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Hepatitis C: indication for anti-viral therapy?

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Abstract Hepatitis C infection is a frequent indication for liver transplantation. In general, recurrent graft hepatitis is assumed to be mild, but may be the cause of lethal postoperative complications in a small patient population. Out of 500 transplants in 458 patients, 123 patients were transplanted due to hepatitis C infection (26.7 %) between September 1988 and April 1994. Cumulative 1- to 6-year patient survival was similar for patients transplanted due to hepatitis C (87.0 %) and those transplanted for other indications (86.0 %). In patients with hepatitis C virus (HCV), death, in 50 % of the cases, was related to HCV recurrence and chronic rejection. Four patients (25.0 %) died because of severe infection and multiple organ failure syndrome unrelated to HCV recurrence and chronic rejection. The incidence of retransplantation was similar in HCV (9.8 %) and other patients (8.4 %). In HCV patients, 6 of 12 retransplantations (50.0 %) were performed due to HCV recurrence and chronic rejection. Of 123 HCV patients, 45 experienced histologically proven recurrent graft hepatitis between 2 weeks and 5.5 years after transplantation. The incidence of acute rejection was similar in both groups. The incidence of steroid-resistant rejection was, however, higher in HCV patients (29.3 %) than in those transplanted for other indications (14.5 %; $P \leq 0.05$). Furthermore, there was a significant association between acute rejection and the development of recurrent graft hepatitis. In conclusion, patients with hepatitis C may be transplanted with as good patient and graft survival rates as patients transplanted for other indications. However, the combination of recurrent graft hepatitis and chronic rejection remains the most limiting factor for some of these patients, which strengthens the neccessity for a specific anti-viral therapy.

Key words Liver transplantation · Hepatitis C · Acute and chronic rejection

Introduction

Posthepatic cirrhosis and acute liver failure due to hepatitis C and NANBNC infection is a frequent indication for liver transplantation. Currently, no prophylaxis of hepatitis C virus (HCV) recurrence or anti-viral therapy has been established. HCV reinfection or the persistence of the virus, as determined by polymerase chain reaction techniques, was observed in almost all patients (> 90 %) during the first year after liver transplantation [1, 2, 4, 5, 10, 13]. Virus elimination is possible, but rare. Recurrent graft hepatitis occurred in approximately 50 % of patients. In general, recurrent graft hepatitis is assumed to be mild in nature and spontaneously resolves over time [4]. However, in a small group of patients, severe recurrent graft hepatitis was associated

with severe immunological or other complications. Therefore, 123 patients transplanted for HCV disease were analyzed and compared with patients transplanted for other indications.

Materials and methods

Patients

Between September 1988 and May 1994, 500 orthotopic liver transplantations (LTX) were performed in 458 patients at the University Clinic Rudolf Virchow. Indications for LTX included 94 patients with hepatitis B virus (HBV) and 118 patients with HCV disease, 79 patients with alcoholic cirrhosis, 45 with primary biliary cirrhosis (PBC), 28 with primary sclerosing cholangitis (PSC), 16 patients with cryptogen cirrhosis, 13 patients with autoimmune cirrhosis, 10 patients with Budd Chiari syndrome, 16 patients with primary bile duct carcinoma, hepatocellular carcinoma (HCC) or other tumors, and 39 patients with various other indications. A further 22 HCC were observed in patients primarily transplanted due to HBV and HCV cirrhosis. A total of 42 retransplantations were performed.

Immunosuppresssion and concomitant treatment

In 61 patients, FK506 was given i.v. for the first 3 days and subsequently oral medication was continued [8]. A total of 44 patients received primarily oral FK506 medication (0.03 mg or 0.05 mg/kg body weight twice daily). Cyclosporine A (CsA) therapy was commenced as quadruple therapy including anti-thymocyte globulin (ATG; Fresenius, Germany) for 1 week in 208 patients or including the interleukin-2 receptor antagonist, BT563 (Biotest, Dreireich, Germany) for 12 days in 145 patients and both groups were subsequently continued on triple therapy [9]. Surgical procedures, aprotinin administration, i.v. antibiotic treatment, selective bowel decontamination and various other prophylaxes were performed perioperatively, as previously described [8, 9].

