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K.-P. Platz
A. R. Mueller
T. Berg
R. Neuhaus
U. Hopf
H. Lobeck
P. Neuhaus

Searching for the optimal management of hepatitis C patients after liver transplantation

K.-P. Platz (✉) · A. R. Mueller · R. Neuhaus · P. Neuhaus
Department of Surgery, Virchow Clinic, Humboldt University Berlin, Augustenburger Platz 1, D-13353 Berlin, Germany
Tel. 49-30-450-52001; Fax 49-30-450-52900

T. Berg · U. Hopf
Department of Hepatology, Virchow Clinic, Humboldt University Berlin, Germany

H. Lobeck
Department of Pathology, Virchow Clinic, Humboldt University Berlin, Germany

Abstract The optimal immunosuppressive regimen in patients transplanted for hepatitis C (HCV) is still under discussion. High immunosuppression may promote viral replication and recurrent graft hepatitis. But acute and chronic rejection frequently seen in conjunction with HCV recurrence may require some rescue therapy. One hundred and thirty-seven patients transplanted for HCV cirrhosis, who were HCV-RNA positive prior to transplantation, were analyzed. Seventy-nine patients received CSA-based immunosuppression and 58 patients FK506-based immunosuppression. One-month patient survival was 100 % in both groups. Three month and 1-year survival rates and the cumulative 1–5-year patient survival was similar in CsA-treated [67/79 (84.8 %)] and FK506-treated patients [50/58 (86.2 %)]. Retransplantations for HCV recurrence were performed in 5.1 % of CsA-treated patients and 6.9 % of FK506-treated patients; it was successful in 50 % and 75 % of patients, respectively. Conversion from CsA to FK506 and vice versa was high with 25 out of 79 patients (31.6 %) converting in the CsA group and 8 out of 58 patients (13.8 %) converting in the FK506 group. Conversion to FK506 was performed due to acute and chronic rejection and to CsA because of toxicity and HCV recurrence. In both groups, 25 % of converted patients died. Five patients of the CsA group and 9 of the FK506 group received OKT3; more than one-third of each group died. Five patients in the CsA group and 6 in the FK506 group received mycophenolate mofetil (MMF) for HCV recurrence or acute and chronic rejection in conjunction with HCV recurrence. All patients of this critical group are alive with good graft function. In conclusion, survival rates of HCV patients were similar to those seen for other indications. Conversion from CsA to FK506 and vice versa was high and reflects a critical group concerning patient survival. OKT3 treatment should be avoided. A promising therapeutic option for critical patients experiencing acute or chronic rejection in conjunction with HCV recurrence may be treatment with MMF.

Key words Liver transplantation · Hepatitis C

Introduction

Posthepatic cirrhosis due to hepatitis C (HCV) is a frequent indication for liver transplantation. HCV reinfection and persistence of HCV as determined by PCR techniques was observed in all patients during within the 1st week following liver transplantation [1–7]. We have previously reported that recurrent graft hepatitis occurred in more than 50 % of HCV patients [8, 9] and it seems reasonable that the incidence and severity of

recurrent graft hepatitis may be related to the extent of viral replication [1]. High immunosuppression may promote viral replication and recurrent graft hepatitis. But acute and chronic rejection, frequently seen in conjunction with HCV recurrence, may require some rescue therapy [10–12]. In order to estimate the most optimal immunosuppressive management, 137 patients transplanted for HCV cirrhosis, who were HCV-RNA positive prior to transplantation, were analyzed.

Materials and Methods

Immunosuppression and concomitant treatment

Out of 900 liver transplantations, 137 were performed for HCV cirrhosis. All patients were HCV-RNA positive prior to transplantation. Seventy-nine patients received primarily CsA-based immunosuppression in conjunction with azathioprine and prednisolone, and ATG, ALG, or the IL-2 receptor antagonist BT563 for induction therapy [13]. Fifty-eight patients received FK506-based immunosuppression primarily in conjunction with prednisolone; some patients received azathioprine and/or ALG in addition to the aforementioned immunosuppressants. Surgical procedure, aprotinin administration, i. v. antibiotic treatment, selective bowel decontamination, and various other prophylaxes were performed perioperatively as previously described [13, 14].

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 (AST, ALT, bilirubin, γGT, and alkaline phosphatase) findings and was confirmed by histological evaluation of graft biopsies as previously reported [14–16]. Patients received methylprednisolone for the treatment of acute rejection at a dose 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 a combination of both immunosuppressive agents for steroid-resistant or severe recurrent rejection [14]. No attempt was made to treat patients with steroid recycles. The criteria for recurrent graft hepatitis were used as previously described [2]. Liver biopsies were routinely performed at postoperative day 7 and whenever rejection or recurrent hepatitis was suspected. HCV-RNA (blood and liver) and second generation anti-HCV ELISA [1, 2] were performed at predefined time points pre- and postoperatively and whenever recurrent graft hepatitis was suspected.

