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ALLOGRAFT TRANSMISSION OF HEPATITIS C VIRUS INFECTION FROM INFECTED DONORS IN CARDIAC TRANSPLANTATION

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Background. **The frequency and outcome of hepatitis C virus (HCV) infection in recipients of hearts from HCV-infected donors remains poorly characterized.**

Methods. **Between 1991 and 1999, 10 anti-HCV-negative patients received hearts from donors who were anti-HCV and HCV RNA-positive. Each recipient was tested for anti-HCV and HCV RNA and serially evaluated for liver dysfunction. Recipient records were reviewed for cumulative steroid boluses in the first posttransplant year and other components of the immune suppression regimen. We analyzed recipient outcome in relation to the virologic status of the donor, including the level of HCV RNA and genotype and the type of antirejection therapy.**

Results. **All 10 recipients became HCV RNA positive. Donor-recipient pairs expressed identical genotypes in each instance. Six of nine evaluable recipients developed biochemical evidence of hepatitis. Recipients with genotype 1 (1a, 1b) accounted for five of the six cases, and all patients with genotype 1 developed hepatitis. Severe liver injury occurred in two patients. Two deaths occurred, both of which were genotype 1 patients who had been given multiple boluses of corticosteroids in the first posttransplant year. No definite relationship between viral load in the donor and recipient outcome was found.**

Conclusion. **Transmission of HCV infection from cardiac donors who are viremic at the time of organ donation occurs with high frequency and can cause severe hepatitis. Hearts from infected patients should probably be restricted to those recipients who already have evidence for hepatitis C or are in need of emergent transplantation.**

Infection with hepatitis C virus (HCV) occurs in 5% to 15% of transplant recipients, and it is known that solid-organ transplantation can transmit infection (*1–3*). As a result, this has raised serious questions about the continued acceptance of organs from donors positive for antibody to HCV (anti-HCV) (*2*). The outcome of renal- and liver-transplant recipients infected with HCV has been extensively investigated (*1*). However, the outcome of de novo HCV infection, particularly as it relates to donor virologic features and other potential infection risk factors, has not been systematically characterized in heart-transplant recipients.

More information is needed regarding the outcome of patients with de novo HCV infection after heart transplantation, and the current data on frequency of transmission and clinical outcome are inadequate to make nationwide policy decisions regarding the use of hearts from anti-HCV-positive donors (*3*). As a result, there are significant variations in policies and practices of cardiothoracic transplant centers with regard to the use of these donors (*3*, *4*). The nonuniformity of donor policy has recently been well illustrated in a study by Lake and associates (*3*) at the Minneapolis Heart Institute and Foundation in which the authors surveyed 72 United Network for Organ Sharing (UNOS) thoracic transplant centers on the policies regarding the use of anti-HCV-positive donors. Twenty-six percent of the responding centers refused to use the hearts of anti-HCV-positive donors, and the remainder restricted the use of these hearts to UNOS status 1 recipients or anti-HCV-positive candidates.

The primary aim of the current study was to retrospectively assess the frequency of HCV infection as well as clin-

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ical outcome of de novo HCV infection in heart-transplant recipients of anti-HCV-positive donors. The secondary objectives of this study were to explore the relationships between patient outcome, virologic features in the donors, and practices relating to the use of corticosteroids.

METHODS

Fifteen of 523 heart donations made to Ochsner Clinic patients between 1991 and 1999 were found to be repeatedly positive for anti-HCV by enzyme-linked immunoabsorbent assay (ELISA) II (Abbott Laboratories, Chicago, IL), and an aliquot of serum that was kept frozen at −70° centigrade was tested in each case for HCV RNA by quantitative polymerase chain reaction (PCR) (Cobas Amplicor Monitor, Roche Diagnostics, Branchburg, NJ). In all instances in which the donor sera were positive by PCR, the paired frozen sera of the recipients obtained before transplantation were also tested for anti-HCV and HCV RNA by PCR to confirm the absence of preexistent infection. To be eligible for the study, recipients had to be anti-HCV and HCV RNA negative in their pretransplant sera. All PCR-positive donor and recipient sera were genotyped (LIPA, National Genetics Institute, Los Angeles, CA).

Charts of the recipients were reviewed to assess for independent risk factors for hepatitis C. Demographic and clinical information at the time of transplant was obtained, including age, sex, race, indication for heart transplant, history of alcohol abuse, UNOS status, and infective markers for hepatitis B virus (HBV), cytomegalovirus, and human immunodeficiency virus.