Clinical and laboratory investigations

Patients were evaluated prior to transplantation by medical history, demographic data, physical examination, and laboratory evaluations. Laboratory investigations, including CsA blood levels (non-specific TDX assay) and whole blood FK506 levels, as well as clinically adverse experiences, were evaluated on a daily basis for the first month, and subsequently, after predefined time intervals. HCV RNA (blood and liver) and second generation anti-HCV enzymëlinked immunosorbent assay (ELISA) [4] were performed at predefined time points pre- and postoperatively, and whenever recurrent graft hepatitis was suspected.

Management of rejection and recurrent graft hepatitis

Diagnosis of acute rejection was based on clinical (fever, change of color, and amount of bile production) and laboratory (aspartate transaminase, alanine transaminase, bilirubin, γGT, and alkaline phosphatase) findings, and was confirmed by histological evaluation of graft biopsies, as previously reported [8]. Patients received methylprednisolone for treatment of acute rejection at a dosage of 500 mg/day for 3 days and either OKT3 monoclonal antibody (Cilag, Sulzbach, Germany) or FK506 (0.1 mg/kg body weight twice daily) or the combination of both immunosuppressive agents for steroid-resistant or severe recurrent rejection [8]. No attempt was made to treat patients with steroid recycles. Criteria for recurrent graft hepatitis were used as previously described [4]. Liver biopsies were routinely performed at postoperative day (POD) 7, and whenever rejection or recurrent hepatitis was suspected.

Table 1 Cause of death in patients infected with hepatitis C virus *(HCV)*. (*CR* Chronic rejection, *MOFS* multiple organ failure syndrome)

Cause of death	*n*	Percentage
HCV recurrence, CR	8/16	50.0
Severe infection, MOFS	4/16	25.0
Neurological complications	2/16	12.5
Others	2/16	12.5

Statistical analysis

Kaplan Meier estimates, Wilcoxon, chi-square and Kruskal-Wallis tests were used as indicated. Results were expressed as means ± standard error of the mean.

Results

Survival

The cumulative 6-year graft and patient survival was similar in patients transplanted owing to hepatitis C infection and other indications with 78.1 % and 77.2 % for graft survival and 87.0 % and 86.0 % for patients, respectively. Of 123 HCV patients, 16 died. In 50 % of these patients, death was related to chronic rejection or recurrent HCV cirrhosis; predominantly a combination of both complications was observed (Table 1). This was followed by severe infections with multiple organ failure syndrome in 25 % of patients. Patients dying because of HCV recurrence and chronic rejection mostly acquired severe atypical or fungal infections, such as *Pneumocystis carinii* pneumonia and *Aspergillus* sepsis, which prohibited retransplantation in this group of patients.

The incidence of retransplantation was similar in patients transplanted because of hepatitis C disease (9.8 %) or other indications (8.4 %). The main cause of retransplantations in HCV patients was recurrent graft hepatitis and chronic rejection followed by refractory acute rejection and initial non-function (INF). The latter two diagnoses occurred significantly more often in HCV than in other patients (Table 2). INF was observed in 1.3 % and refractory acute rejection in < 0.5 % of all liver transplanted patients. Of the 12 retransplanted patients, 5 (41.7 %) subsequently died, including 3 of 6 patients retransplanted for recurrent graft hepatitis and chronic rejection.