Statistical analysis

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

Results

Survival

One-month patient survival was 100% in both groups. Three-month and 1-year survival rates and the cumulative 1–5-year patient survival were similar in CsA-treated [67/79 (84.8%)] and FK506-treated patients [50, 58 (86.2%)]. The most common cause of death was HCV recurrence in conjunction with chronic rejection followed by hepatocellular carcinoma (HCC) recurrence or development of de novo malignancies.

Table 1 Incidence and outcome of retransplantation, conversion, and OKT3 treatment in hepatitis C patients

Immunosuppression	Number of patients	Survival
Retransplantation[a]		
CsA	4/79 (5.1%)	2/4 (50%)
FK506	4/58 (6.9%)	3/4 (75%)
Conversion		
CsA → FK506[b]	25/79 (31.6%)	19/25 (76%)
FK506 → CsA[c]	8/58 (13.8%)	6/8 (75%)
OKT3 treatment		
CsA	5/79 (6.3%)	3/5 (60%)
FK506	9/58 (15.5%)	6/9 (66.6%)

[a] Retransplantation due to recurrent graft hepatitis with or without signs of chronic rejection
[b] Conversion due to acute or chronic rejection
[c] Conversion due to toxicity

Retransplantation, conversion, and OKT3 treatment

Retransplantations due to HCV recurrence with or without concomitant signs of chronic rejection were performed in 4 out of 79 (5.1%) CsA-treated patients and 4 out of 58 (6.9%) FK506-treated patients (Table 1). Retransplantation was successful in 50% of CsA-treated and 75% of FK506-treated patients. Conversion from CsA to FK506 and vice versa was high with 25 of the 79 patients (31.6%) in the CsA group and 8 of the 58 patients (13.8%) in the FK506 group converting. Conversion to FK506 was performed due to acute and chronic rejection and to CsA because of toxicity and HCV recurrence. In both groups, 25% of converted patients subsequently died. Five patients of the CsA group and 9 of the FK506 group received OKT3; 33.3–40% of the patients of either group died (Table 1).

Mycophenolate mofetil (MMF) therapy

Six patients in the CsA group (7.6%) and 5 in the FK506 group (8.6%) received MMF vor HCV recurrence or acute and chronic rejection in conjunction with HCV recurrence (Table 2). Three patients of the FK506 group had been previously converted to CsA and 3 patients had required retransplantation. All patients of this critical group are currently alive with good graft function.

Table 2 Incidence and indication of mycophenolate mofetil (MMF) therapy in hepatitis C (HCV) patients

MMF therapy	Number of patients
Incidence	
CsA	6/79 (7.6%)
FK506	5/58 (8.6%)[a]
Primary indication	
HCV recurrence	6/11 (54.5%)
Acute rejection after HCV recurrence	3/11 (27.3%)
Chronic rejection after HCV recurrence	2/11 (18.2%)

[a] Three of the 5 patients have been previously converted to CsA

Discussion

Early recurrence of hepatitis C viremia has been commonly observed after liver transplantation [1–7]. More than one-third of HCV patients will develop recurrent graft hepatitis at different degrees of severity. Furthermore, an association between recurrent graft hepatitis with acute allograft rejection and augmented immunosuppression has been previously reported [8–12]. 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.

Although patient and graft survival rates were similar in patients with HCV and patients transplanted for other indications, the predominant life-threatening factor of HCV patients was the recurrent graft hepatitis in association with acute and chronic rejection. This was followed by death related to HCC recurrence or development of de novo malignancies as well as neurological complications [11, 12]. Similar to observations by others, the outcome after retransplantation was fairly poor in this small patient population, especially in the CsA group which comprised more patients of the earlier experience [10, 17]. Newer therapeutic approaches included antiviral therapy with ribaverin or the combination of ribaverin with interferon alpha and MMF therapy. However, because of the very short observation periods, no final conclusions can be drawn. But so far, MMF therapy in patients with recurrent graft hepatitis with or without signs of acute or chronic rejection is highly promising. Most patients improved with respect to graft function and general condition and all are alive and well. The positive effect of MMF therapy in patients with recurrent graft hepatitis and rejection may result from the combination of both the immunosuppressive and antiviral properties of MMF.

In conclusion, survival rates of HCV patients were similar to those seen for other indications. Conversion from CsA to FK506 and vice versa was high and reflects a critical group concerning patient survival. OKT3 treatment should be avoided. Retransplantations can be performed with fairly good success. A new therapeutic option for critical patients experiencing acute or chronic rejection in conjunction with HCV recurrence may be the treatment with MMF. Initial results are promising but long-term experience is required.

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