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Liver transplantation for alcoholic cirrhosis

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Abstract Because of the donor shortage, there are concerns for liver transplantation in patients with alcoholic cirrhosis. We therefore analyzed patients transplanted for alcoholic cirrhosis at our center with respect to patient and graft survival, recurrence of disease, and post-operative complications. Out of 1000 liver transplantations performed in 911 patients, 167 patients were transplanted for alcoholic cirrhosis; 91 patients received CsA- and 76 patients FK506-based immunosuppression. Recurrence was diagnosed by patient's or relative's declaration, blood alcohol determination, and delirium. Diagnosis and treatment of acute and chronic rejection was performed as previously described. One- (96.8% versus 91.3%) and 9-year patient survival (83.3% versus 80%) compared well with other indications. Five of 15 patients died due to disease recurrence. Recurrence of disease was significantly related to the duration of alcohol abstinence prior to transplantation. In patients who were abstinent for less than 6 months (17.1%), recurrence rate was 65%, including four of the five patients who died of recurrence. Recurrence rate decreased to 11.8%, when abstinence time was 6–12 months and to 5.5%, when the abstinence times was > 2 years. Next to duration of abstinence, alcohol relapse was sig-

nificantly related to sex, social environment, and psychological stability. The incidence of acute rejection compared well with other indications (38.1%); CsA: 40.1% versus 33.3% in FK506 patients. In all, 18.2% of CsA patients experienced steroid-resistant rejection compared with 2.6% of FK506 patients. Seven patients (7.6%) in the CsA group and one patient (1.3%) in the FK506 group developed chronic rejection. A total of 57.1% developed infections; 5.7% were life-threatening. CMV infections were observed in 14.3% (versus 25% for other indications). New onset of insulin-dependent diabetes was observed in 8.6% and hypertension in 32.4%. In conclusion, alcoholic cirrhosis is a good indication for liver transplantation with respect to graft and patient survival and development of postoperative complications. FK506 therapy was favourable to CsA treatment. Patient selection is a major issue and established criteria should be strictly adhered to. Patients with alcohol abstinence times shorter than 6 months should be excluded, since recurrence and death due to recurrence was markedly increased in this group of patients.

Key words Liver transplantation · Alcoholic cirrhosis · Alcohol relapse · Outcome

Introduction

Alcohol dependency is common in European society, affecting about 10% of the adult population. The incidence of alcoholic disease, including liver cirrhosis, pancreatitis, and cardiomyopathy, is increasing. This may lead to an ongoing discussion on social and economic consequences for the treatment of alcoholic disease [3, 5, 8]. Furthermore, the number of donor organ's is still limited and this problem will not be solved in the very near future. Therefore, the question arises whether transplantation for alcoholic cirrhosis is justified.

In order to answer this question, 167 patients transplanted for alcoholic cirrhosis were analyzed with respect to patient and graft survival, incidence of acute and chronic rejection, incidence of infectious and other complications, and incidence of recurrence of alcoholic disease.

Materials and methods

Patients

Out of 1000 liver transplantation performed in 911 patients, 167 patients were transplanted for alcoholic cirrhosis. The age ranged from 26 to 63 years with a mean of 47.3 ± 8.1 years. The majority of patients were male ($n = 119$; 71.3%); 48 patients were female (28.7%). Surgical procedure, antibiotic and various other prophylaxes were performed perioperatively as previously reported [9].

Immunosuppression

Immunosuppression was either cyclosporine A (CsA; $n = 91$) or FK506-based ($n = 76$). CsA-based immunosuppression was commenced as quadruple therapy in combination with azathioprine or mycophenolate mofetil (MMF), prednisolone, and ATG or ALG, or the IL-2 receptor antagonist BT563 (Biotest, Dreieich, Germany) for the first 7 or 12 postoperative days, respectively, and subsequently continued as triple therapy. FK506-based immunosuppression was predominantly managed by dual therapy in combination with prednisolone. Some patients received triple or quadruple therapy, including MMF or ATG [9].

Management of rejection

Diagnosis of acute rejection was based on clinical (fever, change of color and amount of bile production) and laboratory (AST, ALT, bilirubin, γ GT and alkaline phosphatase) findings and was confirmed by histological evaluation of graft biopsies. Liver biopsies were performed routinely on POD 7 and whenever rejection was suspected. Histological classification of acute rejection was used as previously reported [2, 13]. Patients received methylprednisolone for treatment of acute rejection at a dosage of 500 mg/day for 3 days and FK506 or the combination of FK506 and OKT3 monoclonal antibody (Cilag GmbH, Sulzbach, Germany) simultaneously for steroid-resistant or severe recurrent rejection. Acute rejection was defined as steroid-resistant by a missing response or second increase in liver enzymes after one course of methylprednisolone in combination with histological signs of ongoing rejection

Table 1 Cause of death. Other indications included multiple sclerosis and accident after transplantation for alcoholic cirrhosis

Cause of death	Alcoholic cirrhosis (%)	Other indications
Recurrence	5/15 (33.3)	33.1%
Infection	4/15 (26.7)	22.0%
Malignancies	2/15 (13.3)	10.2%
Cardiologic	1/15 (6.7)	8.5%
Others	3/15 (20.0)	26.2%

in repeated liver biopsies prior to initiation of rescue therapy. Early chronic rejection was classified according to established criteria and treated with high-dose FK506-rescue therapy [8, 13].

