

Primary biliary cirrhosis and liver transplantation

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Summary

Primary biliary cirrhosis (PBC) is an immune-mediated chronic progressive inflammatory liver disease, predominantly affecting middle-aged women, characterized by the presence of antimitochondrial antibodies (AMAs), which can lead to liver failure. Genetic contributions, environmental factors including chemical and infectious xenobiotics, autoimmunity and loss of tolerance have been aggressively investigated in the pathogenesis of PBC, however, the actual impact of these factors is still controversial. Survival of PBC patients has been largely improved with the widespread use of ursodeoxycholic acid (UDCA), however, one third of patients still do not respond to the treatment and proceed to liver cirrhosis, requiring liver transplantation as a last resort for cure. The outcome of liver transplantation is excellent with 5- and 10-year survival rates around 80% and 70%, respectively, while along with long survival, the recurrence of the disease has become an important outcome after liver transplantation. Prevalence rates of recurrent PBC range widely between 1% and 35%, and seem to increase with longer follow-up. Center-specific issues, especially the use of protocol biopsy, affect the variety of incidence, yet, recurrence itself does not affect patient and graft survival at present, and retransplantation due to recurrent disease is extremely rare. With a longer follow-up, recurrent disease could have an impact on patient and graft survival.

Keywords: Primary biliary cirrhosis, liver transplantation, ursodeoxycholic acid

1. Introduction

Primary biliary cirrhosis (PBC) is an immune-mediated chronic progressive inflammatory liver disease resulting in chronic cholestasis, portal inflammation, and fibrosis that can lead to cirrhosis and, ultimately, liver failure. PBC, predominantly affecting middle-aged women, is characterized by biochemical markers of cholestasis, the presence in serum of highly specific antimitochondrial antibodies (AMAs), and histologically progressive destruction of intrahepatic bile ducts (1-4). The most frequent symptoms in PBC are fatigue and pruritus, occurring in up to 85% and 70% of patients, respectively (5,6).

Although numerous studies have revealed that environmental factors, inherited genetic predispositions and loss of tolerance appear to contribute to its autoimmune pathogenesis, the actual impact of these factors is still controversial (7).

Median survival in untreated individuals had been reported to be 7.5 to 16 years (1,8), however, it has largely improved since the introduction of ursodeoxycholic acid (UDCA) therapy and liver transplantation (9-12). Early recognition of the disease with serological tests and treatment with UDCA at an early stage of the disease has not only enabled patients to enjoy equivalent life expectancy to that of the normal population, but also dramatically decreased the need for orthotopic liver transplantation (13,14). However, the beneficial mechanisms of UDCA treatment are still incompletely understood, since about one third of patients fail to adequately respond to UDCA monotherapy, and liver transplantation is still a last resort for those with end stage PBC (2). While the outcome of liver transplantation for PBC is excellent,

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recurrent disease after liver transplantation for PBC occurs in a considerable number of recipients and is currently a matter of concern (15-17).

The aim of this review is to summarize recent studies of PBC with special reference to liver transplantation.

2. Natural history and characteristics of PBC

2.1. Epidemiology

In a systematic review of studies of PBC frequency, the incidence and prevalence of PBC was reported to range from 0.7 to 49 per million and 6.7 to 402 per million, respectively (18). The highest incidence and prevalence rates were reported from the UK (19,20), Scandinavia (21), Canada (22), and the US (23), all in the northern hemisphere, while the lowest were found in Australia (24). At the same time, the incidence was reported to be increasing with time (25).

Most autoimmune diseases are predominant in female patients, and in PBC, this predominance is especially striking, the ratio of affected females to males is as high as 10:1 (26). The equivalent detection of AMAs between females and males in the general population might suggest either that the diagnosis of PBC might be suspected more frequently in women than in man or that progression from loss of tolerance to clinical liver disease might be more common in female patients (26).

