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Risk of Liver Disease in HCV-Seropositive Kidney Transplant Recipients

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Objective

This study determined whether renal allograft recipients with antibodies to hepatitis C virus (HCV) at the time of transplantation experienced increased morbidity or mortality from hepatitis, liver disease, or hepatocellular carcinoma compared with patients without anti-HCV.

Summary Background Data

Chronic liver disease is a cause of significant morbidity and mortality after kidney transplantation and the contribution of HCV to this problem has not been determined. The recent characterization of the HCV genome has resulted in the development of screening tests for antibody to HCV, allowing the identification of end-stage renal disease patients with anti-HCV who are candidates for transplantation. The risk to these patients for the development of hepatic complications after subsequent transplantation is unknown.

Methods

Archived sera obtained from 163 kidney transplant recipients at the time of transplantation were tested for anti-HCV using the Abbott HCV 2.0 second-generation test system. Sera containing anti-HCV were further analyzed for reactivity against specific HCV recombinant proteins, including core, NS3 (c33c), and NS4 (c100-3), to determine whether a pattern could be identified in patients with hepatic complications. The follow-up of all patients was current (mean length of follow-up was 33 months) to identify patients with hepatic complications. All patients had previously been tested for HBSAg.

Results

Twenty-nine patients (18%) had anti-HCV and three (1.8%) had HBSAg. Forty-five patients (28% of total) had transient elevations of AST or ALT without subsequent evidence of liver disease. Three patients had a syndrome of acute hepatitis. Chronic liver disease developed in only six patients (3.6%) after transplantation. Four had anti-HCV only, one had HBSAg only, and one was positive for both. However, of the 29 patients with anti-HCV, chronic liver disease developed in 5 (17%), including 1 patient who was positive for HBSAg. No patient had hepatocellular carcinoma.

Conclusions

Pertubations of liver function were common in the kidney transplant recipients studied, most were self-limited, and few were associated with evidence of viral hepatitis. The risk of developing

chronic liver disease after transplantation of patients with anti-HCV was significant ($p < .0008$ using Fisher's exact test) compared with absence of anti-HCV. No consistent pattern of reactivity to the various HCV proteins could be identified in the patients who developed hepatic complications.

The role of chronic liver disease in the mortality and morbidity after kidney transplantation has been known for many years. In a report by Weir et al.,[1] long-term survival of kidney transplant recipients was significantly reduced in those with chronic liver disease compared with those without liver enzyme abnormalities. Many patients in Weir's study had hepatitis B surface antigenemia (HBSAg) as a cause of their liver disease; however, 47% of patients with chronically elevated liver function studies who tested negative for HBSAg died during the study interval. This suggested that causes of hepatitis other than HBSAg were responsible for post-transplant liver disease. Further, in a report from Melbourne,[2] 27 of 111 (24%) transplant recipients with chronic liver dysfunction had evidence of non-hepatitis B-associated liver disease.

The recent characterization of the hepatitis C virus (HCV) genome[2] has allowed the production of recombinant proteins that react with antibodies in most patients with non-A non-B hepatitis. This has resulted in the development of screening tests for antibodies to hepatitis C. A recent study reported a 36% incidence of advanced liver disease in long-term transplant recipients with anti-HCV,[3] and in another report 10% of transplant recipients were found to have anti-HCV.[4] Klauser et al. described a 15% incidence of anti-HCV after transplantation[5] and a report on 102 hemodialysis patients revealed that 19% had anti-HCV.[6] In all these studies, anti-HCV was determined with first-generation testing against a single recombinant protein — c100-3.

HCV is the predominant agent of transfusion-associated hepatitis[7] and is suspected to be causally related to hepatocellular carcinoma.[2] Because end-stage renal disease patients frequently require transfusion, there exists a group of dialysis patients who have anti-HCV but who otherwise are appropriate candidates for renal transplantation. The risk to these patients for the development of liver complications after transplantation is unknown. This study determined if patients with anti-HCV at the time of transplantation experienced increased morbidity or mortality from acute hepatitis, chronic liver disease, or hepatocellular carcinoma.

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MATERIALS AND METHODS

Archived sera from 163 patients transplanted between October 1986 and September 1991 were studied for the presence of anti-HCV using the Abbott HCV 2.0 second-generation test system, an enzyme immunoassay that determines the presence of antibodies to recombinant proteins expressed from the core, NS3 (c33c), and NS4 (c100-3) regions of the HCV genome. This system differs considerably from first-generation tests that measured antibody against only a single combinant protein, NS4 (c100-3). The presence of anti-HCV was confirmed with repeat testing and with supplemental testing against each of the three separate recombinant proteins using a similar enzyme immunoassay technology.