Alcohol recurrence

Recurrence of alcoholic disease was diagnosed by the patient's or relative's declaration, blood alcohol determination, delirium, and rehospitalization due to alcohol-related problems. Since recurrence of alcoholic disease occurred mainly within the first 2 years after transplantation, 117 patients with an observation period of more than 2 years after transplantation were analyzed for incidence and risk for alcohol recurrence.

Statistical analysis

Kaplan-Meier estimates, Wilcoxon, Chi-Square and Kruskal-Wallis tests and analysis of variance (one-way ANOVA and multivariate analysis) were used as indicated.

Results

Survival

One- (96.8% versus 91.3%), 5-year (85.9% versus 84.7%), and 9-year patient survival (83.3% versus 80%) compared well with other indications. Five of 15 patients died due to alcohol recurrence (33.3%), four patients (26.7%) died due to severe infections, two patients (13.3%) for malignancies, one patient (6.7%) and three patients for other reasons, including multiple sclerosis and accident. This is in good accordance with the cause of death in patients transplanted for other indications (Table 1). The incidence of retransplantation was slightly below the average with 8.1% ($n = 14$) versus 8.8%. The causes for retransplantation were chronic rejection in seven patients (50%), hepatic artery thrombosis in four, initial non-function in two, and refractory acute rejection in one patient.

Rejection

The incidence of acute rejection was below average, with 40.1 for CsA- and 33.3% for FK506-treated pa-

Table 2 Recurrence of alcoholic disease

Time	Incidence of recurrence	Severe recurrence
< 1/2 year	66.4%	84.7% ^a
1/2-1 year	14.3%	60.0%
1-2 years	13.9%	40.0%
> 2 years	5.6%	100% ^b

^a Four patients with severe alcohol recurrence died

^b One patient with severe alcohol recurrence died

tients. Acute steroid-resistant rejection was observed significantly less frequently in the FK506 treatment group (2.8%) versus 18.2% following CsA treatment. Chronic rejection was observed in 7.6% following CsA and in 1.3% after FK506 treatment.

Complications

Serious infections occurred in similar frequency as observed in patients transplanted for other indications. The incidence of cytomegalovirus infection was lower (14.3%) than seen in patients transplanted for other indications (25.0%). No increase in cardiopulmonary complications was observed. The incidence of new onset of insulin-dependent diabetes and hypertension was also similar to other indications (8.6% and 32.4%).

Alcohol recurrence

Recurrence of alcoholic disease was observed in 25.6% of patients transplanted for alcoholic cirrhosis. Recurrence was significantly related to duration of abstinence prior to transplantation (Table 2). Patients with duration of abstinence shorter than 6 months (16.2%), showed a significantly increased alcohol recurrence rate (68.4%) and four of the five deaths related to alcohol recurrence belonged to this group of patients. Severity of drinking prior to transplantation, education, age and pre- and postoperative patient compliance failed to correlate with recurrence of alcohol disease. Sex, social environment, and personal stability assessed by psychologists correlated significantly with recurrence of alcoholic dis-

ease ($P \leq 0.05$; Table 3). Female recipients were at higher risk for alcohol relapse than male patients. A good social environment was observed in 77.8% of patients transplanted for alcoholic cirrhosis, while a psychological stable personality was observed in 57.3% of patients.

Discussion

Patient and graft survival following transplantation for alcoholic cirrhosis compared well with other indications [1, 7, 12]. The incidence of acute and chronic rejection is low, especially after treatment with FK506. Similar observations were made for infectious and other complications after liver transplantation. Patients with alcoholic cirrhosis could easily be cured if there was no risk of recurrence of disease. The incidence of recurrence of alcoholic disease is within the average, which means that the risk for the development of recurrence is similar to hepatitis and lower than seen in tumor patients.

Recurrence of alcoholic disease was significantly related to duration of alcohol abstinence prior to transplantation [4]. Because of high risk of alcohol recurrence and death related to recurrence, patients with a duration of abstinence shorter than 6 months should not be transplanted, in accordance to established criteria [6, 10], although this has been done in a small number of patients (16.2%). A good social environment and a psychological stable personality decreased the risk for alcohol recurrence. Interestingly, no correlation was found for the judgement of good patient compliance pre- and postoperatively. Although younger patients were thought to have worse compliance and be at higher risk for alcohol recurrence, this was not documented by our results [11]. Patients with a higher educational status and profession failed to have a decreased risk for recurrence, in contrast to previous reports [15].

In conclusion, alcoholic cirrhosis is a good indication for liver transplantation with respect to graft and patient survival and development of postoperative complications. FK506 therapy was favourable to CsA treatment. Patient selection is a major issue and should strictly adhere to established criteria, including an abstinence time of more than 6 months, a good social environment, and a psychological stable personality.

Table 3 Risk factors for recurrence of alcoholic disease

Factors	Incidence of recurrence of alcoholic disease	
Severity of drinking		No influence
Age		No influence
Education and profession		No influence
Pre- and postoperative compliance		No influence
Sex	Male: 18.4%	Female: 36.7%*
Social environment	Good: 19.8%	Worse: 36.4%*
Psychological personality	Stable: 13.4%	Not stable: 37.8%*

* $P \leq 0.05$

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