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LIVER TRANSPLANTATION FOR PRIMARY BILIARY CHOLANGITIS (REVIEW)

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Primary biliary cholangitis (PBC) is an autoimmune liver disease resulting from the destruction and inflammation of intrahepatic bile ducts. This end-stage disease was once the most common cause of liver transplantation. The use of ursodeoxycholic and obeticholic acids as a first-line and second-line treatment, respectively, slows down the disease. However, treatment is not effective in about 40% of PBC patients, and the disease may progress to cirrhosis and end-stage liver disease. These patients undergo liver transplantation to save their lives. After surgery, recurrent PBC can develop in a milder form and rarely requires liver retransplantation.

Key words: primary biliary cholangitis, PBC, Liver transplantation, recurrence PBC, risk factors.

After the first clinical liver transplantation (LTx) in 1963, primary biliary cholangitis (PBC) was for a long time the leading indication for LTx. LTx in PBC patients accounted for 30–50% of all liver transplants [1–3]; in the first decade of the 21st century, there was a decline to 10% [1]. Despite the increasing prevalence of PBC, this disease is no longer the leading indication for LTx. In the last decade, there has been a trend toward an even greater decrease in the number of liver transplants for PBC [4], in Europe they represent about 9% of all liver transplants [5], and in Asia only 3.5% [6]. According to the European Liver Transplantation Registry, the proportion of liver transplantations for primary biliary cholangitis decreased from 20% in 1986 to 4% in 2015 ($P < 0.001$) [7].

In the United States between 1995 and 2006, while the total number of liver transplants increased, the absolute number of liver transplantations in the United States increased an average of 249 transplants per year between 1995 and 2006 ($P < 0.001$); the absolute number of transplants performed for PBC decreased an average of 5.4 cases per year ($P = 0.004$). A similar pattern was observed with respect to the absolute number of individuals added to the transplant waitlist showed a similar pattern: (1) an increase in total listings for transplants of all diagnoses ($P = 0.001$); 2) a decrease in the number of PBC patients ($P < 0.001$); (3) no significant change ($P = 0.083$) in the number of patients with primary sclerosing cholangitis [8].

Early detection of the disease by serological tests and treatment with ursodeoxycholic acid (UDCA) at the initial stage of the disease not only increased life expectancy, but also dramatically reduced the need for orthotopic LTx [8, 11], especially in patients with a favorable biochemical response to treatment [9, 10]. In the Netherlands, over the past three decades, there has also been a decrease in both the absolute and relative number of liver transplants in PBC [4]. The authors attribute this trend to the common use of UDCA as a standard treatment for PBC, but do not exclude the possibility of other mechanisms, given the many complex factors determining the final number of patients referred for transplantation and who eventually underwent it [4].

UDCA lowers serum hepatic enzyme levels and significantly reduces the likelihood of death after four years or the need for LTx [12]. Nevertheless, approximately 40% of patients have no biochemical response to UDCA treatment [13–15]. Inadequate response to UDCA treatment is directly associated with an increased risk of death or the need for LTx [16, 17]. Therefore, LTx remains the only option to prevent premature death in patients with advanced PBC [18]. The waitlist mortality rate in PBC patients is 12%, which is significantly higher than the mortality rate of liver failure of other etiologies [19].

There is an increase in the age of patients with PBC at the time of transplantation [20, 21]. In one study [22], the age of some patients exceeded 60 years. In addition, it has been found that an increasing number of men with PBC are undergoing LTx over time [7, 22]. According to the European Liver Transplantation Registry, between 1986 and 2015, the age at LTx increased from 54 (IQR 47–59) to 56 years (IQR 48–62), and the proportion of males increased from 11% to 15% [7].

Indications for liver transplantation in PBC patients. Patients with PBC require LTx if the disease proceeds to an end stage [23]. Liver transplantation is the only effective treatment for end-stage PBC with quite satisfactory results [18].

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Indications for transplantation are poor quality of life or possible death within less than one year. According to G.C. Mac Quillan and J. Neuberger (2003) [24], with many prognostic models available, the simplest guideline for timing of LTx is the level of serologic bilirubin. Deterioration of the condition of patients with PBC can be rapid in the end stages of the disease, requiring timely consideration of LTx [17].

Biochemical indicators of the restoration of transplanted liver function. After LTx, liver function is restored by the end of the fourth week [18]. Alanine aminotransferase and aspartate aminotransferase activities peaked once before this recovery [18]. In a retrospective study, transaminase activity on day 1 after LTx was 10–12 times the upper limit of normal and reached normal levels by day 9. Early peaks of transaminase activity represent a reflection of donor liver damage during its removal followed by reperfusion injury during transplantation [25]. Gamma-glutamyl transpeptidase levels peaked on day 7, and alkaline phosphatase levels peaked on week 2. Gamma-glutamyl transpeptidase levels peaked on day 9 after surgery, and then decreased. An early increase in gamma-glutamyl transpeptidase after LTx may be due to reperfusion injury, as well as surgical stress in the recipient [26]. Total bilirubin and direct bilirubin levels decreased after surgery to normal values at week 4. Bilirubin is an excellent prognostic biomarker for monitoring liver function recovery. Dynamic bilirubin monitoring is useful for early detection of biliary complications [18].