The sera studied herein were obtained from 163 transplant recipients at the time of transplantation and stored at −70 C. The patients were selected for study if serum specimens were available from the time of transplant and if their grafts functioned sufficiently to allow for complete follow-up. The study population is summarized in Table 1; immunosuppression management is shown in Table 2. The follow-up of all patients was complete to that time and included clinical and laboratory assessment. The mean length of follow-up was 33 months (range: 9–66 months). No patient with graft loss was included.

The definitions of liver disease for this study are summarized in Table 3. Patients were categorized as having 1) normal liver function if AST or ALT was never abnormal, 2) transient derangement of liver function if AST or ALT was elevated for less than 14 days, 3) acute hepatitis if enzymes and bilirubin were elevated for less than 90 days and then returned to normal, and 4) chronic liver disease if there was a twofold or greater sustained elevation of enzymes. All patients had previously been tested for HBSAg before transplantation and this study was not repeated.

Table 1. STUDY POPULATION

No. of patients, 163
Age 7–66 (average = 38.5)
Race: 66 Black; 97 White
Transplant type: 139 cadaveric; 24 living donor
Transfused: 96% cadaveric, 91% living donor
1st transplant, 137 (84%)
HBSAg + 3 (2.3%)

Table 2. MAINTENANCE IMMUNOSUPPRESSION OF 163 STUDY PATIENTS

OKT3 induction, 124 (63%)
Cyclosporine maintenance, 160 (98%)
Steroid maintenance, 163 (100%)
Therapy for acute rejection
Acute rejection, 65 (39%)
Rx with pulse steroids, 30 (46%)
Rx with OKT3, 21 (32%)
Rx with both, 14 (22%)

Table 4. LIVER ABNORMALITIES IN 163 PATIENTS

	Relationship to Anti-HCV	
	Anti-HCV +	Anti-HCV −
Normal (n = 110)	15	95
Brief ↑ enzymes (n = 45)	9	36
Acute hepatitis (n = 3)	1*	2
Chronic disease (n = 6)	5	1

* Later developed chronic disease.

The significance of risk for developing chronic liver disease in patients with anti-HCV compared with patients without anti-HCV was calculated using Fisher's two-tailed exact test.

RESULTS

Twenty-nine of the 163 (18%) patients studied had anti-HCV at the time of transplantation and three patients (1.8%) had HBSAg. One hundred and ten (67%) patients never had any evidence of liver disease (15 with anti-HCV, 95 without anti-HCV, and one with HBSAg). Forty-five patients (28% of total) had brief, transient elevations of enzymes without subsequent evidence of chronic liver disease. Nine of the patients with these transient derangements of liver function had anti-HCV and 36 did not (Table 4).

Three patients had prolonged elevation of liver enzymes and serum bilirubin and a clinical course consistent with acute hepatitis. Two of these patients were anti-HCV negative and their acute hepatitis resolved completely. Acute hepatitis developed in one patient who was anti-HCV positive and subsequently chronic liver disease developed after prolonged remission of acute hepatitis.

Chronic liver disease developed in 6 of the 163 (3.6%) patients after transplantation. Four of these six had anti-HCV only, one had HBSAg only, and one was positive for both. Thus, five of the six patients were among the 29 patients with anti-HCV, including the one with HBSAg as well. One patient with chronic liver disease had overt liver failure with ascites, muscle wasting, and elevated bilirubin. Hepatocellular carcinoma has not developed in any patient to date.

The risk for developing chronic liver disease after transplantation of patients with serologic evidence of HCV disease at the time of transplantation was 17% (5/29). If patients with HBSAg were excluded (Table 5), the risk for liver disease in the presence of anti-HCV was significantly greater than the risk in the absence of anti-HCV ($p < .0008$ using Fisher's exact test).

There was no consistent pattern of antibody reactivity in patients with chronic liver disease, although all patients with chronic liver disease had antibody to both the core and NS3 proteins. Thirteen of 29 patients (44%) positive in the second-generation assay did not react with the c100–3 recombinant protein, the only antibody specificity determined with first-generation HCV testing.