Table 2 Cause of retransplantation in patients infected with hepatitis C virus *(HCV)*. *(CR* Chronic rejection, *INF* initial non-function)

Cause of retransplantation	*n*	Percentage
HCV recurrence, CR	6/12	50.0
Refractory acute rejection	2/12	16.7*
INF	2/12	16.7*
Others	2/12	16.7

* $P \leq 0.05$ versus patients transplanted for other indications

Table 3 Incidence of acute rejection in patients infected with hepatitis C virus *(HCV patients)*

	HCV patients	Other indications for orthotopic liver transplantation
Acute rejection	58/123 (47.5 %)	153/335 (45.7 %)
Steroid-resistant rejection	36/123 (29.3 %)*	34/335 (10.1 %)
Recurrent graft hepatitis	45/123 (36.6 %)	–

* $P \leq 0.05$ versus patients transplanted for other indications

Hepatitis C reinfection and rejection

Histologically proven recurrent graft hepatitis was observed in 45 of 123 patients (36.6 %) between 2 weeks and 5.5 years after transplantation. The majority of reinfections occurred between 4 and 12 months after transplantation. One or more rejection episodes were observed in 47.5 % of HCV patients and 45.8 % in patients with other indications. However, the incidence of steroid-resistant rejection requiring FK506 rescue therapy or OKT3 was significantly higher in HCV patients than in patients transplanted for other indications (Table 3).

HCV recurrence was highly associated with acute allograft rejection and anti-rejection therapy. Of 45 patients, 39 (86.7 %) experienced one or more acute rejection episodes prior to the onset of recurrent graft hepatitis. The time interval between acute rejection and onset of recurrent graft hepatitis varied considerably between 1 week to 12 months. A further five patients developed acute rejection from 1 week to 6 months after the onset of recurrent graft hepatitis, while one patient developed chronic rejection requiring retransplantation. Only 1 of these 45 patients developed no immunological complications at all.

Discussion

Persistence or early recurrence of hepatitis C viremia has been commonly observed after liver transplantation (> 90 % of patients) [1, 2, 4, 5, 10, 13]. Recurrent graft hepatitis has been reported to occur in 14–45 % of HCV patients [11, 12]. However, the clinical course varies considerably from being clinically asymptomatic with mild laboratory abnormalities to acute liver failure requiring retransplantation. More than one-third of our HCV patients developed recurrent graft hepatitis to different degrees of severity. More patients may have experienced hepatitis C recurrence, which has not been confirmed as recurrent graft hepatitis by histological studies. Reevaluation of all HCV patients with quantitative HCV RNA determination in serum and blood may more sensitively detect HCV recurrence and increase the number of confirmed recurrent graft hepatitis cases. However, to date, histology in conjunction with abnormalities in liver function tests seems to be most reliable.

An association with acute allograft rejection and augmented immunosuppression has been previously reported [12]. The present data confirm these observations. There was only one patient experiencing recurrent graft hepatitis who never developed acute or chronic rejection. The majority of patients experienced first acute rejection with increased immunosuppressive therapy, which was followed by recurrent graft hepatitis within 1 week to 12 months. In some patients, both events occurred almost simultaneously, while only 5 patients first developed recurrent graft hepatitis and only subsequently acute or chronic rejection.

Although patient and graft survival were similar in HCV patients than in those transplanted for other indications, the predominant life-threatening factor for HCV patients is recurrent graft hepatitis in association with acute and chronic rejection. Others have also observed that the outcome after retransplantation is poor in this small patient population [11, 12]. Since the high incidence of rejection in patients with recurrent graft hepatitis prohibits reduction of immunosuppression, an answer to the current dilemma may only be a prevention of HCV recurrence or treatment with an anti-viral agent.

Of note, furthermore, is the fact that a relatively high number of HCV patients died from neurological complications, which conforms to previous observations [6, 7]. There was also a markedly increased incidence of refractory acute rejection and INF in this group of patients compared with patients transplanted for other indications [3].

In conclusion, we found that hepatitis C is a good indication for liver transplantation with respect to patient and graft survival. However, there was a high association between recurrent graft hepatitis and acute allograft rejection. Furthermore, 50 % of these patients died from problems related to recurrent graft hepatitis and chronic rejection. Therefore, the most optimal solution will be the prevention of viral replication and an anti-viral strategy for patients transplanted because of HCV disease.

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