2.2. Pathogenesis

Precise pathogenic mechanisms of developing PBC remain unknown. However, the development of PBC is believed to result from a combination of multiple genetic factors interacting with environmental triggers (27). Three important observations must be taken into account to understand the current pathogenic considerations of PBC. First, appearance of AMAs before developing liver disease suggests that loss of tolerance to the mitochondrial autoantigen is an initial event and could be independent of the development of liver disease. Second, although the autoantigen is present ubiquitously in all nucleated cells, the immune response is restricted to epithelial cells of intrahepatic bile ducts and less frequently to cells of salivary and lacrimal glands. Finally, recurrence of PBC after liver transplantation supports the idea that bile duct epithelial cells are a genetic target and are not unique to the naïve liver with PBC (4).

Genetic contributions to PBC Genetic factors have an impact on PBC pathogenesis that is stronger than in nearly any other autoimmune disease (28,29). Observations that 1-6.4% of patients with PBC have at least one family member manifesting the disease (30-32), and that a concordance rate of 63% was seen in

monozygotic twins (as opposed to null concordance in dizygotic twins) (33,34) shows the substantial genetic effect on disease susceptibility.

Allelic variations in the human leukocyte antigen (HLA) genes, located in the highly polymorphic major histocompatibility complex (MHC), have been revealed to have an association with a large majority of autoimmune diseases (35). In PBC, the most commonly detected HLA association has been with the MHC class II DRB1*08 allele family (36), especially DRB1*0801 in European and North American Caucasians (37-39) and DRB1*0803 in the Japanese (40,41). A protective association has been demonstrated with DRB1*11 and DRB1*13, but once again, significant population differences were observed (36,38).

Association has also been reported with polymorphisms of genes involved in innate or adaptive immunity. Allelic variations of tumor necrosis factor alfa (TNF alfa) (42,43), cytotoxic T lymphocyte antigen 4 (CTLA4) (42,44), and interleukin 12 (IL12) (45) have so far been reported to be associated with PBC development in previous studies.

Environmental factors Despite the above mentioned strong evidence for genetic contributions, epidemiological studies have since early times suggested a role of environmental factors in triggering or deteriorating PBC (46). A significant effect of environmental factors was supported by the identification of geographic disease "hot spots" (industrial, coal mining, and polluted areas) in previous studies (27,47-49). Additionally, hormone replace therapy (50), frequent use of nail polish (50), and smoking (50-52) have been associated with developing and accelerating PBC. These findings led many to hypothesize the possible association of exposure to chemical environmental compounds and xenobiotics (including drugs, pesticides, or other organic molecules) with PBC if those chemicals are excreted into bile and thereby concentrated in the biliary tree (53). Xenobiotics may affect the pathogenesis of PBC by triggering autoimmune reactions with a potential direct toxic effect on cell/protein or a potential modification of host proteins to form neoantigens (54,55). Infection is another important environmental factor (56). A significantly higher prevalence of recurrent urinary-tract infections than usual in patients with PBC has been reported (50,57). Additionally, a sequence similarity between the E2 enzyme of the pyruvate dehydrogenase complex (PDC-E2), the main autoreactive antigen recognized by AMA identified in PBC, and bacterial proteins has been found in experimental studies (58). Among various pathogens investigated including *Escherichia coli* (59), *Helicobacter spp* (60), *Mycoplasma* (61), *Chlamydia* (62), and human beta retrovirus (63), *Novosphingobium aromaticivorans* had the highest homology to PDC-E2 (64,65). Despite these intriguing associations, no compelling data have

been provided to show that one individual infectious agent can reproducibly be detected in patients with PBC. Thus the model of infections as a cause of PBC is supported by little direct evidence (27).

Autoimmunity and loss of self-tolerance The significant predominance of female patients, frequent co-existence of other autoimmune diseases both within individuals and among families, and most importantly, the presence of autoantibodies to self-mitochondrial proteins have led PBC to be referred to as a "model autoimmune disease" (27,66). The predominant autoreactive antibodies in PBC are AMAs, which, with a high sensitivity and specificity, are actually diagnostic for PBC when detected in serum (67). Follow-up data from AMA-positive individuals without signs of liver disease suggest that autoantibodies appear several years before onset of PBC and have a high predictive value for developing the disease (68).

