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Is hepatitis C virus recurrence a risk factor for chronic liver allograft rejection?

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Abstract Several risk factors have been reported that may favour the development of chronic rejection. From October 1988 to December 1993, 97 liver transplants with survival of more than 3 months were included in the study. Fifty-two patients (54.1 %) had chronic hepatitis C virus (HCV) infection before liver transplantation. Immunosuppression consisted of cyclosporine A and prednisone, whereas 14 patients received FK 506 and prednisone. Severe graft HCV reinfection was present in 32 patients (61.5 %) after liver transplantation and chronic graft hepatitis C was found in 26 cases at the end of the study. Chronic rejection occurred in 8 of 97 allografts (8.25 %); 5 presented chronic rejection and concomitant chronic graft hepatitis C. The incidence of chronic rejection in patients with HCV infection before liver transplantation (9.6 %) did not differ when compared with the negative HCV patients (6.6 %). However, when the 26 cases that developed graft dysfunction due to chronic hepatitis C after liver transplantation were considered, 5 presented chronic rejection, a significantly higher incidence than in the remaining patients (3 of 71) (Yates chi-square test: $P < 0.05$). In our experience, there appears to be a relationship between the development of chronic rejection and chronic hepatitis C in the graft after liver transplantation.

Key words Chronic rejection · Hepatitis C virus · Liver transplantation

Introduction

Chronic rejection of liver allograft is generally considered to be an irreversible condition, characterized by immune-mediated destruction of bile ducts and obliterative vasculopathy involving large- and medium-sized arteries [1]. This results in a syndrome of progressive cholestasis, which is usually unresponsive to immunosuppression, leading to graft failure. Several risk factors have been reported that may favour the development of chronic rejection [2].

Hepatitis C infection is a major cause of end-stage liver disease requiring liver transplantation (LTx). The hepatitis C virus (HCV) remains detectable in serum and other tissues after LTx. and leads to recurrence of hepatitis C in many patients [3, 4]. Our aim was to study HCV infection as a predisposing risk factor for chronic rejection.

Patients and methods

From October 1988 to December 1993, 127 liver transplants were performed in 110 adult patients at the Hospital General Universitario Vall d'Hebron, Barcelona. All liver allografts with survival of more than 3 months (97 grafts) were included in the study. Fifty-two patients (54.1 %) had chronic HCV infection before LTx. No patient received AB0 blood-incompatible grafts. In the early years, Eurocollins solution was used. Thereafter, all remaining grafts were preserved with the University of Wisconsin solution. Mean follow-up was 22 months (range: 3–70 months). Minimum follow-up of living patients was 12 months.

Table 1 Incidence of hepatitis C virus *(HCV)* recurrence and chronic rejection. *(PSC* Primary sclerosing cholangitis, *PBC* primary biliary cirrhosis, *HBV* hepatitis B virus, *LTx* liver transplantation)

Diagnosis pre-LTx	Patients	Severe graft HCV reinfection	Chronic graft hepatitis C	Chronic rejection
Cirrhosis-tumour HCV	52	32/52 (61 %)	26/52 (50 %)	5/26 (19 %)
HBV hepatitis	4	–	–	–
PSC, PBC	9	–	–	–
Alcoholic cirrhosis	15	–	–	2/71 (3 %)
Other	17	–	–	1/71 (1 %)
Total	97	32 (33 %)	26 (29 %)	8/97 (8.2 %)

Immunosuppression

Standard postoperative immunosuppression consisted of cyclosporine A (CsA) and prednisone (P), whereas 14 patients received FK 506 and P. Acute rejection episodes were treated with one to three bolus injections of 1 g methylprednisolone. If rejection persisted, a 14-day course of OKT3 5 mg/day was given. When acute rejection episodes recurred or chronic rejection was suspected or confirmed by histology, patients were converted to FK 506.

Chronic rejection

Chronic rejection as diagnosed if hepatic histology showed evidence of interlobar or septal bile duct loss in more than 50 % of portal tracts. Obliterative vasculopathy involving large- and medium-sized arteries was considered a non-obligatory but supportive feature. Arterial lesions were rarely seen in biopsy specimens. At least 20 portal tracts were reviewed in liver biopsy to exclude sampling error and confirm the diagnosis of chronic rejection. Furthermore, chronic rejection was usually confirmed in explanted livers.

