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Incidence, Prevalence, and Clinical Course of Hepatitis C Following Liver Transplantation

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Hepatitis C virus (HCV) is the agent responsible for posttransfusion hepatitis. The incidence, timing, and clinical course of HCV positive hepatitis in liver transplant recipients are unknown. Three hundred and seventeen donor-recipient liver transplant pairs were grouped on the basis of their pretransplant HCV antibody status. The biopsy findings were examined. Four distinct groups were identified on the basis of HCV serology: group I, both were negative; group II, donor was negative and recipient was positive; group III, donor was positive and recipient was negative; group IV, both were positive. The prevalence of anti-HCV positivity in recipients was 13.6%. The rate of seroconversion was 9.2%. Histologic hepatitis not ascribable to any specific cause other than non-A, non-B (NANB) hepatitis occurred in 13.8%. The incidence of histologic chronic active hepatitis was 1.6%, and none progressed to cirrhosis. The concordance rate for a positive anti-HCV serology and NANB hepatitis was 2.8%. Of the 35 patients (group II and IV) with positive anti-HCV serology pretransplant, only 17 were positive posttransplantation. Based on these data it can be concluded that posttransplant NANB hepatitis occurred in 13.8% of liver recipients. Twenty percent of these were anti-HCV positive. Progression to histologic chronic active hepatitis occurs over a period of 1–5 years in 1.6% of cases.

The hepatitis C virus (HCV) has been identified as the principal etiologic agent responsible for posttransfusion hepatitis.[1] An assay for anti-HCV antibody using the enzyme-linked immunosorbent assay (ELISA) technique was developed in 1989 by Chiron Corporation.[1,2] This test has been shown to be both accurate and reproducible although some false positive tests occur particularly in patients with hypergammaglobulinemia.[3,4] As a result, newer confirmatory tests using molecular biology techniques have been developed.[5] With the availability of the original test and occasionally also the newer confirmatory tests, several studies have been performed defining the incidence and prevalence of hepatitis C antibody in blood donors and in recipients of blood transfusions as well as in patients with various chronic liver diseases.[6–10] These studies have shown that as many as 20%–50% of patients with advanced chronic liver disease are anti-HCV positive. Few studies have been performed in patients being considered for or having a liver transplant.[11,12]

The present study was designed to answer the following questions that are unique to a liver transplant population: (a) What is the effect of an organ donor's HCV serologic status on the recipient's posttransplant clinical course and HCV serology? (b) What is the incidence, timing, and clinical course of anti-HCV positive hepatitis in liver transplant recipients? (c) Should donor organs be rejected for consideration for transplantation if the donor is found to be anti-HCV positive?

Materials and Methods

Data on all patients who received a single orthotopic liver transplant (OLTx) at the Presbyterian University Hospital, Pittsburgh, Pennsylvania, between March 1986 and March 1990 were reviewed (n = 568). Only those recipients for whom both donor and recipient pretransplant and posttransplant serum were available were included in this study (n = 317). When pretransplant parameters such as age, gender disease, and United Network for organ sharing score were compared between patients meeting these criteria and those that did not, no statistical differences were seen between the subjects of this study and those rejected from study because of an absence of sera (Table 1).

All patients received Cyclosporine A and prednisone as the primary immunosuppressive agents. Rejection episodes were treated with bolus (1-g doses) of methylprednisolone or a recycle of prednisone decreasing daily by 40 mg from an initial starting dose of 200 mg. Steroid-resistant rejection was treated with a 5–10 day course of the monoclonal antibody OKT3.

In general, a diagnosis of viral hepatitis was associated with a 20%–25% reduction in the dose of cyclosporine be-

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Table 1. Characteristics and Specific Diseases of Liver Transplant Patients Included and Excluded From the Study Because of Inadequate Sera

	Recipients		
	Not included	Included	
Demographics			
n	251	317	
age (yr)	45.7 ± 0.8	45.9 ± 0.5	NS
Sex			
M (%)	142 (56.6)	169 (53.3)	NS
F (%)	109 (43.4)	148 (46.7)	NS
Biochemical parameters			
Albumin (g/dL)	2.9 ± 0.1	2.9 ± 0.1	NS
Protime (s)	15.8 ± 0.3	16.1 ± 0.7	NS
Total Bilirubin (mg/dL)	9.4 ± 0.7	8.4 ± 0.5	NS
Specific liver disease			Total
Acute hepatic necrosis	10	12	22
Post necrotic cirrhosis	151	159	310
Secondary biliary cirrhosis	4	5	9
PBS or PSC	47	87	134
Metabolic liver disease	14	17	31
Budd–Chiari syndrome	2	7	9
Tumors	22	29	51
Others	1	1	2
Totals	251	317	568

ing used. Otherwise, no specific alterations in the immunosuppressive regimen was associated with such a diagnosis.