The identified targets of AMA are all members of the family of 2-oxo-acid dehydrogenase complexes (2-OADC). This includes PDC-E2, the branched chain 2-oxo-acid dehydrogenase complex (BCOADC-E2), the 2-oxo-glutaric acid dehydrogenase complex (OGDC-E2), and the dihydrolipoamide dehydrogenase binding protein (E3BP), which all localize within the inner mitochondrial matrix, catalyzing oxidative decarboxylation of keto acid substrates (69,70). The targeted E2 subunits all have a common N-terminal domain containing single or multiple attachment sites for a lipoic acid cofactor to lysine. Previous studies have demonstrated that the dominant epitopes recognized by AMA are all localized within these lipoyl domains of the target antigens (71,72).

In addition to AMAs, autoreactive CD8 and CD4 T cells to the same PDC-E2 domain have been identified both in peripheral blood and within the liver of PBC patients (73), and the same accounts for the dominant autoreactive B cells (74). CD8 T cells isolated from livers of PBC patients have been found to exert cytotoxicity against PDC-E2 pulsed autologous cells, supporting the hypothesis of a T cell response contributing to bile duct injury in PBC (75).

It remains a mystery how PDC-E2 and other epitopes localized in the inner membrane of mitochondria become targets for autoimmune injury in PBC. Substantially lower rates of CD4 CD25 high regulatory T cells, acting to prevent autoreactivity, could be an important factor in the breakdown of tolerance (76,77). Increased amounts of polyclonal IgM and hyper-responsiveness to the cytosine-phosphate-guanine dinucleotide motif (78), and enhanced natural killer cell (73,79) and monocyte responses (80), all which are found in PBC patients, also support the role of innate immunity in developing PBC. Another hypothesis is that modifications of 2-OADC by xenobiotics may alter these self-proteins to cause a breakdown of tolerance facilitating an autoimmune response (81).

Once tolerance to AMAs is lost, additional mechanisms entailed in the immune response to a ubiquitous autoantigen begin to be unraveled. These lead to specific injury of biliary epithelial cells and seem to be linked to unique processes of apoptosis (54,82). Unlike other cell types, PDC-E2 seems to remain intact in bile-duct cells after apoptosis, thus preserving its immunogenicity (83). It was found to exist within apoptotic blebs and to be accessible to AMAs and local antigen-presenting cells (84). Additionally, *in-vitro* experiments revealed an intense and specific immune response when macrophages of PBC patients were combined with apoptotic blebs on biliary epithelial cells and AMAs (85). However, recurrence of PBC after liver transplantation suggests that this scenario is not an intrinsic defect of bile-duct cells of affected individuals but is a feature of biliary epithelia in general, not seen in other epithelial cells.

2.3. Diagnosis

Increased awareness of the disease and the increasing availability of diagnostic tools, in particular serological testing, have led to a more frequent and earlier diagnosis of PBC (25). Most recently, more than half of the patients diagnosed with PBC are asymptomatic at first presentation (86,87). The diagnosis of PBC can be established in case two of the following three criteria are fulfilled: a concentration in serum of AMAs at titers of 1:40 or higher; an unexplained rise in the amount of alkaline phosphatase of at least 1.5 times the upper limit of normal for more than 24 weeks; and compatible liver histological findings, especially non-suppurative cholangitis and interlobular bile duct injury (88-90).