Post-liver transplant complications. According to recent data, the frequencies of infection and biliary complications are 62% and 21%, respectively [18]. Bacterial infections are the most common [27, 28]. Biliary complications occur in 10–30% of patients and can even cause mortality [29–31]. Hepatic artery thrombosis is a fatal vascular complication with high mortality (20–60%), with 3–5% incidence and usually requires repeated LTx [30, 32]. In a study by L. Chen et al. (2020) [18], 3 (4.3%) patients had hepatic artery thrombosis and 2 (2.9%) had portal vein thrombosis; fatal complications were abdominal bleeding, infection, and liver failure. Patients suffering from PBC had a high risk of chronic rejection [24].

Survival of PBC patients after liver transplantation. A retrospective analysis of the United Network for Organ Sharing database showed that the estimated patient survival at 1, 3, and 5 years for living donor liver transplants was 95.5%, 93.6%, and 92.5% and for deceased donor liver transplants was 90.9%, 86.5%, and 84.9%, respectively [33]. The overall survival rate of patients with PBC after LTx was reported to be 93–94%, 90–91% and 82–86% at 1, 3, 5 years, respectively [34]. A study by L. Chen et al. (2020) [18] reported that the overall patient survival was 98.6% at 1 year and 95.1% at 3 years. Over 70% of patients live more than 10 years [35, 36]. Long-term follow-up (up to 15 years) of patients after LTx for PBC showed excellent graft function and patient survival [37].

Recurrent PBC. PBC, as well as other autoimmune diseases (primary sclerosing cholangitis and autoimmune hepatitis), can recur after liver transplantation [38, 39]. Transplantation centers have recurrent PBC after both liver transplantation from a cadaveric liver [37, 40] and liver lobe from a living donor [41–43]. Recurrence did not affect patient and graft long-term survival [44]. Recurrent PBC has a mild clinical course, progresses slowly, and is rarely the cause of liver retransplantation [45, 46]. LTx outcomes in patients with PBC are excellent, with 5-year patient and graft survival rates exceeding 90% and 75%. However, in recent years, the problem of PBC recurrence after liver transplantation has been increasingly recognized as a cause of graft dysfunction and death, and the reason for repeated transplantation [47].

Frequency and timing of recurrent PBC. Recurrent PBC after liver transplantation occurs in a significant number of recipients [48]. Its frequency can reach from 32% [37] to 50% [24]. R.F. Liermann Garcia et al. (2001) [49] diagnosed recurrent PBC in 67 (17%) of 400 patients. Histological signs of the return of the disease were observed, on average, three years after liver transplantation. One patient required retransplantation eight years after primary liver transplantation.

During a median follow-up period of 114 months, R. Kurdow et al. (2003) [50] observed 18 patients with PBC who underwent liver transplantation. Six of the patients were reported to have developed a recurrence of primary biliary cirrhosis as indicated by liver biopsies, one patient also developed graft failure. Antimitochondrial antibodies were present in all patients within a period of 1 year after transplantation. Serological parameters were elevated in 16 of 18 patients. In another study [51], recurrent PBC developed in the transplanted liver in seven (15%) of 46 patients who underwent orthotopic LTx for PBC. All of these patients were alive 3 and 5 years after the diagnosis of disease recurrence.

J. Neuberger et al. (2004) [38] cited data on 485 patients with PBC in whom histological signs of disease recurrence were found in 114 (24.8%) patients after liver transplantation in annual protocol biopsy grafts, on average, 79 months after surgery.

J.E. Guy et al. (2005) [52] observed 48 patients with PBC after liver transplantation. One year after surgery, 27 (56.3%) patients had increased serum alkaline phosphatase levels. In graft biopsy specimens, there were reliable signs of recurrent disease in four (8%) patients, suspected recurrence in 11 (23%) patients and non-specific damage possibly related to PBC recurrence in two (4%) patients.