All sera were stored at −70°C before being tested for anti-HCV antibody. The posttransplantation serologic determination was made on the last available serum sample, which was obtained at 18.6 ± 0.65 months post OLTx (range, 1–50 months).

The anti-HCV procedure used was an enzyme-linked assay from Ortho Diagnostics (Raritan, NJ). The test was performed following the procedures recommended by the manufacturer. All specimens found to have an absorbance level less than the cut-off value were considered negative. All specimens with an absorbance level greater than the cut-off value were rerun in duplicate to confirm their positivity. If the sample was consistently positive, it was identified as being positive. Those that were reassayed but fell below the cut-off value were considered negative. The cut-off value was determined by the mean value of known negative controls plus 0.400 absorbance units. When the RIBA-II assay (Ortho Diagnostics, Raritan, New Jersey) became available, all samples for both the donors and the recipients were reassayed with this assay system. The results confirmed the results obtained with the original ELISA System in >91% of the cases.

All donor charts were reviewed for the latest available laboratory values of serum alanine aminotransferase (ALT), prothrombin time (PT), and total bilirubin before organ donation. ALT values >40 Karmen U/mL, a PT >13 seconds, and total serum bilirubin >1.0 mg/dL were considered to be abnormal values.

A total 86.4% of the recipients had a liver biopsy performed sometime during their follow up posttransplant care for a specific clinical indication. In general, liver biopsies were performed if either the bilirubin level increased by >25% and biliary obstruction could be ruled out on the basis of the absence of intrahepatic bile duct dilation or an increase in the serum level of either the alanine or aspartate aminotransferase level of >25%. All liver biopsies were read by a single staff pathologist at the Presbyterian University Hospital and rereviewed by the authors and graded using the Knodell criteria.[13] A histological diagnosis of non-A, non-B (NANB) hepatitis was made when the serum aminotransferase levels were increased and histologic evidence for hepatitis consisting of liver cell necrosis, Kupffer cell hyperplasia, and a portal inflammatory infiltrate were present in the absence of histology and serologic evidence for hepatitis A, B, D, cytomegalovirus, Epstein-Barr virus, and herpes simplex virus infection or rejection. Thirty-one of 44 (70.4%) recipients with a posttransplant diagnosis of putative NANB hepatitis (whether anti-HCV positive or negative) had one or more liver biopsies during the posttransplant follow-up period. These were reviewed to determine the rate of progression of the histologic liver disease to chronic active hepatitis (CAH) and cirrhosis.

Statistical Analysis

All data are reported as mean values ± SEM. The Students' *t* test was used to compare mean values between groups. Survival curves were prepared according to the method of Kaplan and Meir.[14] A P value <0.05 was considered significant.

Results

All 317 recipients could be grouped into one or another of four categories based on the serologic status of their pre-OLTx serum and that of their donor for anti-HCV (Table 2).

The ages of recipients ranged from 16 to 68 years (45.9 ± 0.5 years). There were no differences between the four groups for age. There were 169 male and 148 female recipients. Again, no differences in distribution between the four groups was evident based on gender. Based on clinical criteria, none of the recipients who were anti-HCV positive before transplantation were thought to have acute hepatitis.

Of the 317 donors, only 244 (77.9%) had complete biochemical data (ALT, PT, and total bilirubin) avail-

Table 2. HCV Serology of the 317 Donor-Recipient Pairs at the Time of Transplantation

		Anti-HCV antibody status	
Group	n	Donor	Recipient
I	273	Negative	Negative
II	34	Negative	Positive
III	9	Positive	Negative
IV	1	Positive	Positive

able at the time of organ donation. Sixty-three (19.9%) had one or more missing data points. Seven (2.2%) had no data at all. Each of these donors without any laboratory data assessing liver injury and/or function were in group I. No evidence of pre-existing histologic liver disease was evident in any of the donors for whom liver biopsies were obtained before actual organ engraftment (n = 56).

Twenty-six of 282 (9.2%) recipients in group I and group III combined who had a negative HCV serology before the OLTx became anti-HCV positive following OLTx at a time interval ranging between 2–45 months (mean 18.9 ± 2.38 months) since the date of the transplant. Twenty-five of these were from group I (negative donor to negative recipient) while only 1 was from group III (positive donor to negative recipient) (Table 3).

