

Recurrence of Primary Biliary Cirrhosis after Liver Transplantation

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Abstract

Recurrent disease following liver transplantation does occur in selected patients with primary biliary cirrhosis. The frequency of recurrent primary biliary cirrhosis is highly variable and is influenced by several factors, including the specificity of diagnostic criteria. The diagnosis is usually confirmed by histological features in the liver of granulomatous change or florid duct lesions. Risk factors that may predict recurrent primary biliary cirrhosis following liver transplantation include donor and recipient age, human leukocyte antigen profile, and immunosuppressive therapy. The management of recurrent primary biliary cirrhosis remains unclear. However, the administration of ursodeoxycholic acid and utilization of cyclosporine as primary immunosuppression may be encouraging strategies to apply prospectively. (Trends in Transplant. 2011;5:133-8)

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Key words

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Introduction

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease characterized by progressive bile duct destruction, leading to liver fibrosis and ultimately cirrhosis.

Liver transplantation is a valuable option that can be utilized to treat end-stage

liver disease from PBC where excellent patient outcomes are observed, as demonstrated by the high one-, five-, and 10-year survival rates¹.

Therefore, it does not come as a surprise that PBC is the sixth leading indication for liver transplantation in the USA^{1,2} and a major indication for liver transplantation in Europe³.

Despite good outcomes and long-term survival, recurrence of PBC may occur. Following liver transplantation, the first case of recurrent PBC was described by Neuberger, et al. in 1982⁴ and current estimates suggest the cumulative risk for recurrent PBC is around 20-25% at 10 years¹.

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Table 1. Indications for referral of primary biliary cirrhosis patients to liver transplant services

	EASL ⁶	AASLD ⁷
Model for End-Stage Liver Disease	> 12	≥ 10
Mayo Risk Score	≥ 7.8	NA
Child-Turcotte-Pugh score	NA	≥ 7
Bilirubin level	> 6 mg/dl	NA
Major complication	Severe pruritus, encephalopathy	Ascites, variceal bleed, hepatic encephalopathy

This table shows the various clinical indications suggested by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) for referral of patients with a diagnosis of primary biliary cirrhosis to the liver transplant service.

Recurrent PBC lacks the typical clinical and biochemical features seen in *de novo* PBC². Therefore, recognition of granulomatous destruction or florid duct lesions on liver histology are important in defining recurrence following liver transplantation⁵.

To date, the impact of recurrent PBC has not significantly affected the excellent clinical outcomes after liver transplantation in the short term. Longer term follow-up, however, will be necessary to confirm this observation. In addition, several investigations to date have identified risk factors for recurrent PBC, while other studies have examined the clinical efficacy of ursodeoxycholic acid (UDCA) as therapy for recurrent PBC.

Indications for Liver Transplantation

In general terms, patients with PBC undergo liver transplantation due to histological progression of disease that translates clinically to an intolerable quality of life or anticipated survival ≤ 1 year.

Specific indications for referral of PBC patients to liver transplant centers have been identified by clinical practice guidelines issued by the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD), which can be found in table 1^{6,7}.

Trends and Outcomes of Liver Transplantation

The European Liver Transplant Registry reports that liver transplantation for biliary tract disease accounts for 12% of all activity⁸. However, despite the steady increase in annual incidence of PBC, the number of patients undergoing liver transplantation for advanced liver disease from PBC is decreasing². According to the United Network for Organ Sharing (UNOS) registry, the number of liver transplants performed for the indication of PBC decreased by a mean of 5.4 cases per year⁹, while in Europe a fivefold reduction was observed¹⁰. It is also worth noting that in the past 10 years, the number of patients with PBC requiring transplantation has declined by approximately 20%¹. This may be attributed to the effect of UDCA in reducing progression of the disease as well as early detection of new asymptomatic cases.