The data on posttransplant clinical course and overall clinical status during follow-up were collected. Charts were reviewed for cumulative corticosteroid dose, the number of steroid boluses in the first posttransplant year, induction therapy with OKT3, and the specific type of immunosuppression regimen. Each of the organ recipients of the HCV viremic donors was tested for anti-HCV as well as HCV RNA on one or more occasion during routine clinical visits.

Serial alanine aminotransferase (ALT) testing was available for all recipients. For purposes of the study, biochemical evidence for hepatitis was defined as the detection of two or more abnormal ALT values, separated by at least 1 month, one of which had to be at least two times the upper limits of normal. An attempt was made to study the outcome of the recipient in relation to the virologic status of the donor, including donor level of HCV RNA and genotype. This study was approved by the Ochsner Clinic Foundation Institutional Review Board.

RESULTS

Eleven of the 15 (73%) anti-HCV-positive donors were found to be HCV RNA positive by PCR. One of the 11 recipients of the PCR-positive donors was excluded from the study because he was found to be anti-HCV-positive before transplantation. The age of the remaining 10 recipients ranged from 39 to 61 (mean 52) years (Table 1). Only one patient was female, and the majority of patients (9/10) were over the age of 40. Each of the recipients was UNOS status 1 (in need of urgent transplantation) at the time of transplant and all had ischemic cardiomyopathy. Only one individual had a history of alcohol abuse, but this individual quit 15 years before transplant. None were taking potentially hepatotoxic medications either immediately before or after transplantation.

Each recipient ultimately became HCV RNA positive (Table 2). Only nine recipients were analyzed as to outcome because one HCV infected patient died of sepsis at the third month after transplant. Anti-HCV seroconversion occurred in only four of the nine (44%) recipients. Donor-recipient pairs expressed identical genotypes in each instance (Table 2). Five donor-recipient pairs were genotype 1 (1a, 1b). Four donor-recipient pairs were genotype 2 or 3. In contrast with these findings, none of the four patients who received a heart from an anti-HCV-positive/HCV RNA negative donor demonstrated clinical or laboratory evidence of hepatitis C during posttransplant observation periods of 8.5 to 11 years.

Six of the nine recipients developed biochemical evidence of hepatitis, which became chronic in each instance (Table 2). All six developed clinical signs and symptoms of hepatitis C such as fatigue (n=3), malaise (n=1), jaundice (n=2), and ascites (n=1) within 1 year of transplantation. None of the three infected recipients with persistently normal ALT status, in contrast, developed clinical features of liver disease. Recipients who were genotype 1 (1a, 1b) accounted for five of the six cases with biochemical evidence of hepatitis, and all patients with genotype 1 developed hepatitis. Only one of the four patients with genotype 2 or 3 developed biochemical evidence for hepatitis.

Biopsies were performed on three of the six patients with abnormal ALT status and one individual with persistently normal ALT. Two patients who met the biochemical criteria for hepatitis C had severe liver injury with bridging fibrosis and fibrosing cholestatic hepatitis, respectively (Table 2) (Fig. 1). In the single patient with normal ALT who had a liver biopsy, the liver parenchyma was unremarkable, and only an occasional portal triad contained a few inflammatory cells (Fig. 1). Only one of these patients (case 2 with cholestatic hepatitis) was treated with interferon, and this proved unsuccessful.

Three of the 10 transplanted patients died, including the single patient who died of sepsis at the third month after transplant. The overall survival rate (70%) was lower than

TABLE 1. Baseline characteristics of nine non-HCV-Infected recipients

Recipient	Sex	Race	Age	Etiology	ETOH abuse	UNOS status	HBsAb	CMV Ab
1	M	W	61	ICM	No	1A	Neg	Pos
2	M	W	48	ICM	No	1A	Neg	Neg
3	M	W	54	ICM	No	1B	Neg	Pos
4	M	W	47	ICM	No	1A	Neg	Neg
5	M	W	59	ICM	No	1A	Neg	Neg
6	M	AA	60	ICM	No	1B	Neg	Neg
7	M	W	54	ICM	No	1A	Neg	Neg
8	M	W	52	ICM	No	1A	Neg	Neg
9	F	W	39	ICM	No	1B	Neg	Neg

ICM, ischemic cardiomyopathy; HCV, hepatitis C virus; ETOH, ethyl alcohol; UNOS, United Network for Organ Sharing; HBsAb, hepatitis B surface antibody; CMV, cytomegalovirus; W, white; AA, African American.