Thirty-five recipients in group II and group IV who were seropositive for anti-HCV before OLTx were followed for 6–44 months (mean 22.0 ± 1.88 months) and only 17 (48.6%) persisted in having a positive anti-HCV at the time of last follow up (Table 3). Seventeen of the 34 patients from group II who were found to be seronegative for anti-HCV post-OLTx were evaluated further. Charts were reviewed to obtain data on γ globulin levels before transplantation to rule out the possibility of hypergammaglobulinemia causing false positive serology for anti-HCV. These 17 patients had mean γ globulin levels of 3.01 ± 0.16 and ELISA ratio with a mean level of 1.6 ± 0.18 pre-OLTx. Four recipients had low ELISA ratios (1.01, 1.09, 1.08, and 1.11; mean 1.07 ± 0.02). The remaining 13 recipients had ELISA ratio with a mean level of 1.79 ± 0.21. The 4 recipients with a low ELISA ratio had a mean γ globulin level of 3.18 ± 0.42, whereas the 13 recipients with an increased ELISA ratio had a mean γ globulin level of 2.95 ± 0.16. These data suggest that the 17 recipients from group II who became seronegative post-OLTx were unlikely to have had an initial false positive HCV serology pre-OLTx as a result of having hypergammaglobulinemia.

Of the 274 recipients who had a liver biopsy performed sometime during their follow up, 78.8% (216/274) had more than 1 liver biopsy. A total of 935 liver biopsies were performed in these 274 recipients (average 3.4 per recipient) (Table 4). Thirty-nine of the 43 recipients with a positive HCV serology following OLTx had a liver biopsy. An average of 4 liver biopsies per such recipient were obtained. Four recipients never had a liver biopsy obtained during their follow up because no clinical indication for a biopsy was ever present.

Histological evidence of putative NANB hepatitis was found in 13.8% (44/317) of the recipients. These 44 recipients had an average of 5.4 liver biopsies each (Table 4). Thirty-four (77.3%) of these recipients were in group I. 7 (15.9%) were in group II. 3 (6.8%) were in group III. The time interval from OLTx to first histological evidence of putative NANB hepatitis ranged from 1–27 months with the mean being 9.6 ± 1.15 months (Table 5).

Only 9 (2.8%) recipients had both a positive HCV serology and a histologic evidence of putative NANB hepatitis. Five of these were from group I and 4 were from group II (Table 4). Thirty-five (79.5%) of recipients with histological evidence of putative NANB hepatitis post-OLTx were anti-HCV negative (Table 5). Conversely, 79% of the recipients with a positive HCV serology post-OLTx never had any histological evidence for NANB hepatitis post-OLTx (Table 6).

Only 1.6% of the 317 recipients developed histologic CAH post-OLTx. Four of these were from group I and 1 was from group II. None have developed cirrhosis. All five of those who developed CAH were seronegative for antibody post-OLTx. The time interval from OLTx to first evidence of CAH was 1–27 months (mean 13.2 ± 4.7 months). The Knodell scores for these 5 subjects ranged from 13–17 with the severity of the periportal and bridging necrosis component of the score contributing most to the overall score (Table 7).

The survival was best for those in group III (positive donor into a negative recipient) with 100% sur-

Table 3. The Frequency and Timing of HCV Positivity in the 317 Recipients Studied

Groups	No. with positive HCV serology (%)[a]	Interval for recipient with positive HCV serology [*mo* (mean ± SEM)][b]	Interval for recipient with negative HCV serology [*mo* (mean ± SEM)][b]	Interval for all recipients [*mo* (mean ± SEM)][b]
I (n = 273)	25 (9.2)	2–45 (19.2 ± 2.46)	1–50 (17.6 ± 0.73)	1–50 (17.8 ± 0.70)
II (n = 34)	17 (50)	6–36 (20.2 ± 2.46)	6–42 (22.4 ± 2.73)	6–42 (21.3 ± 1.82)
III (n = 9)	1 (11.1)	12	5–37 (19.5 ± 4.4)	5–37 (18.6 ± 4.01)
IV (n = 1)	0 (0)	NA	44	44
Totals (n = 317)	43 (13.6)	2–45 (19.4 ± 1.72)	1–50 (18.1 ± 0.71)	1–50 (18.6 ± 0.65)

NA, not available.
[a]Determined at last follow up.
[b]Interval from OLTx to last available serum sample of recipient.