Table 3. DEFINITION OF LIVER DISEASE IN TRANSPLANT RECIPIENTS

Normal: No ↑ of enzymes or bilirubin
Transient: Brief ↑ of enzymes (<14 days)
Acute hepatitis: Prolonged ↑ enzymes with recovery
Chronic disease: Sustained ↑ enzymes to present time

DISCUSSION

The cloning of the HCV genome and the subsequent development of recombinant HCV proteins has ushered in a new era in the understanding of hepatitis and infectious complications associated with transplantation. In this study, the prevalence of anti-HCV in the study group of 163 patients was 18%. This was considerably lower than the 48% prevalence reported by Ponz[8] and the 66% prevalence described by Huang.[9] This finding

Table 5. ANTI-HCV AND CHRONIC LIVER DISEASE

	Anti-HCV +	Anti-HCV −
Liver disease	4*	0
Normal	24	132

* $p < .0008$ (Fisher's exact test) compared with patients without anti-HCV. Patients with HBSAg excluded.

may possibly be explained by differences in selection criteria for the study populations and by differing transfusion practices and waiting times for transplantation among the groups. The Abbott HCV 2.0 anti-HCV test system used in this study identified 29 patients with anti-HCV. When the sera of these 29 patients were confirmed with additional testing to each of the separate recombinant proteins comprising the second-generation test, 44% did not react with c100-3, the only antigen used in the first-generation tests. Thus, 13 patients were identified who presumably would not have been so identified with earlier test systems. This confirms the considerable improvement in anti-HCV testing with second-generation technology.

One limitation of this study is that we have no data about the presence of HCV RNA in any of our patients, and patients can be infected with HCV in the absence of detectable anti-HCV.[2] The correlation of the presence of anti-HCV and infectivity has been studied by Lelie et al., who showed that 78% of blood donors implicated in confirmed post-transfusion HCV infection were seropositive for anti-HCV.[10] Further, Yuki et al. showed that HCV RNA sequences were detected in 91% of patients with anti-HCV and chronic liver disease and in only 2% of patients without anti-HCV.

This study shows that there is significant risk for developing chronic liver disease in patients with anti-HCV at the time of transplantation. Persistent elevations of serum transaminase levels developed in 17% of patients with anti-HCV and one patient progressed to overt liver failure. It was not possible to show any decrement in graft or patient survival associated with the presence of anti-HCV, because the design of the study excluded patients with graft failure or death. Further, the incidence of chronic liver disease may have been underestimated because of the relatively short observation period. In a report by Weir et al.[1] liver failure was the most common cause of patient death in recipients whose allografts had functioned for more than 5 years. In contrast, Ranjan et al. found no detrimental effect on patient or graft survival in patients with HBSAg or anti-HCV followed for 10 years.[12] Since the mean follow-up in our study was only 33 months, the impact of chronic liver disease on the study population was not determined.

This study showed that abnormalities of liver function, including transient increases in liver enzymes, acute hepatitis, and chronic liver disease, were common in transplant recipients. Abnormalities in liver function may have been due to other hepatitis viruses not yet described or to other causes. Only 3 (1.8%) patients studied had HBSAg, and these patients were excluded for purposes of statistical calculations of risk. However, other viruses commonly infect transplant recipients, including all members of the herpes virus family, which includes cytomegalovirus. We have no data about cytomegalovirus infections in this study group. However, cytomegalovirus is thought to be an uncommon cause of chronic liver disease. Because these transplant recipients were commonly treated with numerous drugs, including antihypertensives, H-2 receptor blockade drugs, and multiple immunosuppression drugs, some of the hepatic enzyme abnormalities may have been due to drug-induced hepatitis. Although it is uncommon for drug-induced hepatitis to cause chronic liver disease, this variable cannot be excluded.

The 17% incidence of chronic liver disease associated with anti-HCV in this study indicates that there is risk for morbidity in such patients after transplantation. Whether that risk is greater with transplantation than with chronic dialysis cannot be determined from this study. Hence, although we can make no recommendation regarding transplantation of patients with anti-HCV, we do caution that such patients should be apprised of the risk of chronic liver disease. Since we are *in media res* with our understanding of hepatitis C virus disease, clarification of the risks to patients with anti-HCV will likely be forthcoming with further study.

