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Hepatitis C in liver transplant patients

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Abstract The aim of this study was to determine whether infection by the hepatitis C virus (HCV) recurs after orthotopic liver transplantation (OLT) and to define the natural history of post-transplantation chronic hepatitis due to HCV. Of 70 patients, 10 (14.3%) were found to have antibodies to HCV before transplantation. After OLT 14 of the 70 patients (20%) had positive anti-HCV antibodies: 8 of 10 positive pre-OLT (80%) and 6 of 60 negative pre-OLT (10%). Of 14 patients anti-HCV+ post-OLT (57%), developed 8 chronic hepatitis: chronic persistent hepatitis in three patients, chronic lobular hepatitis in three patients and chronic, active hepatitis in two patients. We treated four patients with interferon obtaining normalization of transaminases in three of them after 6 months, but with a severe relapse in two. These results suggest that hepatitis C recurs in a majority, of liver transplant recipients and that morbidity is an important consideration. Interferon treatment of these patients requires further study to obtain conclusive results.

Key words Orthotopic · Liver Transplantation · Hepatitis C Interferon

Introduction

The recent identification of the genome of the hepatitis C virus (HCV) [2] and the development of various diagnostic tests to determine anti-HCV antibodies have led to initial studies on the course of hepatitis C in orthotopic liver transplantation (OLT) [1, 3, 5–8]. These studies have demonstrated that HCV can reappear in the transplanted liver, or that it can be newly acquired after OLT either from the transfused blood or from the transplanted organ.

The aim of the present study was to determine the recurrence or new appearance of HCV after OLT and to define the natural history of post-transplant HCV hepatitis. We also report our experience with interferon (IFN) treatment in four patients with chronic hepatitis due to HCV after OLT.

Patients and methods

Between October 1989 and December 1992 75 patients underwent OLT at our institution. Included in the present study were 70 patients receiving 79 OLT, with a minimum follow-up of 6 months (mean ± SE 14.2 ± 8.8 months, range 6–36 months) and a mean age of 44 ± 11 years (range 10–63 years). The indications for OLT were: 44 cirrhosis (63%), 13 fulminant hepatic failure (FHF) (18.5%) and 13 other indications (18.5%). The other indications were four Corino-Andrade type amyloidosis, three Wilson's diseases, two hepatocarcinoma, two primary sclerosing cholangitis, one Budd-Chiari syndrome and one giant adenoma of the liver. Nine patients underwent retransplantation.

Table 1 Frequency and timing of post-OLT hepatitis

Patients	No. with histological C hepatitis	Time from OLT to first histological evidence of C hepatitis (months)
Anti-HCV + pre/ + post-OLT ($n=8$)	5 (62%)	3.8 ± 2.7
Anti-HCV + pre/ + post-OLT ($n=6$)	3 (50%)	4 ± 2.4
Total ($n=14$)	8 (57%)	3.9 ± 2.6

Anti-HCV antibodies were determined preoperatively, then monthly for 3 months postoperatively and bimonthyl thereafter using a first-generation ELISA (Ortho Diagnostics) in 20 patients and a second-generation ELISA (Abbot) in 50, the latter confirming all the cases that were positive in the first-generation assay. If there was any alteration in liver biochemistry, hepatic ultrasonography was performed with Doppler assessment of the portal vein, hepatic veins and hepatic artery. Liver biopsy was performed when the ultasonographic data were not diagnostic.

Results

HCV serology before OLT

Of the 70 patients, 10 (14.3%) were anti-HCV+ before OLT. These were 6 from 32 patients with ethanolic cirrhosis (19%), 3 from 8 NANB postnecrotic cirrhosis (37%) and 1 from 13 FHF (8%). Two of the 79 donors were anti-HCV+ (2.5%).

HCV serology after OLT

Of the 70 patients, 14 had anti-HCV positivity (20%) after OLT. Of the 10 pre-OLT anti-HCV+ patients, 8 (80%) had reappearance of the antibodies between the 1st and 11th month of follow-up (mean ± SE 3.6 ± 3 months). Of the 60 pre-OLT anti-HCV− patients, 6 (10%) developed post-OLT anti-HCV positivity between the 1st and 13th month of follow-up (mean ± SE 5.3 ± 4 months).

Post-transplant hepatitis

Of the 14 post-OLT anti-HCV+ patients, 8 (57%) developed chronic hepatitis (5 from 8 with positive pre-OLT serology (62.5%) and 3 from 6 with negative pre-OLT serology (50%), Table 1). Histological findings were chronic persistent hepatitis in three patients, chronic lobular hepatitis in three patients and chronic active hepatitis in two patients. In 11 patients out of 56 (20%) with post-OLT anti-HCV negativity we found three chronic persistent hepatitis, one chronic active hepatitis, two chronic rejections, three steatosis, one with minimal lesions and one with possible recurrence of primary sclerosing cholangitis.

We treated four patients with IFN-alpha 2b 5 MU three times per week subcutaneously for 6 months and obtained normalization of the transaminases in three patients after 3 months, but with an evolution towards more severe lesions after the treatment had finished in two of them. One patient did not respond to the treatment.

There were nine retransplantations in our series: 7 of the 56 (12.5%) anti-HCV- and 2 of the 14 (14.2%) anti-HCV+ patients, both due to chronic active hepatitis with septa, secondary to the HCV.

Discussion

HCV-related liver disease is a commonly diagnosed indication for liver transplantation in various centres [7]. In our centre, 14% of the patients were anti-HCV+ pre-OLT.

The recurrence of C virus infection occurs frequently after OLT, with most of the pre-OLT anti-HCV+ patients remaining seropositive after the transplant [1, 3, 5–8]. In addition, the polymerase chain reaction (PCR) technique has enabled the RNA of the virus to be demonstrated directly in serum and liver in most pre- and post-OLT anti-HCV+ patients [5]. In this study, 80% of the pre-OLT anti-HCV+ patients were positive after transplant, and in 10% of the cases the infection was new. The possible explanation for this may lie in the existence of false pre-OLT negatives, and the transmission of the HCV in the transfused blood or the transplanted organ. However, two of our patients receiving an organ from an anti-HCV+ donor did not develop anti-HCV antibodies or liver disease after a follow-up of over 1 year.

From a clinical point of view, the greatest interest lies in the consequences that the appearance of the C virus post-transplant may have in the natural course of the liver function. In our series, 57% of the patients anti-HCV+

after OLT developed chronic hepatitis with no difference in the incidence between those in whom the HCV recurred and those in whom it newly appeared. The clinical consequences were serious in half of the cases, either because a retransplant was required or because they caused the death of the patient.

IFN treatment has proved effective in 50% of patients with chronic hepatitis due to HCV [4]. There has so far been no experience with such treatment in post-OLT hepatitis C. In this study, we treated four patients with IFN with transaminases becoming normal in three of them. After completion of the treatment, only one patient with chronic persistent hepatitis had normal transaminase levels, whereas the other two developed chronic active hepatitis with septa, which led to severe hepatic failure with progressive cholestasis and severe ductal destruction.

In conclusion, our results suggest that hepatitis C recurs in most anti-HCV+ patients undergoing OLT. In these patients and in those newly developing the infection, the hepatic lesions are usually moderate or severe in half of the cases. IFN treatment requires further study to obtain conclusive results.

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