TABLE 2. Donor/recipient features and outcome

Case no./ year of transplant	Donor HCV RNA, copies/mL	Donor genotype	Recipient genotype	Immune suppression	OKT3 induction	Anti-HCV conversion	Recipient HCV RNA (copies/mL, unless specified)	Biochemical evidence of hepatitis	Peak ALT	Time to peak ALT	Biopsy grade/ stage	Death
1/1996	1.49×10^6	1b	1b	pred/cya/myco	Yes	Yes	8.61×10^6	Yes	198	Mo 14	1/3[b]	No
2/1999	1.00×10^6	1a	1a	pred/mycp	No	No	7.42×10^6	Yes	833	Mo 2	4/2[c]	Yes[f]
3/1996	2.13×10^6	1b	1b	pred/aza/tacro	Yes	No	62.65[a]	Yes	126	Mo 15	2/3[d]	Yes[g]
4/1992	9.30×10^6	1b	1b	pred/cya/aza	No	Yes	1.86×10^6	Yes	886	Mo 2	ND	No
5/1993	1.31×10^4	1a	1a	pred/cya/aza	Yes	Yes	3.92×10^6	Yes	110	7 days	ND	No
6/1998	1.26×10^4	3a	3a	pred/tacro/myco	Yes	No	4.25×10^5	No	—	—	ND	No
7/1998	1.77×10^7	2b	2b	pred/cya/myco	Yes	Yes	7.59×10^6	No	147	Mo 23	1/0[e]	No
8/1998	1.09×10^7	2b	2b	pred/myco/tacro	Yes	No	35.68[a]	Yes	177	Mo 37	ND	No
9/1991	3.18×10^3	2b	2b	pred/cya/aza	No	No	3.46×10^6	No	58	Mo 59	ND	No

aza = azathioprine; cya = cyclosporine; myco = mycophenolate mofetil; tacro = tacrolimus; HCV, hepatitis C virus; ALT, alanine aminotransferase.

[a] Results expressed in Meq/mL.

[b] Biopsy at 57 months after transplantation revealed mild inflammation and bridging fibrosis.

[c] Marked cholestasis and severe ballooning degeneration 3 months after transplantation.

[d] 26 months after transplantation.

[e] 31 months after transplantation.

[f] Death was secondary to end-stage liver disease 16 months after transplantation.

[g] Death was secondary to worsening cardiac function 27 months after transplantation.

the average survival of 89% observed at this institution during the same period. Two of the nine recipients who survived the first 90 days after transplant subsequently died, and both deaths occurred in patients with genotype 1 infection. The major contributing cause of death in the patient (case 2) with severe cholestatic hepatitis was liver disease, whereas the second patient (case 3) had biochemical evidence of hepatitis but died of worsening cardiac failure. The patient with cholestatic hepatitis died at the end of the first posttransplant year, whereas the second individual died at month 27 posttransplant.

The two deaths that occurred after the first 90 days posttransplant were in patients who received multiple boluses of corticosteroids in the first posttransplant year. Both patients had severe liver injury. The patient who died with cholestatic hepatitis had received four corticosteroid boluses for rejection, and the second death occurred in an individual who received two boluses. None of the seven survivors received more than one steroid bolus, and this was the standard bolus immediately after transplantation. There was no apparent difference in outcome based on induction with OKT3 or immunosuppressive regimen (Table 2) and nor was there any relationship to age at the time of transplantation or ethnicity.

No definite relationship between viral load in the donor and recipient outcome was found. However five of the six recipients who received an organ from a donor with an HCV RNA level greater than 7.0×10^5 copies/mL developed hepatitis versus only one of three recipients of donors with lower HCV RNA level (Table 2).

DISCUSSION

The frequency of HCV infection after transplantation of solid organs from anti-HCV-positive donors has varied widely in the literature. A study by Pereira et al. (*2*) estimated that 48% of organ recipients from anti-HCV-infected donors acquire HCV infection. That study looked at transmission rates after transplantation of a variety or organs. Studies reporting on transmission rates from anti-HCV cardiac-organ donors have also found rates that have varied substantially, from 7% to 82% (*5–8*). Most of these studies are seriously limited by the lack of HCV RNA testing in the

