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M. Knoop
R. Lüsebrink
J. M. Langrehr
V. König
T. Berg
A. Wedell
U. Hopf
P. Neuhaus

Incidence and clinical relevance of recurrent hepatitis C infection after orthotopic liver transplantation

M. Knoop (✉) · R. Lüsebrink
J. M. Langrehr · A. Wedell · P. Neuhaus
Department of Surgery,
University Hospital Rudolf Virchow,
Free University of Berlin,
Augustenburger Platz 1,
D-13353 Berlin, Germany

V. König · T. Berg · U. Hopf
Department of Internal Medicine,
University Hospital Rudolf Virchow,
Free University of Berlin, Germany

Abstract From September 1988 to November 1992 318 liver transplants were performed at our hospital. Of these patients 68 had end-stage cirrhosis due to non-A, non-B, hepatitis, 44 of whom (64.7%) had hepatitis C virus RNA in the serum. Of this subgroup 35 patients (79.5%) were also anti-HCV positive. Postoperatively most recipients remained anti-HCV positive and after 1 year more than 90% had HCV RNA in the serum. About 40% developed a mild, chronic hepatitis and 50% were carriers of HCV without histopathological signs. Two patients suffered from a temporary severe acute hepatitis and one patient had a fulminant liver failure due to reinfection. In general, in liver recipients transplanted for end-stage HCV hepatitis there was a high incidence of reinfection with HCV. The clinical course, however, was less severe than in hepatitis B recurrence.

Key words Liver transplantation
Hepatitis C infection

Introduction

With the evolution of specific tests for anti-hepatitis C virus (HCV) antibodies and direct demonstration of the virus by polymerase chain reaction (PCR) a high prevalence of HCV infection in patients with non-A, non-B (NANB) hepatitis has been detected [1, 5]. End-stage cirrhosis due to NANB hepatitis is one of the major indications for orthotopic liver transplantation (OLT). Since data on the postoperative course of these patients with special reference to hepatitis C reinfection and diagnostic parameters are scarce [4], the aim of the present study was to determine the serological patterns of anti-HCV antibodies and HCV RNA pre- and post-transplant and the postoperative incidence of hepatitis C.

Materials and methods

Patients

From September 1988 to November 1992 318 OLTs were performed at the University Hospital Rudolf Virchow in Berlin. Of these patients 137 were suffering from end-stage cirrhosis due to viral hepatitis, and 68 patients of this group had chronic NANB hepatitis of sporadic origin. The average intraoperative blood requirement was 6.7 units of red blood cells. From January 1990 blood products were screened routinely at our blood bank with the anti-HCV ELISA. After OLT a quadruple immunosuppression was given comprising cyclosporine, prednisolone, azathioprine, ATG or FK 506 and prednisolone as part of the European multicentre trial of FK 506. Antiviral prophylaxis consisted of acyclovir administration for 6 weeks, anti-CMV hyperimmunglobulin on day + 1 and + 14 and Cytotect in the case of a CMV-positive donor/CMV-negative recipient constellation.

Diagnostic methods

Sera of NANB transplant candidates, and of liver recipients 1–3 months and more than 6 months post-transplant (mean follow-

up 20 months) were collected and stored at −20 °C until tested. Anti-HCV antibodies were detected with second generation diagnostic kits (ELISA 2, Ortho Diagnostic Systems; RIBA 2, Chiron [11]). Indeterminate results in the RIBA 2 test were classified as negative. HCV RNA was prepared and assessed with a nested PCR using two sets of primers (NCR1–NCR4; PT1–PT4) from the highly conserved (> 99%) 5 noncoding region as previously described [7].

Biopsies were obtained from the donor liver before transplantation, from the resected diseased liver and from the donor liver after reperfusion, after 7 days and at defined intervals thereafter. Liver function parameters were analysed on a routine basis.

Results

Serology

Before OLT

Anti-HCV was detectable in the sera of 37 (54.4%) of the patients with end-stage cirrhosis due to hepatitis NANB, and 44 were HCV RNA positive (64.7%). Of these 44 patients 35 were anti-HCV positive (79.5%). Two patients were anti-HCV positive with negative HCV RNA.

One to three months after OLT

All patients who were anti-HCV positive before OLT retained this status during the early phase after OLT. Of nine previously negative patients three became anti-HCV positive. HCV RNA was present in the serum of 91% (40/44) of the liver recipients with HCV RNA before OLT.

Six or more months after OLT

Two patients who were anti-HCV positive pretransplant became anti-HCV negative. Six patients transplanted for indications other than NANB cirrhosis acquired anti-HCV de novo after transplantation without detection of HCV RNA. HCV RNA was detected 6 months post-transplant in 42/44 patients (95%). After 1 year two patients stayed HCV RNA negative and another patient later became HCV RNA negative (HCV RNA in 39/42 patients, 93%).

Clinical course of HCV reinfection

After a mean follow-up of 20 months 16/42 recipients (38.1%) had signs of a mild or moderate chronic hepatitis. Two patients (4.8%) developed a temporary severe acute hepatitis that spontaneously decreased. One patient died of fulminant liver failure due to hepatitis C reinfection (2.4%). One patient developed cirrhosis by the same cause but had not yet been retransplanted (2.4%). Of the 42 recipients with HCV RNA in the serum 22 showed no histological evidence of an inflammatory response due to reinfection and were considered as carriers (52.4%).

Discussion

A previous study by our group showed a nearly 100% positive correlation between HCV RNA detection in serum and in liver tissue pre- and post-transplant [7]. In the present study we used serum as the only source for diagnosis of anti-HCV and HCV RNA. The major finding was that reinfection occurred soon after OLT in more than 90% and that the course of reinfection, in contrast to hepatitis B recurrence was usually smooth. Histological evidence of a mild, chronic persisting hepatitis occurred in about 40% of HCV RNA-positive recipients. However, the majority of HCV RNA-positive patients had no specific histological finding indicating graft reinfection and were classified as virus carriers. A severe acute hepatitis or fulminant reinfection was a rare event after OLT in accord with other reports [2, 3, 10, 12, 13].

Three patients became HCV RNA negative after OLT. Whether this indicates a loss of replication or a definite elimination remains unclear. The source for recurrence of HCV after OLT is most likely located in Lymphocytes and mononuclear cells [6]. Since tissue samples of the graft after implication and reperfusion were HCV RNA negative in a former study [7] this extrahepatic site seems to be responsible for graft reinfection.

De novo hepatitis C infection after OLT with detection of HCV RNA before seroconversion occurred has recently been described [9]. Our six patients with de novo anti-HCV antibodies, however, were HCV RNA negative in the serum. Since blood products were screened routinely with an ELISA, blood donors were carefully selected and donor organs were PCR negative, the route of viral transmission is unclear. Follow-up studies as well as more precise donor evaluation with second generation anti-HCV kits and PCR concerning this aspect are clearly needed.

The high incidence of reinfection raises the question of an anti-HCV prophylaxis in a manner analogous to the use of anti-HBs hyperimmunoglobulin to prevent hepatitis B recurrence. Even though reinfection with hepatitis C

has a less severe course than that with hepatitis B [8], it remains uncertain how the patients with mild chronic hepatitis C will perform in the long-term follow-up. Only one patient developed HCV cirrhosis after OLT during the study period. The use of neutralizing anti-HCV antibodies in viraemic patients after hepatectomy would be useful, but the antibodies still have to be defined. Other treatment schedules currently being tested to prevent or ameliorate HCV reinfection include the use of interferon-alpha [15] and the nucleoside analogue ribavarin [14].

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