The outcomes following liver transplantation for patients with PBC are outstanding. One-, five-, and 10-year survival rates exceed outcomes associated with liver transplantation for chronic viral hepatitis and alcohol-related liver disease^{1,11}. The reported survival rates for patients with PBC undergoing liver transplantation is similar among different centers, with one-, five-, and 10-year survival rates of 83, 77, and 69%, respectively, reported by the European Liver Transplant Registry, and 83, 78,

and 67%, respectively, reported by the Liver Unit at Queen Elizabeth Hospital in Birmingham^{10,12}. A study analyzing PBC patient survival in the UNOS registry showed a one-, three-, and five-year survival of living donor and deceased donor transplants of 92.8, 90.1, and 86.4%, and 86.4, 89.6, and 87.0%, respectively¹¹. In our population, patient survival after transplantation at one-, two-, and five-years was 93, 90, and 88%, respectively¹³.

Recurrent Primary Biliary Cirrhosis after Liver Transplantation

The recurrence rate of PBC following liver transplantation varies between centers. Overall, the cumulative incidence of recurrent PBC is estimated at 20-25% over 10 years.¹ However, some studies report a higher rate of 21-37% at 10 years and 43% at 15 years^{12,14,15}, while other centers describe recurrent PBC in as many as 50% of patients at 10 years¹⁶. The prevalence rate of recurrent PBC varies as well, ranging from 0-35%^{12,17-21}.

Differences in the reported rates of recurrent PBC may be attributed to several factors. An important consideration is the utilization of non-uniform diagnostic criteria to define recurrent PBC among different centers⁵. This is clearly displayed in a study by Sylvestre, et al. where incorporating strict diagnostic criteria (such as the presence of a florid duct lesion or destructive lymphocytic cholangitis with dense portal infiltrates) was associated with a recurrence rate of 17% during a mean period of 4.7 years. Conversely, when the criteria were expanded to include moderate lymphocytic cholangitis with lymphoplasmacytic portal infiltrates during the same period, the recurrence rate of PBC was reported as 26%²².

It is also worth noting that biopsies have an intrinsic sampling error and can reduce the accuracy of histology in verifying

the presence of recurrent PBC^{19,22}. Furthermore, the frequency and indication for liver biopsy after transplantation would also seem to affect the detection rate of recurrent PBC²³. Studies where liver biopsy is performed for clinical indications have reported lower rates of recurrence, as opposed to centers utilizing protocols for regularly scheduled biopsies as recurrent PBC can be seen on liver histology even when serum liver biochemical test values are entirely within the normal range²².

Diagnosis and Features of Recurrent Primary Biliary Cirrhosis

Recurrent PBC is difficult to diagnose as clinical features are of little value after liver transplantation²⁴. For example, serum antimitochondrial antibodies (AMA) have a significant role in diagnosing PBC in the native liver, yet serum AMA levels persist in nearly 75% of patients after liver transplantation and therefore have a limited value in diagnosing recurrent disease²⁵.

The diagnosis of recurrent PBC requires excluding other causes of allograft dysfunction, including acute cellular rejection, chronic ductopenic rejection, biliary obstruction, drug-induced liver injury, and rarely, graft versus host disease²⁴. As mentioned earlier, the cornerstone for diagnosing recurrent PBC is liver histology. Proposed histological features required for diagnosis of recurrent PBC are characteristic portal tract lesions that include a mononuclear cell inflammatory infiltrate, lymphoid aggregates, epithelioid granulomas, and bile duct damage^{5,26}. If three out of four portal tract lesions are present, then the diagnosis of recurrence is definite, whereas if two of four features are present, then the diagnosis of recurrence is probable⁵. New evidence also suggests a value for anti-parietal cell autoantibodies in detecting recurrence²⁵.

Fortunately, studies to date have suggested that recurrent PBC appears to be mild and slowly progressive, with few cases requiring hepatic retransplantation^{27,28}.