Serum alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), and cholesterol are commonly elevated in patients with PBC, however, the presence of AMA could be the first expression of PBC and could be found in an asymptomatic stage or in the absence of abnormal biochemical tests (89,90). To elucidate the frequency and antigen specificity of AMAs in the asymptomatic population and to identify patients with early PBC, Mattalia *et al.* (91) investigated the prevalence of AMA in a healthy population, and found that approximately 0.5% of the population was positive for AMA. Importantly, the pattern of reactivity to PDC-E2 in non-PBC individuals differed from that found in PBC patients in most of the AMA positive sera, demonstrating that AMA as a "natural" autoantibody is different from a "pathological" autoantibody in PBC patients. Mitchison *et al.* (92) evaluated and followed biochemical/histologic/clinical outcomes of AMA-positive individuals with normal liver function, which revealed 24 out of 29 patients developed biochemical evidence of cholestasis and 22 became symptomatic, confirming a high predictive value of positive AMA testing for the development of PBC during a 10-year

follow-up (68). By contrast, individuals with AMA-negative PBC diagnosed on the basis of elevated ALP and liver histologic findings comprise 5% of the PBC population and manifest a similar course compared to their seropositive counterparts (93).

The need to undergo liver biopsy in PBC is controversial, although most clinicians agree that this procedure is valuable for disease staging, particularly in clinical trials. From a diagnostic point of view, liver biopsy specimens are not required when the other two criteria are fulfilled (89,90).

2.4. Clinical features and natural history of PBC

The clinical findings and natural history of PBC differ significantly among patients, ranging from asymptomatic with slow progression to symptomatic and rapidly evolving (94,95).

Clinical findings Although non-specific, fatigue is the most common symptom of PBC, up to 80% of PBC patients complain about chronic fatigue and more than 40% suffer moderate-to-severe symptoms (96,97). No correlation with the severity of liver disease has been demonstrated, however, fatigue can be associated with decreased overall survival (98,99). The mechanism of fatigue in PBC patients remains unknown, despite many proposals including autonomic dysfunction (100), muscle impairment (101), daytime somnolence (102), and altered central nervous system excitability (103,104).

PBC is more frequently associated with pruritus than other chronic cholestatic liver diseases. During the course of the disease, 20% to 70% of patients complain of pruritus as the most distressing symptom. It develops independently of the degree of cholestasis and the stage of the disease (105).

Bone density reduction is common in patients with PBC, with osteopenia (33%) and, less frequently, osteoporosis (11%) (106,107). Contrary to this, recent reports suggested that PBC might not represent an additional risk factor for bone demineralization in women with compensated disease when supplemented with calcium and vitamin D (108). Therefore, in clinical practice, such supplementation, along with monitoring of bone density and vitamin D, is highly recommended, even in patients at an early stage (89,90).

Several autoimmune diseases could coexist with PBC in up to a third of patients, most frequently with Sjogren's syndrome and autoimmune thyroid disease. Coexistence of other autoimmune disease does not modify the course or clinical manifestation of PBC, with the exception of a reported slower progression of liver fibrosis in patients with scleroderma (109,110).

Once PBC has progressed to cirrhosis, clinical features of liver dysfunction do not differ from those seen in patients with cirrhosis due to other causes, with the exception of esophageal varices, which can

develop early in the disease course, sometimes before other signs of cirrhosis (111). The occurrence of hepatocellular carcinoma in PBC patients is similar to those with cirrhosis of other etiologies and warrants surveillance in patients at an advanced disease stage (112).

Natural history The natural history and prognosis of PBC has become notably benign with significantly decreased mortality within the last two decades (1,8,113). Although these observations could be secondary to early diagnosis (1,8) and a consequent lead-time bias (4), falling rate of liver transplantation for PBC in western countries since widespread use of UDCA suggest an actual change in the natural history of PBC (13,14).