HCV infection

Donor and recipient serum samples were obtained immediately before LTx. Recipient samples were also obtained after transplantation during hospitalisation and at outpatient visits. Serum samples were rapidly frozen and stored at –40 °C until analysis.

Donor and recipient pre-transplant and selected post-transplant samples were tested for anti-HCV by second-generation enzyme-linked immunoassay (ELISA II) (Abbott Laboratories, Chicago, Ill.). All positive samples were confirmed by second-generation recombinant immunoblot assay (RIBA 2; Chiron, Emmeryville, Calif.). In patients with more than one serum sample available, the latest sample, at least, was determined for anti-HCV and serum HCV-RNA. HCV-RNA was tested by polymerase chain reaction [5].

Liver biopsies were routinely obtained in HCV-infected patients between 6 and 15 months after transplantation or when graft dysfunction was present, and were evaluated by a single staff pathologist. If more than one liver biopsy was obtained during this period, the latest one was evaluated. Alanine aminotransferase (ALT) levels and clinical evaluation were performed at regular intervals.

Severe graft reinfection was defined by histological findings indicative of hepatitis infection including portal and parenchymal mononuclear infiltrates of varying degrees, acidophilic necrosis and swollen hepatocytes in patients with graft dysfunction (maintained increase in ALT levels for at least 6 weeks). Other common findings included lymphoid aggregates, bile duct damage and fatty changes.

Results

Table 1 shows pretransplant diagnosis and incidence of severe graft HCV reinfection, chronic graft hepatitis C and chronic rejection.

Thirty-two of 52 patients with pretransplant HCV infection developed severe graft reinfection after LTx; 9 of these 32 were treated with alpha-interferon (INF). Chronic graft hepatitis C was found in 26 grafts at the end of the study. Chronic rejection occurred in 8 of 97 allografts (8.25 %); 5 presented chronic rejection and concomitant chronic graft hepatitis C. In seven of eight grafts, chronic rejection or chronic rejection with HCV infection was confirmed in explanted livers. No patients treated primarily with FK 506 had chronic rejection.

The incidence of chronic rejection in patients with HCV infection before LTx (9.6 %) did not differ when compared with negative HCV patients (6.6 %) (Yates' chi-square test: *P* not significant) However, when the 26 cases that developed graft dysfunction due to chronic hepatitis C after liver transplantation were considered, 5 presented chronic rejection, a significantly higher incidence than the in remaining patients (3 of 71) (Yates' chi-square test: $P < 0.05$). Furthermore, 2 of 9 patients (22 %) treated with INF for HCV recurrence developed chronic hepatitis and concomitant chronic rejection.

Discussion

The incidence of chronic rejection after liver transplantation in our experience was 8.25 %, similar to that of other reports [1]. Our finding of an increased incidence of chronic rejection in patients with HCV reinfection was found only in patients who developed chronic hepatitis C [6]. Five of our patients suffered severe hepatitis C recurrence concomitant with chronic rejection. All these patients developed cholestasic features with duct damage or mixed portal infiltrates and difficulties arose in determining whether chronic rejection or hepatitis was responsible for duct damage [5, 7].

Explanations for the increased incidence of chronic rejection in patients with chronic hepatitis C remain unknown. Viral infections such as cytomegalovirus (CMV) may up-regulate the immune system, and an association

between CMV, hepatitis B virus, and HCV infection and both acute and chronic rejection has been reported [8, 9]. HCV reinfection may play a direct role in the pathogenesis of chronic rejection. Immunosuppression permits higher viral replication and, therefore, higher viraemia levels in the liver recipient. This large amount of cytopathological virus and/or specific viral strains could produce a different and more aggressive chronic hepatitis with duct damage in certain transplant recipients [5, 10]. Owing to the lack of satisfactory therapy to eradicate HCV, lower baseline immunosuppression should be considered in patients with severe graft HCV recurrence [6, 8].

In our experience, there appears to be a relationship between the development of chronic rejection and chronic graft hepatitis C after LTx. INF therapy may favour chronic rejection, whereas FK 506 therapy may prevent the evolution of chronic rejection [11].

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