Liver Transplantation in Primary Biliary Cirrhosis

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Although primary biliary cirrhosis was first described by Addison and Gull in 1851 [1], the term primary biliary cirrhosis (PBC) was used for the first time by Ahrens and colleagues in 1950 [2]. PBC is considered an organ-specific autoimmune disease, but its origin is far from being fully understood. It primarily affects middle-aged women and is frequently associated with various autoimmune conditions. No curative therapy for PBC exists, but available medications may slow progression of the disease and ameliorate clinical symptoms in most patients. Unfortunately, a proportion of patients develop end-stage liver disease and require liver transplantation, which is currently the only established curative treatment of this condition. In the past, PBC was the most common indication for liver transplantation, with patients who have cirrhosis constituting approximately 55% [3]. This proportion has now decreased significantly predominantly because of the increased number of patients undergoing transplantation for other indications, but also possibly as a result of a protective effect of ursodeoxycholic acid (UDCA) on disease progression [4,5]. PBC may recur after transplantation, a diagnosis that can be reliably established only through histologic examination [6]. Recurrent PBC seldom impairs graft function in the medium-term, but its study may provide important clues about disease pathogenesis.

Primary biliary cirrhosis: transplantation trends

A recent study in North America based on the United Network for Organ Sharing database and analyzing the period between 1995 and 2006 showed a clear trend toward decreased rates of liver transplantation for PBC [4]. During that period, the absolute number of transplants showed...
an average increase of 249 per year. Over the same period the absolute number of transplants performed for PBC decreased steadily by an average of 5.4 cases per year (Figs. 1 and 2). The median age at transplantation remained unchanged. These findings are important considering that the incidence and prevalence of PBC show a steady increase [7]. The authors' believe their study suggests that UDCA, which is now almost universally prescribed in patients who have PBC, may affect the natural history of this condition and decrease the need for liver transplantation. During the same period the absolute number of transplants conducted for another chronic cholestatic liver disease, namely primary sclerosing cholangitis (PSC), remained stable. As UDCA is increasingly prescribed in patients who have PSC, this finding may suggest that this bile acid is either not effective in patients who have PSC or is prescribed in suboptimal doses.

A similar tendency has also been observed in Europe. Of the 34,811 liver transplants performed between January 1988 and June 2006 and documented by the European Liver Transplant Registry (ELTR) (http://www.eltr.org/publi/index_rv.php3), 3828 (11%) were performed in patients who had PBC. This proportion decreased fivefold, being as high as 55% in the early days of liver transplantation [3]. An analogous trend toward decrease in liver transplants for PBC was observed in the Liver Unit in Birmingham, United Kingdom, which has the largest experience in liver transplantation for this condition worldwide. In their retrospective study of 400 consecutive patients who underwent transplantation for PBC, Liermann-Garcia and colleagues [8] showed that the proportion of patients undergoing

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Fig. 1. The absolute number of liver transplantations graphed by year from 1995 to 2006. Trend line is denoted by the thin black line. (From Lee J, Belanger A, Doucette JT, et al. Transplantation trends in primary biliary cirrhosis. Clin Gastroenterol Hepatol 2007;5:1314; with permission.)
transplantation for PBC decreased from 35% in 1990 to 21% in 1999. Unlike the American study, the Birmingham series found that the median age at transplantation increased from 53 to 56 years. The median serum bilirubin also decreased from 270 $\mu$mol/L to 132 $\mu$mol/L. An argument can be made that these findings reflect a beneficial effect of UDCA on the natural history of PBC, slowing the progression of the disease so that these patients undergo transplantation at an older age.

**Indications**

In patients who have PBC who reach end-stage liver disease, the indications for liver transplantation are no different from those for any other condition. The most common indications include treatment-resistant ascites and spontaneous bacterial peritonitis; hepatocellular carcinoma fulfilling Milano criteria, or in some centres San Francisco criteria; recurrent variceal bleeding; progressive muscle wasting; or encephalopathy. More specifically for chronic cholestatic conditions, intractable pruritus and chronic fatigue may also merit consideration for transplantation [9]. The origin of pruritus in chronic cholestasis is far from being fully understood [10], and the properties, origin, and nature of the causative pruritogen remain unknown. Experts have suggested that it may be produced in the liver and subsequently
secreted in bile. This notion has been supported by the fact that pruritus usually decreases with progression of the disease and decline of synthetic function of the liver. Recently, endogenous opioids have been postulated to cause this distressing symptom [11].