According to D.A. Jacob et al. (2006) [37], between April 1989 and April 2003, 1,553 liver transplants were performed in 1,415 patients at the Virchow Clinic in Berlin. Protocol liver biopsies were taken after 1, 3, 5, 7,

10 and 13 years after surgery. One hundred (7%) patients suffered from histologically proven PBC. Primary immunosuppression consisted of cyclosporine (n = 54) or tacrolimus (n = 46). Immediately after LTx, all patients received ursodeoxycholic acid. Corticosteroids were withdrawn three to six months after LTx. The median age of the 85 women and 15 men was 55 years (range 25–66 years). The median follow-up after liver transplantation was 118 months (range 16–187 months) and after recurrence 30 months (range 4–79 months). Actuarial patient survival after 5, 10 and 15 years was 87, 84 and 82% respectively. Ten patients (10%) died after a median survival time of 32 months. Two of these patients developed organ dysfunction owing to recurrence of PBC. Histological recurrence was found in 14 patients (14%) after a median time of 61 months (range 36–122 months). Patients with tacrolimus immunosuppression developed PBC recurrence more often ($p < 0.05$) and also earlier ($p < 0.05$). Fifty-seven patients developed an acute rejection and two patients a chronic rejection episode. Liver function did not alter within the first five years after histologically proven PBC recurrence.

A meta-analysis by M. Gautam et al. (2006) [53] found that recurrent PBC developed in 204 (16%) of 1,241 patients, averaging 46.5 months (range 25–78); the mean age of patients at the time of liver transplantation was 52 years (range 46.2–56); most were women (90%).

T. Kogiso et al. (2017) [54] conducted a retrospective multicenter study of recurrent PBC in 388 female patients after living-donor LTx. Postoperative factors were evaluated in 312 patients who survived for more than 1 year after living-donor LTx. Recurrent PBC was defined as abnormal hepatic enzyme levels with typical histological findings in liver biopsies. Fifty-eight patients (14.9%) developed recurrent PBC with a median of 4.6 (0.8–14.5) years post-LTx.

In a study by L. Chen et al. (2020) [18] included 69 patients with PBC who underwent living-donor LTx. Five-year overall survival and recurrence rates were estimated as 95.1% and 21.8%, respectively. A recipient aspartate aminotransferase-to-platelet ratio index greater than 2 was negatively associated with survival ($P = 0.0018$).

The incidence of recurrent PBC was quite high in Japan. At median follow up of 10.0 years (range 1.4–18.7 years), 29 (48%) patients were diagnosed with PBC after living-donor LTx at 4.6 years (range 1.3–14.5 years) [55].

Recurrent PBC develops, on average, 3 to 5.5 years after LTx [37, 49, 56]. Only in the study by J.E. Guy et al. (2005) [52] that the average time of PBC recurrence was found to be 1.6 years. PBC recurrence rate ranges from 1% to 35% [14, 58]. There were 9.6%, 20.6%, and 40.4% PBC recurrences at 5, 10, and 15 years, respectively, after LTx [57]. PBC recurrence in the short- and medium-term rarely affects patient and graft survival, but it can have a negative impact on these indicators in the long-term [18].

Etiology and pathogenesis of recurrent PBC. The etiology of recurrent PBC is the same as that of native liver disease. The mechanism of bile duct damage by antimitochondrial antibodies is related to an immune attack on expressed antigen molecules (e.g., E2 – pyruvate dehydrogenase complex) of bile duct epitheliocytes.

Risk factors for recurrent PBC. The risk of recurrent PBC increases with time following a LTx, but does not correlate with the frequency of loss of liver function [59]. In a study by H. Chen et al (2020) [18], the incidence of PBC recurrence after transplantation increased as the time after surgery increased: 3.5% after one year, 8.1% after three years, and 21.8% after five years. Half of the patients show histological signs of PBC recurrence 10 years after surgery, but they rarely have clinical problems [24]. As the follow-up period has increased, it becomes evident that the return of this disease in the transplanted liver is not a rare complication [60].

Immunosuppressive therapy can affect the timing and rate of PBC recurrence. However, there is no consensus on this issue; there are contradictory views in the literature. Some authors have found differences in the frequency of this complication depending on the immunosuppressive drugs used [59], while others, and most of them, deny such a dependence [36, 38, 51, 61]. Calcineurin inhibitors were previously thought to be associated with the risk of relapsed PBC [38, 62]. Later it was found that they have no significant effect on the development of relapsing PBC [36].

Relatively high incidence of recurrent PBC was associated with early steroid withdrawal after liver transplantation and withdrawal of calcineurin inhibitors. According to T.C. Schreuder et al. (2009) [59], the risk factor for recurrent PBC is the use of tacrolimus rather than cyclosporine. Multivariate analysis has confirmed this position [37].

A.J. Montano-Loza et al. (2019) [63] suggest that cyclosporine treatment prevents recurrent PBC. On the contrary, T. Kogiso et al. (2017) [54] believe that initial treatment with cyclosporine is significantly ($P < 0.05$) associated with recurrent PBC. A Japanese multicenter study also found that cyclosporine was a risk factor for recurrent PBC. However, switching from tacrolimus to cyclosporine one year after LTx significantly reduced its risk [57].