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Discussion

DR. JOHN L. HUSSEY (New Orleans, Louisiana): Michael, you are to be congratulated for this very scholarly and well-presented paper. However, knowing you as I do, I would have been very surprised if it had been otherwise. As HCV infection is more common than previously thought, more specific screening tests have been developed, the Abbott HCV second-generation being the most recent that I'm aware of. The disturbing reality that you point out is the significant risk of HCV seropositivity in transplant patients. In fact, as you mentioned, this is probably an underestimation. The 50% or greater risk in some studies of false negativity reported with the original ELISA test, the one which you referred to, the C100-3, was reduced to less than 20% by the second generation test and really has been further reduced to less than 5% with the so-called RIBA test, the recombinant immunoblot assay. A greater incidence will probably be shown as more refined tests are developed. It is chilling to note the 17% risk of chronic liver disease that you report. You might ask, how can this be reduced? We can eliminate blood and blood products transfused. The widespread use of EPO, the human recombinant erythropoietin will certainly reduce and possibly eliminate transfusion in dialysis patients. Certainly specific antigen testing techniques should be developed to develop those who are at the greatest risk for the ravages of the HCV infection that you pointed out. And of course anti-viral agents specifically directed against HCV are much needed and long awaited. What about other sources of HCV that you perhaps did not discuss completely, the seropositive organ being a good example? In the February 1991 meeting at the Southeastern Organ Procurement Foundation, members unanimously stated that they would not use organs from HCV-positive donors. The United Network for Organ Sharing held a similar opinion stating that the majority of American transplant centers would not accept HCV-positive organs. However, because we really incompletely understood HCV at that time and because of the shortage of donor organs, we took a bolder position stating that we would use HCV-positive organs under the following circumstances: 1) When the recipient was also HCV-positive by conventional testing, 2) for patients with 90% or greater panel reactive antibodies and having a negative cytotoxic crossmatch with the donor, and 3) for those individuals who had been on a waiting list for greater than 5 years and had not received a first kidney transplant. I think in view of your work and the work of others coming out that we may want to rethink our position in the light of this, although in point of fact we have never used this scheme in any of our transplants.

DR. RICHARD J. HOWARD (Gainesville, Florida): Dr. Rohr, I enjoyed your paper and its furthering of our understanding of hepatitis and liver dysfunction following renal transplantation. We also recently looked at 100 patients who had undergone kidney transplants with both serological testing for antibody to hepatitis and by the polymerase chain reaction, and our findings were substantially similar to yours, that is 18% of the patients had evidence of hepatitis C before transplantation. We also found that 25% had dysfunction of their liver or elevated ALT levels after transplantation. If they were hepatitis C positive, 52% had elevated liver ALT levels. What I would like to ask you is, how good the second-generation test is for antibody to hepatitis C. The first-generation test, as you pointed out, the C100-3 assay, had a very poor sensitivity and specificity when compared to PCR testing. In fact, in our own studies and those of Arida from Japan approximately 50% of individuals who were negative by first-generation test for antibody to hepatitis C were positive by the polymerase chain reaction. If they were positive by antibody testing, they also generally were positive by PCR testing. Do you have any idea how much better the second-generation test is than the first test? You showed that 16 out of 29 individuals reacted by the first-generation testing, but 13 individuals did not. But do you have any independent study of how many individuals who were positive by the second-generation test, in fact, had hepatitis C as determined by any other means? And similarly do you have any measurements of how many individuals who were negative by your testing for antibody to hepatitis C, in fact, were positive when measured by some other test? We've thought that until now the gold standard for hepatitis C testing was the polymerase chain reaction. Is the second-generation test as good?

DR. FREDERICK BENTLEY (Louisville, Kentucky): I also would like to congratulate the authors for another piece of the puzzle and adding to the chapter that is currently being written about hepatitis C. It is a very curious virus that I find in that it has many similarities to hepatitis B but yet it has many dissimilarities to it. Certainly in renal transplantation in the past, chronic liver disease has been one of the more common causes of death in renal transplant patients who have survived 5 years or longer. In patients who have chronic liver disease at the time that they received a renal transplant, mortalities as high as 50% occurred in the 2 years after transplantation. Therefore, the implications of hepatitis C positivity in chronic renal failure patients and their suitability for transplant has yet to be defined. This paper adds to the developing body of information on hepatitis C in patients with chronic renal failure. I have a couple of questions for Dr. Rohr. First of all, do they have sera available from any of the donors of these patients to be able to check this for the presence or absence of the hepatitis C antibody in a retrospective fashion? There have been reports looking at sera from donors in a retrospective fashion and then looking at how the recipients did when they received these hepatitis positive C organs. Their conclusion was that it was a very safe thing to do. That study was also before the second-generation of testing. The patients with chronic liver disease, were they biopsied to determine exactly what type of chronic liver process was going on, such as a histology pattern consis-