Table 4. Number of Liver Biopsies Performed on the Recipients of Each Group Separated as to the Presence of Positive HCV Serology, Positive Histology, or Both

Groups	No. with LBx post-OLTx	Total LBx (avg/pt)	No. with positive HCV serology post-OLTx	Total LBx (avg/pt)	No. with histologic NANB hepatitis post-OLTx	Total LBx (avg/pt)	No. with histologic NANB hepatitis and positive HCV serology post-OLTx	Total LBx (avg/pt)
I (n = 273)[a]	237	797 (3.4)[b]	25	97 (4)	34	190 (5.6)	5	28 (5.6)
II (n = 34)[c]	29	101 (3.5)	17	61 (4)	7	31 (4.4)	4	19 (4.7)
III (n = 9)	8	37 (4.6)	1	1 (1)	3	18 (6)	0	0
IV (n = 1)	0	0	0	0	0	0	0	0
Totals[d]	274	935 (3.4)	43	159 (4)	44	239 (5.4)	9	47 (5.2)

LBx, liver biopsy.
[a]One recipient did not have a liver biopsy.
[b]Mean number of liver biopsies per patient.
[c]Two recipients did not have a liver biopsy.
[d]Four recipients did not have a liver biopsy.

viving through 4 years. The survival of those in group II (negative donor into positive recipient) at 4 years was 94%, which did not differ from that in group I where the survival was 89% at 4 years. It is not possible to calculate a survival curve for the single patient in group IV, but this single patient is still alive at 4 years. Thus, the overall survival of all groups was excellent ranging between 89 and 100% at 4 years.

Graft survival was also calculated for each group. The graft survival at 4 years for those in group I was 87%, whereas it was 94% for those in group II and 100% for those in group III and IV. Again, because of the overall excellence in results, no statistical differences exist among the 4 groups for graft survival.

Discussion

Several important observations can be made from this study. First, the incidence of anti-HCV positivity following transplantation was found to be 13.6% in liver recipients at the time of last follow up. The incidence of histological NANB hepatitis was quite similar, being 13.8% with a follow-up period of 1–27 months (mean 9.6 months). However, the concordance of an HCV positive serology and histologic hepatitis was quite low, being only 2.8%. A highly likely possibility for this finding is that the identification of HCV infection among transplanted patients with current anti-HCV assay techniques grossly underestimates the magnitude of the problem. The use of PCR techniques to detect HCV-RNA in serum and tissue not yet available to the current investigators should rectify this problem.

Hemophiliacs have an anti-HCV positivity rate of 40%–70% because of their frequent and repetitive exposure to blood and blood products.[15,16] Patients with OLTx also have a high exposure to a variety of blood products and might be considered to be at increased high risk for posttransfusion NANB hepatitis. However, the actual incidence of NANB hepatitis found in the liver transplant population was remarkably lower than that reported for hemophiliacs.

Only 2.8% (9/317) patients had histological evidence of NANB hepatitis as well as being anti-HCV positive at the time of last follow up post-OLTx. Thus there was little concordance between the serologic status of the recipient and the histologic findings of NANB hepatitis post-OLTx. This is unlike the 60%–

Table 5. Frequency, Timing, and Severity of the Posttransplant Hepatitis in the 4 Groups Studied

Groups	No. with histologic NANB hepatitis post-OLTx (%)	No. with histologic NANB hepatitis and negative HCV serology post-OLTx (%)	No. with CAH post-OLTx (%)	Time interval for NANB hepatitis [range (mean; *mo*)][a]
I (n = 273)	34 (12.4)	29 (10.6)	4 (1.5)	1–27 (9.5)
II (n = 34)	7 (20.6)	3 (8.8)	1 (2.9)	1–27 (11.0)
III (n = 9)	3 (33.3)	3 (33.3)	0	5–15 (9.3)
IV (n = 1)	0	0	0	0
Totals (n = 317)	44 (13.8)	35 (11.0)	5 (1.6)	1–27 (9.6)

[a]Interval from OLTx to first histologic evidence.