In most patients, pruritus may be alleviated in response to available therapies, which include cholestyramine, rifampicin, sertraline, ondansetron, nalatrexone, plasmapheresis, or biliary drainage. Although in practice UDCA may seem to have ameliorated pruritus in some subjects, a large study failed to confirm a significant effect of this bile acid on pruritus in patients who have PBC [12]. Liver transplantation remains the last resort for treating intractable pruritus, but it might be proposed even in a patient who has otherwise well-preserved liver function [3].

Chronic fatigue is a frequent symptom associated with PBC [13]. Chronic fatigue is neither related to physical exercise nor improved by rest. It exerts a profound effect on quality of life and generates severe disability and distress, often disproportionate to the patient’s physical status. As many as 70% to 80% of patients who have PBC complain of various degrees of fatigue [14,15]. Various treatments have been attempted to alleviate this devastating symptom, including antioxidants and different antidepressants, but none has proved effective [16,17]. In patients who have PBC, chronic fatigue has been a rare indication for transplantation, but available evidence suggests that it may not be fully reversed by this procedure [18].

Timing

For obvious reasons, liver transplantation should be considered when the probability of survival surgery is higher than without. Christensen and colleagues [19] have shown that in patients who have PBC, this goal occurs when serum bilirubin reaches 10 mg/dL (170 μmol/L). Patients should be referred to a liver transplant center for initial assessment when their bilirubin approaches 5.9 mg/dL (100 μmol/L). The Mayo risk score (http://www.mayoclinic.org/gi-rst/mayomodel2.html), which was introduced in 1989 and is based on the patient’s age, bilirubin, albumin, prothrombin time, presence of peripheral edema, and necessity of the treatment with diuretics, has been shown to be superior to the Child-Pugh score in predicting the outcome of transplantation in patients who have PBC [20]. A threshold Mayo risk score of 7.8 points identifies patients who have a significantly increased risk for death after transplantation [21].

The MELD (Model for End-Stage Liver Disease) score (http://www.mayoclinic.org/meld/mayomodel6.html) has also been found superior to Child-Pugh score in predicting mortality in patients who have end-stage liver disease and are awaiting liver transplantation [22]. This mathematical formula takes into account serum bilirubin, international normalized ratio, creatinine, and necessity of dialysis and is used to decide about liver allocation on the transplant list. Using MELD score significantly decreases the
chance of liver transplantation in a small proportion of patients who have PBC whose main indication is intractable pruritus or chronic fatigue, because they may have well-preserved liver function and a correspondingly low MELD score.

**Posttransplant complications**

Acute rejection (AR) is rarely of clinical significance because it responds very well to increased immunosuppression. It also may exert a tolerogenic effect and in fact improve survival [3]. The incidence of AR in patients who have PBC is estimated to be between 46% and 56% [23–25] and is less frequent than in those who have autoimmune hepatitis but more common than in those who have undergone transplantation for other indications, such as viral or alcoholic cirrhosis [24].

Chronic rejection (CR) is a considerably more significant complication, commonly leading to graft loss. Similar to AR, it occurs less frequently in patients who have PBC than in those who have autoimmune hepatitis, but more commonly than in subjects who have undergone transplantation for other indications [24]. Various studies have shown the incidence of CR in PBC to be between 2% and 9.3%. In the largest study on the effect of immunosuppression on recurrence of PBC, comprising 485 patients, the incidence of CR in patients treated with cyclosporine A (CyA) was 8.7% compared with 3.7% in those treated with tacrolimus [26].

Causes of death after liver transplantation for PBC were reported in two large studies. Liermann-Garcia and colleagues [8] reported 102 posttransplant deaths (25.5%), with 60% dying within 6 months of their surgery, mostly because of sepsis and multiorgan failure. The most common causes of late death were again sepsis and de novo malignancies, renal failure, and chronic rejection. In their series of 100 patients who had PBC who underwent transplantation at Charite Hospital in Berlin, Jacob and colleagues [25] reported 10 deaths after this procedure. Three patients died within 6 months of transplantation from infections. Late deaths were caused by infections (three patients) de novo malignancies (two patients), and disease recurrence (two patients).