Classically, PBC patients can progress from an asymptomatic stage to symptomatic stage with symptoms attributable to liver damage, such as itching, jaundice, esophageal varices, ascitis, and/or encephalopathy (1). The natural history of PBC has become more difficult to characterize given the rising number of asymptomatic cases which require long-term follow-up (113). Formerly, the presence of symptoms at diagnosis was an important determinant of disease progression and survival (114,115). The 10-year survival of asymptomatic patients ranged from 50 to 70%, whereas the median duration of survival for symptomatic patients ranged 5 to 8 years from the onset of symptoms (87,114-116). Additionally, asymptomatic PBC patients were shown to have shortened survival compared to a healthy population (87,116). However, in a study from the UK of a large cohort of patients followed up for 24 years, although mortality due to liver disease was greatest in symptomatic patients, overall survival was similar in individuals with and without symptoms at the time of presentation (95). It seems difficult to conclude the impact of the presence of symptoms in PBC patients at present, however, considering the prognostic relevance of the presence of symptoms is well documented, and the higher proportions of asymptomatic patients enrolled in the more recent cohort studies explain, at least, the observed improvement in the natural history of PBC since the 1980s (117).

Prediction of patients' survival with PBC has been attempted, and the Mayo model is the most well regarded, which includes five independent variables (age, total bilirubin, albumin, prothrombin time, and severity of ascitis), with amount of bilirubin in serum as the most heavily weighed (118).

2.5. Treatment of PBC

The only currently established treatment for PBC is UDCA 13-15 mg/kg a day (119). UDCA was shown to improve serum biochemical markers such as bilirubin, ALP, GGT, cholesterol, and IgM levels (120-125).

UDCA may slow down histologic progression to liver cirrhosis (124,126), improve quality of life, survival free of transplant, and overall survival (9-12,127). However the mechanisms of UDCA in chronic cholestasis remain enigmatic (128), and about a third of patients are not sufficiently controlled with UDCA monotherapy, necessitating liver transplantation or an additional therapeutic approach (2).

UDCA treatment for PBC-Natural history in the UDCA era UDCA is currently considered as the mainstay of treatment for PBC (89,90). Mechanisms of action of UDCA remain unclear, yet the hydrophilic nature of it could lead to a reduction in amounts of bile acids, and it might also regulate cellular signaling and protect against apoptosis (129,130).

The rate of progression to cirrhosis was 13% in patients with UDCA and 49% in those without UDCA after a 6-year follow-up (131). Another study revealed that the rate of progression to cirrhosis was 7% in patients with UDCA and 34% in those without UDCA after a 4-year follow-up, with 76% of UDCA-treated patients remaining in an early disease stage, as compared to 29% of placebo-treated patients (126). A combined analysis of four clinical trials including 367 patients also found significantly decreased disease progression in patients with UDCA (132). Another two also revealed improved survival without liver transplantation or reduction in the risk of death in patients with UDCA (127,133).

The risk of developing varices was 16% for UDCA-treated patients which was significantly lower than that of 58% for those receiving the placebo in a 4-year prospective observation (134). Additionally, many studies have demonstrated an improvement of biochemical and histological features with UDCA administration (120-125).

Recently four long-term trials have found improved survival in UDCA-treated patients (9-12). Corpechot *et al.* (9) reported in 262 patients who had received 13-15 mg/kg UDCA daily for a mean of 8 years that the overall survival rates were 84% and 66% at 10 and 20 years, respectively. In early-stage patients, predictions to progress to liver transplantation or death were 6% and 22% at 10 and 20 years, respectively. The survival of early-stage patients was similar to that of the control population. In contrast, the probability of death or liver transplantation was significantly increased in patients treated in late-stages. Three other studies (10-12) also reported similar results. The survival rate of patients in early stages who biochemically responded to therapy was similar to that of the control populations in these studies. "Response" here is defined as a decrease in ALP to < 40% (10), or serum bilirubin < 1 mg/dl, ALP < 3x upper limit of normal, and AST < 2x upper limit of normal (11,12). 10-year transplant-free survival of 90% in responders was reported, while it was 51% in non-responders (11).