Table 6. Frequency of Posttransplant Hepatitis in the 317 Recipients Studied Separated as to Positive HCV Serology and Histology

Groups	No. post-OLTx (%)	No. with histologic NANB hepatitis post-OLTx (%)	No. with no histologic NANB hepatitis post-OLTx (%)
I (n = 273)	25 (9.15)	5 (1.8)	20 (7.3)
II (n = 34)	17 (50)	4 (11.8)	13 (38.2)
III (n = 9)	1 (11.1)	0	1 (11.1)
IV (n = 1)	0	0	0
Totals (n = 317)	43 (13.6)	9 (2.8)	34 (10.7)

100% concordance rate found in cases of posttransfusion hepatitis as reported by Alter et al. using the same techniques as in the present report.[17]

As noted above, the application of PCR techniques to detect HCV-RNA in serum and tissue in future studies should improve on the present findings. The prevalence of seroconversion from anti-HCV negative to anti-HCV positive was found to be 9.2% (26/282, groups I and III) in this population. This is comparable to the seroconversion rate of individuals receiving one or more transfusions reported by Esteban et al.[18] Overall, the incidence of posttransfusion hepatitis has been found to range from 2%–15% in several different studies from various countries.[19–23] The results of this study suggest that the blood transfusions given before, during, and after the liver transplant procedure were more likely to be the source of NANB hepatitis in the recipients who developed hepatitis than was the donor organ. When all blood units are tested for the presence of HCV before transfusion, the incidence of NANB hepatitis post-OLTx may be reduced.[24–26]

An interesting observation was made in group II. Specifically, 17 (50%) of the surviving recipients were anti-HCV antibody positive at the time of last follow up although all 34 had been anti-HCV positive before their transplant. The reason for the disappearance of HCV antibody in 50% of these patients is unclear. Whether this reflects an effect of the immunosuppression used, insensitivity of the assay, a unique characteristic of this population, or some other cause is as yet unclear. The possibility of false positivity of anti-HCV secondary to hypergammaglobulinemia was eliminated by obtaining, calculating, and comparing total γ globulin levels and ELISA ratios and finally by confirming the results obtained with the Ortho Diagnostic assay with those obtained using the more recently available RIBA-II assay. Overall, a concordance rate of 91% was seen between the ELISA procedure and the RIBA-2 assay in this study population.[27] However, a similar observation has been made after liver transplantation by Trainer et al. and Grendele et al.[28,29] However, the number of patients studied by these authors was rather small (9 and 6, respectively). They observed a rate of 33% for persistence of anti-HCV antibody in liver recipients who were seropositive before their OLTx. These observations suggest that the obligate immunosuppression required following OLTx can block the expression of anti-HCV and/or prevent its development.

A very low incidence (1.58%) of CAH was found in this unique group of patients after 4 years of follow up; none developed cirrhosis. All of those who developed histologic CAH were anti-HCV negative. Eleven percent (5/44) of the recipients with histological evidence of NANB hepatitis progressed to CAH. This is also lower than the incidence of CAH and cirrhosis found in histologically proven cases of posttransfusion NANB hepatitis as determined by Mattson et al.[29] These authors found a 59% incidence of CAH, and 46% of their patients showed early cirrhosis after a follow-up period of 5 years.

Ten patients in groups III and IV received livers from donors who were seropositive for anti-HCV. Only 1 of these recipients (10%) was anti-HCV posi-

Table 7. Knodell Scores for the 5 Recipients With CAH

No.	Periportal positive/negative bridging necrosis	Intralobular degeneration and focal necrosis	Portal inflammation	Fibrosis	Final score
1	6	1	3	3	13
2	6	4	4	3	17
3	4	3	3	3	13
4	4	3	3	3	13
5	5	3	3	4	15

tive and only 3 (30%) have developed putative NANB hepatitis post-OLTx; none have developed CAH. Nonetheless, the relatively high incidence of NANB hepatitis in 33% of those receiving a liver from an anti-HCV positive donor should be noted and should suggest caution when using such organs except in critical situations and until more data concerning the issue of the progression of NANB hepatitis in an allograft recipient is available.

Both patient and graft survival was excellent (87%–100%) in all four groups studied at 4 years. Surprisingly, the best survival rates (100%) were found in groups III and IV who received organs from donors that were anti-HCV positive. Although the number of recipients in groups III and IV combined was small, the evidence does not support a policy of rejecting scarce organs for transplantation solely because the donor is anti-HCV positive, providing the liver appears histologically normal and there is no evidence of active hepatitis in the donor using standard biochemical parameters. Two large studies in blood donors are consistent with this position and have shown an absence of hepatitis C in recipients of blood obtained from donors who are anti-HCV positive but have no liver disease when biopsied.[25,26] In contrast, both of these studies showed a very high rate of HCV transmission to recipients of blood obtained from HCV antibody positive donors with histologic evidence of liver disease. Therefore, it is suggested that a histological examination of a donor liver with a frozen section may be the best screening technique presently available for general use in selecting or rejecting a donor organ obtained from an anti-HCV positive donor. The use of PCR to detect HCV-RNA in serum and liver in the future should allow for the elimination of all donor livers containing replicating HCV.

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