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Clinical significance of recurrent primary biliary cirrhosis after liver transplantation

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Abstract Primary biliary cirrhosis (PBC) represents a classic indication for orthotopic liver transplantation (OLT); as an autoimmune disease, however, the existence and incidence of recurrent PBC is a matter of significant controversy. Between September 1988 and September 1994 a total of 544 OLTs was performed at our institution. Forty-nine patients (40 female) with a median age of 50.5 years and previous surgery in 36.4 %, received a liver graft for PBC. The mean serum bilirubin level was 8.9 mg/dl (range 0.7–29.7). Immunosuppression was commenced as a cyclosporine A-based quadruple therapy or with FK 506 and prednisolone. Protocol liver biopsies were taken at defined intervals posttransplant. Two patients died due to *Legionella* pneumonia and hypoxic brain damage 2 and 8 weeks after OLT, resulting in an actuarial 5-year survival rate of 95 % with 47/49 patients being alive compared to 83.5 % of all other liver recipients. Evidence of recurrence of PBC, as defined by elevated cholestatic parameters and histological features of PBC, was found in four patients, another five patients showed only histological signs. Recurrence of PBC, which might compromise the long-term outcome after OLT, was suspected in 4/47 patients (8.5 %). This evidence of recurrent PBC is in conflict with findings of other groups that did not report recurrent PBC. OLT is still the optimal therapy for advanced PBC, with an excellent prognosis.

Key words Liver transplantation · Primary biliary cirrhosis

Introduction

Among end-stage liver diseases, primary biliary cirrhosis (PBC) represents one of the most common indications for orthotopic liver transplantation (OLT). PBC, which is characterized by a chronic, slowly progressive inflammatory destruction of small intrahepatic bile ducts, is considered as a classic indication for OLT, with 5-year survival rates of over 70 % [15]. The course of the disease is usually prolonged over an asymptomatic and symptomatic period leading to a sudden terminal deterioration of liver function that is usually not associated with significant impairment of other vital organs. Due to the inflammatory, autoimmune character of PBC, medical treatment consists of immunosuppressive and inflammatory drugs with, however, only marginal success [3, 10]. In contrast, ursodeoxycholic acid has been shown to decrease the severity of cholestasis [12, 14, 18, 19].

The indication for OLT in PBC is given in the case of rising serum bilirubin levels (> 8–10 mg/dl), recurrent esophageal hemorrhage, irretractable ascites, progressive hepatic osteodystrophy, pruritus, muscle dystrophy, vitamin depletion (A, D, E, K), hepatic encephalopathy or recurrent spontaneous bacterial peritonitis. Beyond these symptoms, PBC bears a significant risk of developing into hepatocellular carcinoma [16]. By follow-up of patients receiving conservative treatment, parame-

Table 1 Indications for orthotopic liver transplantation September 1988–September 1994, University Hospital Rudolf Virchow (*PBC* primary biliary cirrhosis, *PSC* primary sclerosing cholangitis)

Preoperative condition	Number of patients	Total
Postnecrotic cirrhosis		252
HbsAg positive	72	
HbsAg + delta positive	11	
NANB, Hepatitis C	89	
Alcoholic cirrhosis	80	
Fulminant liver failure		34
PBC		49
PSC		29
Others		180
Total		544

ters have been identified on which prognostic models are based that predict quite accurately the individual course of PBC [4, 5, 8, 20]. Taken the calculated life expectancy of an individual patient into account, choosing the appropriate time for OLT has become easier and safer. A common feature of the different prognostic models is the high significance of serum bilirubin as the most important single prognostic parameter.

While there is no doubt that advanced PBC is an excellent indication for OLT [2], considerable scientific dispute has gathered on the existence and recurrence of PBC in liver recipients. In this retrospective study we analyzed the peri- and postoperative course of patients with PBC after liver transplantation and possible recurrence of the underlying disease.

Patients and methods

Patients

Between September 1988 and September 1994 a total of 544 OLT was performed at the Department of Surgery, University Hospital Rudolf Virchow, Free University of Berlin. Forty-nine patients underwent primary OLT for PBC. The other indications for OLT are listed in Table 1.

Liver transplantation

All OLT were performed using standard surgical techniques. All grafts were preserved using University of Wisconsin solution. A veno-venous bypass was used during the anhepatic phase and all vascular anastomoses were completed before reperfusion of the graft. The bile duct anastomosis was accomplished as side-to-side choledocho-choledochostomy using a T-tube for 42 days.