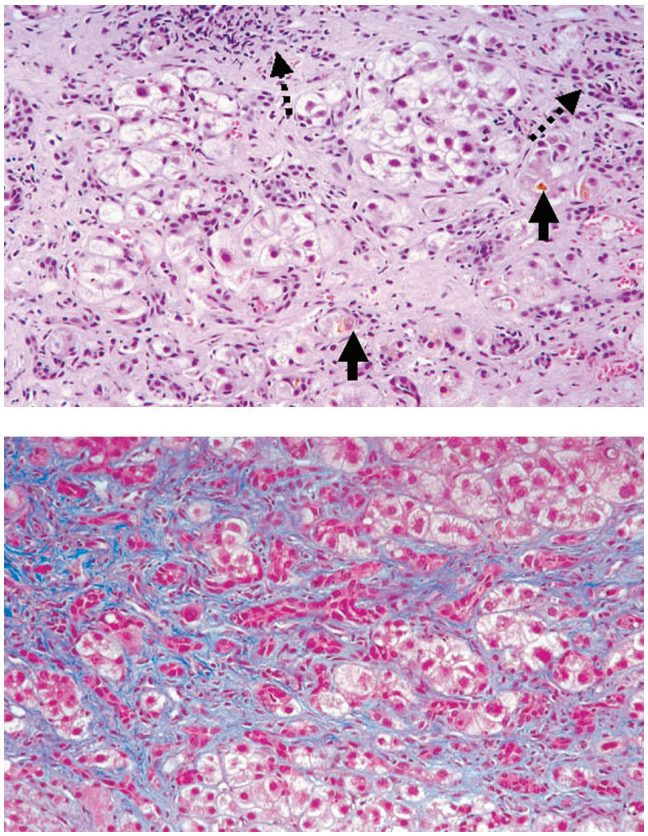

FIGURE 1. (A) Severe ballooning and intracellular and canalicular cholestasis (*closed arrows*) in a heart recipient with fibrosing cholestatic hepatitis. Note the mononuclear cell infiltration interspersed between degenerating hepatocytes (*dashed arrows*). (B) Severe ballooning degeneration and perisinusoidal fibrosis in the same patient.

donors because some of the anti-HCV-positive donors may not have been truly infected or expressive of high-level viremia, which has been shown to correlate with infection risk in other settings (*7*, *8*). In the current study, the transmission rate of HCV infection from viremic heart donors was shown to be 100% irrespective of the level of viremia at the time of transplantation. An important aspect of the study is that donor-recipient pairs were tested for genotype because the identical genotypes in each of our donor-recipient pairs provides relatively strong evidence that infection came from the allograft rather than exposure by way of other routes such as blood products.

It is likely that the amount of replicating HCV in solid-organ tissue is a better correlate of transmission of infection, but little is currently known about the extrahepatic reservoirs of this virus. It has been speculated that the viral load in a heart is lower than that in liver or a unit of blood, thus decreasing the potential risk of transmission (*9*). A study by Yan et al. (*10*) sheds further light on this issue. In that study, the authors looked for evidence of HCV replication and antigens in a number of organ systems from nine patients with chronic HCV infection using PCR, in situ hybridization, and immunohistochemistry. All patients were positive for HCV RNA in the kidney, heart, pancreas, and intestine by PCR. Of note, both HCV RNA and HCV antigen was detected in myocardial cells in five of nine (56%) cases. However, the signal intensity in heart tissue was less than that in the other organs. Further support for the ability of myocardial tissue to support HCV replication comes from studies that have detected HCV in the heart tissue of patients with hypertrophic cardiomyopathy and chronic myocarditis (*11*, *12*).

A main objective of our study was to assess the outcome of HCV infection in cardiac-organ recipients. Six of nine evaluable patients with de novo HCV infection developed HCV-related liver disease. Two of these patients underwent liver biopsy, which revealed severe liver injury with bridging fibrosis and fibrosing cholestatic hepatitis, respectively, and, in the latter individual, this was the immediate cause of death. This entity has been previously described in cardiac-, renal-, and liver-transplant recipients with chronic hepatitis C (*13–15*). Although biopsies were not performed in the other four patients with persistently abnormal ALT, symptoms of chronic hepatitis C were observed in each patient, and one patient developed ascites and jaundice approximately 1 year after his first ALT abnormality. In contrast with these findings, none of the three patients with persistently normal ALT levels developed signs or symptoms of liver disease. One of these patients underwent a liver biopsy 31 months after transplantation that revealed only mild inflammation.

In our study, there was a trend for genotype 1 patients to develop more severe liver injury, but the small number of patients prevented definitive conclusions. All five patients with genotype 1 infection developed HCV-related liver disease, and the only two deaths in the recipients were in genotype 1 patients with biochemical and histologic evidence of chronic hepatitis C. Only one of the four patients with genotype 2 or 3, however, developed biochemical evidence of HCV-related liver disease, and all survived. These findings are reminiscent of the study by Gane and associates (*16*) wherein liver transplant recipients patients with genotype 1 more often developed severe liver disease.