Despite these encouraging results, the beneficial effects of UDCA on survival have been questioned repeatedly. Actually, among a number of randomized placebo-controlled studies on UDCA (121-125,135,136), none of them could find a survival benefit with UDCA, and only two studies of an extension follow-up found a positive effect on survival (137,138). Accordingly, several studies of meta-analysis based on these randomized studies concluded that UDCA has no benefit on the reduction of mortality and liver transplantation (139-141). The reported overall mortality and the rate of liver transplantation in PBC patients were both around 6% irrespective of the use of UDCA (140). However, when meta-analysis is performed with studies of a follow-up period over 2 years and with those using an effective dose of UDCA of more than 10 mg/kg/day, UDCA significantly improves quality of life and transplant-free survival, and delays histologic progression in early-stage patients (142,143). Current guidelines therefore recommend to treat PBC with UDCA using doses of 13 to 15 mg/kg/day and to start treatment early (89,90).

Considering the established autoimmunity of the disease, corticosteroids and other immunosuppressive agents have been evaluated for therapeutic use in PBC. Prednisolone in combination with UDCA was proved to improve biochemical/histologic findings (144,145), however, not only the lack of survival benefit but also serious side-effects have precluded its use except for overlapping autoimmune hepatitis disease (146,147). Other immunosuppressive agents including budesonide (148), azathioprine (149), cyclosporine (150), mycophenolate mofetil (151), or methotrexate (152), and drugs with antifibrotic properties including penicillamine (153), colchicines (154), and silymarin (155) have been investigated, however, none of these drugs was shown to provide any additional benefit, in terms of clinically relevant events, when compared to UDCA monotherapy.

Currently, about two thirds of patients treated with UDCA according to guidelines respond adequately and may have a normal life expectancy, while in the remaining one third of patients who fail to achieve a biochemical response or who are at an advanced stage at presentation, therapeutic options are extremely limited (156) and liver transplantation is necessitated as a last resort for cure (13).

3. Liver transplantation for PBC

PBC represents a major indication for liver transplantation in western countries, and to date over 6,000 liver transplants have been performed for PBC in the US and Europe (16,157). Over time, however, a notable decline in the number of liver transplantations and waiting list additions for PBC has been observed (13,14). Data from United Network for Organ Sharing (UNOS)

show that the absolute number of liver transplantations increased by a mean 249 per year between 1995 and 2006, while the absolute number of liver transplantation performed for PBC decreased steadily by a mean of 5.4 cases per year in the same period (13). This is the case in Europe where a five-fold reduction of liver transplantation for PBC has occurred from 1988 to 2006 (158). Despite the decrease in number of transplant cases among increasing numbers of PBC patients, liver transplantation still remains as a last curable option for end-stage PBC patients.

3.1. Indication and timing of liver transplantation for PBC

Indications for liver transplantation in individuals with PBC do not differ from those in patients with other liver diseases, namely decompensated cirrhosis with intractable ascites and spontaneous bacterial peritonitis, recurrent variceal bleeding, encephalopathy, or hepatocellular carcinoma (90). Christensen *et al.* (159) demonstrated that the optimal timing for liver transplantation in PBC (defined as the point when the probability of survival after transplantation is greater than the probability of survival without transplantation) is when the serum total bilirubin reaches around 10 mg/dl. It is recommended to refer to the liver transplant unit when the total bilirubin reaches 6 mg/dl, the Mayo risk score is over 7.8, and the MELD score is over 12 (90).

Treatment-resistant pruritus, severe recurrent encephalopathy, and recurrent variceal bleeding (despite preserved liver function) may also merit consideration for liver transplantation (160). In selected cases with severe pruritus that is refractory to medical treatment, liver transplantation remains the last resort (18). On the contrary, fatigue, one of the principle factors contributing to impairment of the quality of life, is not an indication for transplantation as available evidence does not support the efficacy of the procedure (161).

3.2. Survival after liver transplantation for PBC

Patients with PBC have more favorable outcomes after liver transplantation than those with viral hepatitis or alcoholic associated disease (162). An analysis of data from the ELTR in 2003 revealed a 1-, 5-, 10-year patient and graft survival of 83, 77 and 69%, and 79, 71 and 64%, respectively, among 2,959 patients (163). Kashyap *et al.* (164) reported a retrospective analysis of the UNOS database of liver transplantation for PBC patients, in which a 1-, 3-, and 5-year patient survival among living donor liver transplantation (LDLT) and deceased donor liver transplantation (DDLT) was 93, 90 and 86 %, and 90, 87 and 85%, respectively, while a 1-, 3-, and 5-year graft survival among LDLT and DDLT was 86, 81 and 77%, and 85, 83 and 81%, respectively.

