reported HCV seroconversion in as many as 60% of solid organ recipients from HCV-infected donors (7). From this series, one may infer that half of those who seroconvert may eventually develop significant liver disease.

Lake et al. have performed a survey regarding the use of HCV-positive cardiac allograft donors, but the results were varied (2). The majority of centers surveyed restricted use of HCV-positive organs to status I or to HCV-positive candidates. By matching recipient with donor risk, an effective expansion of the donor pool can occur while patient outcomes are maintained and organ wastage is minimized. These authors further reported that there was no difference in clinical course for patients with pre-existing HCV. In our series, the deaths of both recipients who were HCV positive before transplantation were attributed to high preoperative surgical risk as well as liver-related complications. The HCV-positive organ could have reactivated the recipient's hepatitis and worsened liver function. This could be attributed to the many preoperative risk factors present in these patients. Both patients were retransplants with other risk factors.

The use of anti-HCV donors is limited. The possibility of viral transmission and the effects of immunosuppression on the natural history of the carrier state remains a concern. In patients who contract HCV from blood transfusions or through sexual contact, hepatitis can take years to affect liver function or cause active illness (8). Although hepatitis is a relatively slowly progressing disease, the immunosuppression regimens used for transplant recipients may allow the disease to progress more quickly. We observed that one HCV-naïve recipient who became positive post transplant began to show elevated liver function tests at 1-year follow-up.

The heart may not be a viral reservoir that can be compared to the liver or kidney, and so results extrapolated from other organs need to be confirmed with clinical data. Preiksaitis et al., reported that serologic responses to HCV are often delayed and sometimes absent in heart and kidney recipients (9). The HCV responses observed in heart transplant recipients are more impaired than those observed in kidney recipients, which may be the result of a more intense immunosuppression regimen in the latter group (10–12).

Hepatitis C-positive recipients appear to be at risk for early death relating to patient risk factors. In our series, HCV-positive recipients died in the early postoperative period. The HCV-naïve recipient who died at less than 30 days had a high inotropic requirement and a very high preoperative total bilirubin. Careful patient selection is necessary to ensure success with hepatitis C-positive donors. In status I patients who are in extremis, this approach may be justified in selected cases when a long-term ventricular assist device (VAD) bridge to orthotopic heart transplant (OHT) may not be ideal (e.g. postcardiotomy shock or after aortic valve replacement) or is judged to be insufficient for severe biventricular failure. The series in the present study dates back to 1992, when mechanical support was not yet in widespread use. As mechanical technology and experience with hepatitis C donors grow, the use of hepatitis C donors may no longer be justified in status I recipients. It may be

that in such cases, unlike the previous series, the heart allocated to the status I in extremis patient is being allocated away from a lower-risk recipient.

Survival outcome was better in elderly (alternate list) recipients in whom immunosuppression could be reduced. At a 3-year follow-up, 70% of all elderly recipients were alive and doing well. These elderly recipients were transplanted as alternates and had similar 3-year survival to other alternates ($p = 0.22$, log rank test, unpublished data). One of these recipients had a positive anti-HCV test and slightly elevated liver function tests. Heart transplantation using hepatitis C-positive donors appears acceptable in older recipients in whom immunosenescence permits the use of decreased doses of azathioprine or mycophenolate mofetil; such tailored regimens may delay or actually prevent the onset of chronic hepatitis. Comparisons with group I patients are limited by the severity of illness in group I patients at the outset.

Informed consent and spousal counseling are essential when using organs from anti-HCV-positive donors. Patient consent should be obtained prior to using an HCV-positive heart. It is important to explain during the consenting process that the recipient's spouse can be at risk. Additionally, any family or friends who are in close physical contact may also be at risk.

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