Many authors attach great importance to the recipient age [49, 54]. Recipients younger than 48 years of age are considered to be at greater risk of recurrent PBC [57]. In a recent study, multivariate regression analysis showed that the age of recipients younger than 48 years was an independent risk factor for PBC recurrence ($P = 0.03$) [18]. A multicenter study including 785 patients with PBC who underwent LTx showed that tacrolimus use and

liver dysfunction early after surgery were associated with increased risk of PBC recurrence at a younger age [63].

The risk of development of relapsed PBC is also associated with many other factors: shorter operation time [54], persistence of serum antimitochondrial antibodies, higher serum immunoglobulin M level [54], mismatch with donor gender [54, 57, 64], different HLA types, HLA mismatch [42, 61, 65–67] and presence of HLA B60 [54].

The development of recurrent PBC is influenced not only by recipient factors, but also by donor factors. However, they are less numerous and less significant. These include the age of the donor and warm ischemia time [49].

Recurrent PBC diagnosis. The main indicator in recurrent PBC diagnosis is the presence of histological signs in puncture biopsies of the transplanted liver; biopsies are performed not earlier than the first three months after surgery [59]. In contrast to biopsies performed only after the appearance of liver dysfunction, regular protocol biopsies can detect recurrent PBC earlier [40]. Therefore, biopsies performed according to the protocol play a particularly large role in early diagnosis of PBC [59]. They allowed to detect the return of the disease in 14 (14%) patients, only two of them developed graft dysfunction [37]. Antimitochondrial antibodies are not a reliable marker of recurrence, as they can persist in patients' serum after surgery [24]. Thus, liver puncture biopsy is the gold diagnostic standard for recurrent PBC [18].

Pathomorphology of recurrent PBC. Granulomatous destructive cholangitis or florid duct lesion is the most specific histological sign of PBC and its recurrence [68]. Unfortunately, it is often absent from biopsy specimens and has been found in only 4.8% of patients in transplanted liver biopsy specimens, on average, 2.75 years after surgery. [46]. Nevertheless, many authors regard granulomatous cholangitis, although rare, as the most characteristic feature of recurrent PBC [45, 56, 62].

Epithelioid granulomas in the portal tract, a less specific and also rare histological sign, only suggest a return of PBC. They were found in 3.8% of patients, on average, 2.75 years after surgery.

Other signs of recurrent PBC include bile duct injury and loss, chronic portal inflammation, reactive changes in the bile ducts, and fibrosis. It should be kept in mind that in the transplanted liver, there is often not one but a combination of two or more diseases simultaneously, which makes it difficult or impossible to make an accurate histologic diagnosis of recurrent PBC. Therefore, there may be hypodiagnosis because of the rigorous approach to evaluating histologic criteria and the short follow-up time for patients [46].

P.B. Sylvestre et al. (2003) [56] compared the morphology of transplanted liver biopsy specimens from 100 patients with PBC and 35 patients whose primary native liver disease was different. In the protocol biopsy specimens of the transplanted livers of the 100 patients with PBC, 14 of them showed florid duct lesion, and three had destructive lymphocytic cholangitis within dense portal infiltrate. In the control group of 35 patients, no such lesions were found.

Differential diagnosis. At differential diagnosis it is necessary to exclude viral hepatitis, biliary obstruction and acute or chronic rejection [68], graft-versus-host disease, drug influences [69], also hepatitis or injury to the large bile duct [68]. Differentiating PBC return from other late complications, more often from rejection, is difficult. Recurrent PBC is particularly difficult to differentiate from chronic rejection [38]. Therefore, the Banff Working Group on Liver Allograft Pathology proposes a set of consensus criteria for the most common and problematic causes of late liver allograft dysfunction occurring more than one year after surgery [70].

CONCLUSION

Primary biliary cholangitis was for a long time one of the leading indications for liver transplantation and accounted for up to 50% of such operations. Currently, there has been a significant decrease in the number of LTx in PBC. This is associated with early diagnosis and timely initiation of treatment with ursodeoxycholic acid and other drugs. However, the disease proceeds into an end stage in about 40% of patients, which still requires LTx. Patient and graft survival rates exceed 90% and 75%. After surgery, the frequencies of infection and biliary complications are 62% and 21%, respectively. In recent years, the problem of PBC recurrence following a LTx has been increasingly recognized as a cause of graft dysfunction, death and the reason for repeated transplantation. The risk of recurrent PBC increases with time after LTx. The presence of histological signs in puncture biopsies of the transplanted liver is the main method of diagnosis. It is necessary to consider that in the transplanted liver, there is often not one but a combination of two or more diseases simultaneously, which makes it difficult or impossible to make an accurate histological diagnosis of a recurrent PBC. To timely diagnose recurrent PBC, the Banff Working Group on Liver Allograft Pathology proposes a set of consensus criteria for the most common and problematic causes of liver allograft dysfunction occurring more than one year after surgery.

The authors declare no conflict of interest.

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