**Survival after transplantation**

PBC—along with primary sclerosing cholangitis, Wilson’s, and other metabolic diseases—is one of the best indications for liver transplantation. According to ELTR, 1, 5 and 10-years’ survival rates in PBC are 83%, 77%, and 69%, respectively [3]. Patients who had PBC who underwent liver transplantation in 1997 in North America had a 5-year survival rate of 86.2% [3]. These data are comparable to those reported from large European centers, in which 5-year survival is reported to be between 78% and 87% [8,26,27]. As for other indications for liver transplantation, a significant
improvement of posttransplant survival is seen compared with patients who underwent transplantation in the 1980s and 1990s. Birmingham data showed that patients who underwent transplantation in 1980s had 3- and 5-year survival rates of 70% and 66%, respectively, compared with 83% and 80% in those who underwent transplantation in the 1990s [8]. Similarly, Mayo and Dallas data have shown an improvement in 3-year survival from 72% in the 1980s to 88% in the 1990s [21,28].

Quality of life after liver transplantation

Patients who have chronic cholestatic conditions, such as PBC or PSC, experience symptoms that occur only occasionally in other groups of patients who are listed for liver transplantation. These symptoms, including pruritus and chronic fatigue, significantly affect quality of life. Gross and colleagues [18] applied the NIDDK LTD–QOL questionnaire for the study of various aspects of quality of life in patients who had PBC shortly before liver transplantation (mean time before grafting, 2.3 months) and 1 year after operation. They found that 51% of patients described one or more of the following symptoms: chronic fatigue, sleeplessness, and pruritus, as extremely distressing before surgery. At 1 year after surgery, this proportion was reduced to 25%. The most spectacular improvement was seen with pruritus, whereas chronic fatigue remained the most distressing symptom after transplantation, although the intensity was diminished. Before transplantation, 29% of patients were “able to carry out normal activity with effort, some symptoms,” whereas 61% could achieve normal activity with minor or no symptoms after grafting. Significant reduction in sick days was reported after transplantation, but this finding did not correlate with employment rate, which at 1 year before and after surgery was found to be 38% and 27%, respectively. Patients also reported significant improvement of their home, social, and sex life after transplantation. As many as 86% of patients reported their health status as poor or fair before surgery, and this proportion was reduced to 23% after surgery. Furthermore, only 7% of patients would call themselves “very happy” before transplantation compared with 42% after surgery. This proportion is higher than in the general population, among whom approximately 33% of subjects would call themselves “very happy.” In the study by Gross and colleagues [18], no pretransplant variables were found that predicted the outcome in terms of quality of life after transplantation.

Recurrence of the disease

Numerous studies have shown that PBC recurs after liver transplantation. However, results must be interpreted cautiously, because different criteria have been used to diagnose recurrent disease. Pretransplant, three
criteria, namely typical histology, elevated alkaline phosphatase (ALP), and positive antimitochondrial antibodies (AMA), permit the diagnosis of definite PBC [9]. However, AMA remains positive in many patients after transplantation without any suggestion of disease recurrence [29]. Similarly, an elevated ALP can be caused by various causes after transplantation, such as acute or chronic rejection, cytomegalovirus infection, and many others. Thus, the only reliable criterion for diagnosing PBC after transplantation remains liver histology [6]. In several studies, histology was a main criterion, but liver biopsies are generally performed only when patients present with clinical symptoms or elevated liver biochemistry, and therefore tend to underestimate the prevalence of this phenomenon. In six studies, protocol biopsies, taken even in the absence of any clinical abnormality, were used to establish the diagnosis of recurrent PBC (Table 1). The prevalence of recurrent PBC was found to be between 11% and 34%, with median time to diagnosis of recurrence between 36 and 61 months after transplantation. In four of these studies, tacrolimus-based immunosuppression was found to be a significant risk factor for recurrence. Furthermore, patients treated with tacrolimus were found to have histologic features of recurrent PBC significantly earlier than those treated with CyA. In two studies, multivariate analysis also depicted male gender and recipient age as factors that significantly increased the risk for recurrence [23,25]. The role of human leukocyte antigen (HLA)—matching in the development of recurrence remains controversial. Morioka and colleagues [30] in their study of 50 patients who underwent living related donor liver transplantation (LRDLT) found that lower number of HLA-A, B, and DR mismatches may increase the risk for recurrence. These findings were not confirmed by the most recent study on a larger cohort of LRDLT recipients, also from Japan [31]. Treatment with UDCA has been shown to improve liver biochemistry and histology in patients who have PBC before liver transplantation. Unfortunately, no systematic study has been performed on the effect of UDCA on incidence of recurrence or its effect on patients who have recurrent PBC. Charatcharoenwitthaya and colleagues [23] showed that subjects who had recurrent PBC and were treated with UDCA had a significant improvement of their transaminases and ALP at 3 years after transplantation but no significant effect on the progression of histologic stage of the disease. The latter finding must be interpreted cautiously, however, because two thirds of patients analyzed were treated with suboptimal doses of UDCA. Some studies have shown (in univariate analysis) that shorter duration of posttransplant treatment with steroids may increase the risk for recurrence [23,32].