Risk Factors

The risk factors for recurrent PBC remain uncertain. It has been proposed that human leukocyte antigen (HLA) matching between donor and recipient may increase the risk of recurrence¹⁶. Alleles that were denoted as significantly similar in patients with recurrence are A1, B48, B57, B58, DR44, DR57, and DR58¹⁹.

Studies report that the effect of HLA mismatching is evident in patients with recurrent disease, and patients with absent HLA-B match or low number of matching HLA-A, HLA-B, and HLA-DR are at increased risk of disease recurrence^{15,29-31}. On the other hand, some studies report that the risk of recurrence does not seem to be associated with HLA profile, including the degree of HLA matching between the donor and recipient^{12,17,19,32}. These results suggest that recurrent PBC may not be restricted to variations within the HLA region³³.

Several studies indicate that immunosuppression with tacrolimus is strongly associated with an increased risk of recurrent PBC in patients receiving deceased or living donor liver transplants^{1,12,14,15,26,32,34,35}. Moreover, patients receiving tacrolimus have a significantly shorter median time to recurrent PBC¹⁴ and are more likely to have a recurrence versus patients receiving cyclosporine¹⁹. On the other hand, a recent meta-analysis showed no difference in developing recurrent PBC between patients receiving either cyclosporine or tacrolimus³⁶. Recent evidence shows a decrease in the rate of recurrence with usage of cyclosporine, azathioprine³⁷, or combination therapy with cyclosporine and azathioprine³⁶. This remains somewhat controversial as several

other studies have not arrived at this conclusion^{14,18-20,38}. For example, the recurrence of PBC was associated with nonuse/discontinuation of azathioprine in one investigation³⁹. Corticosteroids and mycophenolate mofetil have not been associated with the development of recurrent PBC¹⁹, and corticosteroid discontinuation does not appear to have a dramatic impact on susceptibility for recurrence⁴⁰. However, the duration of corticosteroid usage may act as a prognostic factor for patients with PBC in terms of mortality or need for hepatic retransplantation³².

Another factor demonstrating mixed results is the donor age of the liver allograft. In a cohort of 154 patients undergoing liver transplantation, older donor age denoted a greater risk of PBC recurrence³². On the other hand, it is also thought that an association between younger age and an increased risk of recurrent PBC exists¹². This relationship could have a bimodal distribution, but further study is required to verify this hypothesis. Donor organs from individuals > 65 years of age act as an independent risk factor for the development of recurrent PBC³².

Recurrence of PBC may also be influenced by donor histology, as the presence of liver fibrosis, fatty degeneration, and liver cell hydrops significantly increase the risk of recurrent PBC following liver transplantation⁴¹.

A single study showed that cold ischemic time is an independent risk factor for the development of recurrent PBC¹⁷. However, a study involving warm ischemic time failed to show a significant relationship to recurrence¹².

Management

The treatment of recurrent PBC is center-dependent as no standard plan for management exists at the current time.

Some experience with the institution of UDCA (12-15 mg/kg/day) after the diagnosis of recurrent PBC has been published^{29,32}. UDCA improves liver biochemistries and may delay histological progression, but its effect on the natural history of recurrent PBC is as yet undetermined^{1,29,32}. Moreover, many patients have normal biochemistries at the time of diagnosis, which may hinder the decision to start UDCA and the ability to monitor the effects of therapy. Some studies suggest that converting tacrolimus immunosuppression to cyclosporine reduces the incidence of recurrent PBC, yet this would require further study³².

Conclusion

The development of recurrent PBC following liver transplantation is common, yet the need for aggressive therapy and hepatic retransplantation is rare. With continuing improvement in posttransplant management and prolonged periods of follow-up, the effects of recurrent PBC may be better identified in the future. The uniform usage of diagnostic criteria may further enhance the detection of recurrent PBC and make the evidence regarding management less controversial. Recognition of an agent that could modify the natural history of recurrent PBC would be interesting to pursue and may lead to a better understanding of the pathophysiology of the disease.

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