A Japanese study investigating LDLT for PBC revealed 1- and 5-year survival of 80% and 75%, respectively (165). With excellent survival, recurrent disease has become a high-lightened problem in recipients who had received liver transplantation for PBC.

3.3. Recurrent PBC after liver transplantation

Recurrent PBC after liver transplantation was first reported in 1982 (166). Despite initial controversy, the recognition of recurrent PBC is now firmly established in the liver transplant community (16). Recent studies (14,167-181) of liver transplantation for PBC in individual programs (with over 40 PBC transplant cases) are summarized in Table 1. Although most studies at present have concluded that recurrent PBC has little impact on patient or graft survival following liver transplantation in the short- and medium-term, taking into account a considerable number of patients developing recurrent disease, continued longer follow-up may identify impaired long-term patient/graft survival in patients with recurrent PBC. Ongoing debates for recurrent PBC focus on defining the factors associated with recurrent PBC so that strategies for prevention and treatment can be established. Additionally, investigation of recurrent PBC after liver transplantation may also provide helpful insights into the pathophysiology of PBC in the native liver.

3.4. Diagnosis of recurrent PBC

Unlike PBC in the native liver, clinical manifestations of recurrent PBC is not specific. Pruritus and jaundice, typical disease-related symptoms in PBC are rarely encountered in recurrent PBC. Fatigue, the most common complaint in PBC, and metabolic bone disease can be multifactorial and remain nonspecific in post-transplant patients (16). Disease-related symptoms in recurrent PBC have been reported in about 10% patients in previous reports, with fatigue and pruritus being the most common complaints as in pre-transplant PBC (173,174). Yet, most studies do not address disease-related symptoms, which might represent the rarity and difficult recognition of manifestations of recurrent PBC.

Similarly, most patients with recurrent PBC have normal or clinically insignificant elevation of serum liver biochemistry tests at the time of diagnosis (169,174,182,183), unlike at the diagnosis of PBC with native liver. Serum AMA, the most important criterion for the diagnosis of PBC, is not a marker for recurrence (182,184). The persistence of serum AMA has been demonstrated in previous studies, with immediate reduction after liver transplantation and subsequent identification in postoperative serial investigations (175,185-187). There seems to be no correlation between the presence or titer of serum AMA and the development of recurrent disease (182).

Table 1. Recent studies reporting transplantation for PBC

Author	Year	Country	PBC cases (n)	Protocol biopsy	Follow-up period (yr) mean (range)	Patient survival (5-/10-year) (%)	Recurrence rate n (%)	Time to recurrence (yr)	Graft loss due to recurrence (n)
Sebagh <i>et al.</i> (167)	1998	France	69	Yes	1-10	NA	6 (9)	6.3	0
Renz <i>et al.</i> (168)	2002	US	58	Yes	5.3 ± 2.4	NA	8 (14)	NA	2
Sanchez <i>et al.</i> (169)	2003	US	156	Yes	6 (1-15)	NA	17 (13)	4.1 (1.1-7.1)	1
Levitsky <i>et al.</i> (170)	2003	US	46	No	NA	NA	7 (15)	6.5 (2.3-10)	0
Khettry <i>et al.</i> (171)	2003	US	43	No	7 (1-17)	NA	8 (19)	3.5 (0.1-14)	0
Neuberger <i>et al.</i> (14,172)	2004	UK	485	Yes	6.6	78/67	114 (23)	10 (cyclosporine)/5.2 (tacrolimus)	3
Guy <i>et al.</i> (173)	2005	US	48	No	4.2 (1-12)	NA	17 (35)	3.3 ± 2.8	1
Charatcharoenwathaya <i>et al.</i> (174)	2007	US	154	Yes	11 (1-21)	90/66	52 (34)	3.5 (0.3-18)	2
Morioka <i>et al.</i> (175)	2007	Japan	50	No	2.4 (0-10)	NA	9 (18)	1.6 (0.2-5.7)	0
Campese <i>et al.</i> (176)	2009	US	70	No	7.8 (0.3-17)	72/54	18 (26)	4.8 (0.4-13)	0
Jacob <i>et al.</i> (177,178)	2010	Germany	121	Yes	10 (0.4-19)	87/84	18 (15)	5 (3-10)	2
Montano-Loza <i>et al.</i> (179)	2010	Canada	108	No	7.3 (0.2-19)	86/76	28 (26)	5.8 (0.5-16)	NA
Manousou <i>et al.</i> (180)	2010	UK	103	Yes	9 (1-20)	NA	36 (35)	3.7 (1-17)	6
Kaneko <i>et al.</i> (181)	2011	Japan	81	No	6.2 (0.1-13)	NA	1 (1)	5.1	0