All these findings may have significance in understanding the pathogenesis of PBC. PBC is considered to be an autoimmune condition. This etiology is supported by its frequent association with other autoimmune conditions and presence of disease-specific autoantibodies, such as AMA, gp-260, and sp-100. Twin concordance data show PBC concordance in
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monzygotic twins to be of 0.63, one of the highest seen in autoimmune conditions and comparable to Crohn’s and celiac disease [33]. Furthermore, a proportion of patients who have PBC respond well to treatment with immunosuppressive drugs, including steroids [34–36], azathioprine [37], or CyA [38,39]. An immunomodulatory effect of UDCA, the only treatment of this condition approved by the U.S. Food and Drug Administration, may also support this etiology [40]. However, PBC shows no association with HLA phenotypes typically seen in patients who have autoimmune conditions and has never been reported to occur in children (the two youngest cases ever reported were postpubertal female patients aged 15 and 16 years) [41]. It has been suggested that infectious agents may be involved in the pathogenesis of PBC through either a “molecular mimicry” phenomenon or the direct effect of a virus or bacterium. Molecular mimicry is the concept that “self-like” immunogenic determinants on an exogenous agent (bacterium, virus, xenobiotic) may trigger production of antibodies or effector T cells that mistakenly interact with similar epitopes on a host cell or protein [42]. Various microbes such as Escherichia coli, Pseudomonas aeruginosa, Chlamydia Pneumoniae, and Novosphingobium aromaticivorans have been linked with PBC [43–45]. Data showing viral-like particles in biliary epithelial cells incubated with lymph node homogenates from patients who have PBC and an induction of phenotypic features of PBC in these cells suggest viral involvement in the pathogenesis of PBC [46,47]. Also high levels of beta viruses were identified in lymph nodes of patients who had PBC, and a pilot study showed that antiretroviral agent, Combivir, improves liver biochemistry and histology in patients who have PBC [48].

The observed increased risk for recurrence in subjects treated with tacrolimus rather than CyA may support the role of an infectious agent in the pathogenesis of PBC. Tacrolimus is a more potent immunosuppressant than CyA and therefore may more effectively encourage viral replication after transplantation. This notion can be supported by recent findings in patients who had hepatitis C, in whom mycophenolate mofetil, when compared with azathioprine (less-potent immunosuppressive agent), seemed to enhance progression of graft fibrosis [49] and to increase viral load [50]. Although CyA has been found to have antiviral properties [51] and has even been used to treat viral hepatitis C [52], recent meta-analysis did not show its superiority over tacrolimus in terms of outcome after transplantation in patients who had hepatitis C [53].

However, no single study has shown a significant effect of recurrent disease on patient survival, although in some studies a very small proportion of patients lost their grafts or even died of recurrence.

Summary

Liver transplantation is a preferred treatment in patients who have PBC who reach end-stage liver failure. The survival after this procedure is
excellent. The disease may recur after transplantation but in the medium-term does not exert a significant effect on patient or graft survival.

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References