Immunosuppressive therapy

Immunosuppression was given according to our conventional protocol with a cyclosporine A (CsA)-based quadruple induction therapy for the first 7 days and continuation as triple therapy thereafter, or with FK 506 and prednisolone as part of the European multicenter trial of FK 506. The quadruple protocol consisted of CsA, azathioprine, prednisolone, and of rabbit antithymocyte globulin (ATG).

Rejection therapy

Rejection was diagnosed by histopathological evidence, deteriorating liver function, and changes in the amount and composition of bile. Acute rejection was treated by i.v. bolus application of 500 mg methylprednisolone for 3 days and OKT3 mAb for steroid-resistant or severe recurrent rejection. Non-responders to rejection therapy were switched to FK 506 rescue therapy. If OKT3 and FK 506 rescue therapy failed, patients were candidates for retransplantation.

General medication

Before administration of i.v. CsA and ATG, patients received dimethindene (4 mg) and ranitidine (50 mg). Anti-infectious prophylaxis consisted of systemic antibiotic therapy for 2 days (4×1 g cefotaxim, 3×40–80 mg gernebcin, 2×500 mg metronidazol) and selective bowel decontamination (100 mg polymyxin B, 80 mg gernebcin, and 0.5 MU Nystatin 4 times/day) starting at least 5 days prior to transplantation, and given for at least 3 weeks posttransplant. The identical antibiotic combination was used as an oral paste 4 times/day. Microbial screening was performed routinely twice a week by testing body fluids (including bile) and orifices. Specific antibiotics were given according to sensitivity tests (predominantly vancomycin and imipenem due to positive selection of enterococci and gram-positive bacteria after selective bowel decontamination). Antiviral prophylaxis consisted of acyclovir against herpes for the first 6 postoperative weeks. All patients received 10 g of Ig7S and anti- (CMV) hyperimmunoglobulin on postoperative days (PODs) 1 and 14, and daily medication of 500 mg ursodeoxycholic acid, vitamins, and minerals.

Histology

The histological criteria of recurrent PBC are delineated in Table 2.

Results

Patient characteristics

Patients with PBC had a median age of 50.5 years, females being predominant (77.5 %, 40/49) and previous operations, mainly cholecystectomy, had been performed in 36.4 %. The median serum bilirubin level was 8.9 mg/dl. All patients received AB0-compatible grafts. HLA antigen mismatches between donor and recipient were not analyzed.

Table 2 Histological criteria for recurrence of PBC; differential diagnosis of bile duct alterations

Criteria	PBC grade I/II	Chronic rejection	Chronic cholangitis
Number of bile ducts	⇒/⇑	⇓	⇑
Basal membranes	Destroyed	Intact	Intact
Epithelium	Altered	Altered	Altered
Lumen	Narrow	Narrow	Large
Cholestasis	Mild	Indifferent	Elevated

Survival

Kaplan-Meier estimates for 3-, 6-, 12-month and 1 to 5-year patient survival in the PBC group were 95.83 % for all intervals since two patients died 2 and 8 weeks posttransplant due to *Legionella* pneumonia and hypoxic brain damage after a prolonged course of intensive care with various complications. These two patients were excluded from this analysis. No other patient with PBC died during this 5-year period. One patient had to be retransplanted on POD 3 for initial non-function of the graft, resulting in a 5-year graft survival of 94 % (47/50) in the PBC group.

The 5-year survival rate of all other patients transplanted between September 1988 and September 1994 is 83.5 %.

Recurrent PBC

In 4/47 patients there were histological signs of recurrent PBC (8.5 %) that correlated with elevated aP and serum bilirubin (4–10 mg/dl). In five patients there were histological signs of recurrent PBC with, however, apparent normal liver function (10.6 %). PBC-specific epitheloid granulomas, however, were not found in both groups. A common feature in these nine patients was the finding of non-suppurative destructive cholangitis (19.1 %), which is typical for PBC stage II but is also seen in ischemic-type biliary lesions or in the early stage of chronic rejection. In eight patients, elevated cholestatic parameters were not accompanied by histological findings indicative of recurrent PBC. AMA titers have not been analyzed in these patients yet. One patient has developed cirrhosis, obviously due to recurrent PBC, but has not been retransplanted yet.

Discussion

Concerning the treatment of end-stage PBC by liver transplantation, three points are of great importance: prognostic models for conservative therapy of the disease to determine the individually optimal time for transplantation; disease-specific aspects and their relevance for liver transplantation; and the prognosis after liver transplantation, with special emphasis on the recurrence of PBC.