A potentially important finding in the current study is that the only patient who died of severe liver disease had received multiple boluses of corticosteroids during the first postoperative year. This patient also had high-level viremia. It remains controversial as to whether the specific immunosuppressive regimen has any bearing on the clinical outcome in this setting, but the use of corticosteroids has been associated with higher levels of viremia in vitro and in vivo and higher risk of cholestatic liver injury (*17*, *18*). In the study by Ong and associates (*6*), the use of mycophenolate mofetil and high-viral load at the onset of acute liver disease were significantly associated with lower survival in 23 patients with de novo hepatitis C after cardiac transplantation. In our study, patients were placed on various immunosuppressive regimens including a combination of prednisone and either one or two of the following: mycophenolate mofetil, azathioprine, tacrolimus, or cyclosporine. The particular immunosuppressive regimen did not appear to be associated with altered survival or the development of HCV-related liver disease, but the numbers of patients were too small to provide definite conclusions. The one patient who died of severe liver disease had been treated with adjunctive mycophenolate mofetil. However, two of the three patients who had no biochemical evidence of liver disease were also taking this agent.

In summary, there appears to be an extremely high rate of transmission of hepatitis C from anti-HCV donors who are viremic at the time of organ donation. Antibody testing for HCV in the recipient underestimates the true de novo rate of infection. The myocardium may be a reservoir for infection in these patients, and the role that specific immunosuppressive agents have in promoting disease expression needs to be better defined. The results of the present study suggest that HCV RNA negative donors who are anti-HCV-positive are less likely to infect recipients with HCV, but at the current time, it is not practical to evaluate donor serum or plasma for HCV RNA by PCR to assess the potential risk for transmission of hepatitis C. However, because of our findings that HCV infection universally occurs when hearts from viremic donors are transplanted into seronegative recipients and severe, life-threatening hepatitis C may occur, it is the opinion of the authors that hearts from potentially infected donors should be restricted to those recipients who already have evidence for hepatitis C or are in need of emergent transplantation.

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IS SELENIUM DEFICIENCY AN IMPORTANT RISK FACTOR FOR CHRONIC GRAFT NEPHROPATHY?

A PILOT STUDY

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Background. **Lipid peroxidation by free radicals is a key step in the development of atherosclerosis. Chronic graft nephropathy (CGN) is a common cause of allograft failure and shares many histologic features with atherosclerosis. Although hyperlipidemia is a common finding in renal transplant recipients, not all patients develop CGN. We hypothesized that the degree of damage sustained is related to recipient antioxidant status and that only those who are antioxidant deficient succumb to free radical attack and develop CGN. We aimed to determine the antioxidant profiles of patients with biopsy-proven CGN and to compare their profiles to transplant patients with good renal function.**

Methods. **Plasma selenium and vitamin A and E concentrations were measured in 10 patients with CGN and 10 contemporaneous, sex-matched patients with normal renal graft function, who received the same immunosuppressive therapy.**

Results. **Patients with CGN had significantly lower plasma selenium concentrations compared with those with normal renal allograft function ($P<0.05$). There were no significant differences in plasma vitamin A or E concentrations between the two groups. There was no difference in the prevalence of any of the immunologic or nonimmunologic risk factors: human leukocyte antigen mismatches, panel-reactive antibody status, number of rejection episodes, cold ischemic time, hyperlipidemia, hypertension, diabetes, and cytomegalovirus infection between the two groups.**

Conclusions. **Patients with CGN have evidence of selenium deficiency, suggesting that impaired antioxidant status may contribute to the development of CGN.**

The introduction of cyclosporine to clinical practice in the early 1980s led to a marked reduction in acute rejection rates and a 30% improvement in 1-year graft survival rates. However, cyclosporine does not seem to have had much impact on long-term outcome, and renal allograft half-life has changed minimally since 1966 (*1*). One of the commonest causes of graft failure is chronic graft nephropathy (CGN). This is a complex and poorly understood process whose etiology probably includes both immunologic and nonimmunologic factors.

Dyslipidemia is a common complication of solid organ transplantation, with an incidence of between 50% and 80% after renal transplantation (*2*). The association between hyperlipidemia and CGN has been noted in several studies (*3–5*). Isoniemi et al. (*3*) in a study of renal allograft recipients 2 years after transplantation noted that elevated cholesterol and low-density lipoprotein were positive predictors for graft loss during the subsequent 2 years. Similarly, Di-

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