Prognostic models

Prognostic models to predict the survival of conservatively treated, non-transplanted patients with PBC have been developed by long-term follow-up and identification of important parameters. Christensen et al. [5] and Dickson et al. (Mayo model) [8] described models which have bilirubin, age, and albumin as parameters in common. Markus et al. [15] compared the outcome of liver recipients with PBC to a group of patients with conservative treatment. By using the Mayo model they found from 3 months posttransplant onwards a higher survival probability in the transplant group and concluded that OLT is an efficacious treatment for advanced PBC. Bonsel et al. [4] compared the actuarial survival of 30 patients with PBC in Child-Pugh stages B and C after OLT to the calculated survival rate if these patients had been treated conservatively. The Christensen model, the Mayo model, and his own model (AZG, Akademisch Ziekenhuis Groningen) were used. During a follow-up period of 7 years, a growing advantage of OLT versus medical therapy emerged. The three models revealed remarkably consistent results. Since the models are based on data from just one time during the course of the disease, criticism was raised concerning the precision of prediction of survival. Christensen et al. [6] presented an improved model by incorporating follow-up data that changed their former model from a time-fixed to a time-dependent one, with a more accurate predictive capability.

The common feature of all statistical models is the significance of a raised serum bilirubin level. However, if patients receive ursodeoxycholic acid, bilirubin loses, to a certain extent, its predictive value and is replaced by the determination of hyaluronic acid and type III procollagen amino-terminal peptide [19]. Accordingly, prognostic models for the need for OLT should be adapted if patients receive ursodeoxycholic acid. A recent trial showed that long-term therapy with ursodeoxycholic acid slows the progression of PBC and reduces the need for OLT [19].

Disease-specific aspects

Disease-specific aspects of PBC that reduce the quality of life drastically are osteoporosis, with fracturing, and severe pruritus due to cholestasis. While the jaundice disappears soon after OLT if no complications arise, the duration of osteopenia after OLT and its reversibility has not been well investigated. A histomorphometric

study of premenopausal women with PBC showed that bone formation at the remodeling site is reduced and that the overall level of bone remodeling and turnover is influenced by the degree of hepatic dysfunction [13]. The degree of hepatic osteodystrophy in female PBC patients and its reversibility by OLT was analyzed by measuring bone density pre- and posttransplant [9]. The density of spine bodies was reduced by 7 % compared to controls. Three months after OLT there was a further decline and a significant incidence of atraumatic fractures. One year after OLT the preoperative baseline was reached and after 2 years the initial level was surpassed by 5 %. The further decline in the early period after OLT is certainly caused by high doses of corticosteroids, which subsequently tapered off, and coincides with the consolidation of hepatic metabolism in the medium term after OLT.

Prognosis after liver transplantation

The excellent outcome of OLT for PBC in our study with a 5-year survival of 95.6 % is in accord with similar reports in the literature [15]. To assess the long-term effect of OLT for PBC, detection of recurrence of the underlying disease is of extreme importance. There is still controversy whether PBC which recurs after OLT can be attributed in part to non-standardized criteria for the diagnosis of recurrence. In OLT for PBC it is essential to differentiate between chronic allograft rejection and recurrence of PBC. PBC, chronic allograft rejection, and graft-versus-host disease share common histopathological features. Neuberger et al. [17] reported on three patients who had undergone OLT more than 3.5 years previously and had apparently developed a recurrence of PBC. This suggestion was based on histopathological findings such as reduction of small bile ducts and portal inflammation, a clinical course after OLT resembling PBC with mild jaundice, and detection of AMA. Demetris et al. [7], however, found in a large group of liver recipients with PBC a higher incidence of chronic rejection but no evidence of recurrent PBC, according to Neuberger's criteria. A recent study by Balan et al. [1] demonstrated histological evidence of recurrent PBC in approximately 10 % of the liver recipients for PBC but no evidence of progressive disease. In 19 PBC patients, followed-up for 11 years, no distinctive histological nor serological findings for recurrent PBC were detectable [11]. The role of posttransplant AMA titers and the PBC-specific subtypes, anti-PDH-E2 and anti-BCKD-E2, and their correlation to recurrence of PBC is still unclear.

Conflicting reports on the recurrence of PBC after liver transplantation may reflect differences in patient selection, medical management, and immunosuppressive therapy. Cyclosporine A, for example, may postpone the onset of recurrent PBC, as seen in precirrhotic patients. A much longer observation period may be necessary to definitely prove or rule out the existence of recurrent PBC.

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