Abbreviations: NA, not available; PBC, primary biliary cirrhosis

The gold standard for the diagnosis of recurrent PBC is histologic confirmation (188). The histologic hallmark of recurrent PBC is granulomatous cholangitis or the florid duct lesion (167,170-172,183,184,186,189), which are present in approximately 60% of initial diagnostic liver biopsies (174). Less frequent inflammatory features, such as dense lymphoplasmacytic or plasma cell infiltrates within the portal tract, may correlate with subsequent disease recurrence (167,183,190). At the same time, it is important to differentiate between recurrent disease and other causes of bile duct damage in the graft, such as acute or chronic allograft rejection, ischemic injury, infection, or drug damage, though it may often be difficult or indeed impossible. The diagnostic criteria advocated by Neuberger *et al.* are presented in Table 2 (188).

3.5. Epidemiology of recurrent PBC

The reported prevalence rates range from 1-35% in recent studies (Table 1). This wide variety may be due to different diagnostic criteria, the use of protocol biopsies by transplant units, and difficulty in histologic diagnosis. The most important factor relates to the use and timing of liver biopsies in follow-up (190), meaning performing biopsies for clinical indications alone will underestimate the prevalence rate (16).

The time to recurrence also varies between studies, as shown in Table 1. The serial investigation at the same centers have reported increasing rates of recurrent disease over time indicating that more cases would be identified with a longer follow-up period (14,174,182,191). Among centers with over 100 cases of PBC transplants with long follow-up, the time to recurrence, and 10- and 15-year cumulative incidence rate were reported to range from 3.5-5.8 years, and 21-37% and 43%, respectively (14,172,174,176,178,179).

3.6. Factors associated with recurrence

As described in the previous section, there is increasing evidence for a genetic predisposition for developing PBC in native liver. Accordingly genetic predominance, especially, the effect of HLA matching between donor and recipient, has been investigated in the disease recurrence of PBC patients after liver transplantation, however, it remains controversial so far. HLA allele frequency analysis by Sanchez *et al.* (169) demonstrated that patients with recurrence did have significant allele similarities; the donor alleles A1, B57, B58, DR44, DR57 and DR58 and the recipient allele B48 were found more often in recurrent PBC. Morioka *et al.* (175) suggested that a lower number of HLA mismatches between donor and recipient was an independent risk factor for disease recurrence following LDLT. Similarly, two large studies of DDLT reported

Table 2. Diagnostic criteria for recurrent PBC

1. Liver transplant for well-described PBC
2. AMA seropositive after liver transplant
3. Liver histology with the following characteristics
 - a) Mononuclear inflammatory infiltrate
 - b) Lymphoid aggregates
 - c) Epithelioid granuloma formation
 - d) Bile duct destruction

Definite recurrent PBC: 3 of 4 portal tract lesions are observed

Probable recurrent PBC: 2 of 4 portal tract lesions are observed

Abbreviations: AMA, antimitochondrial antibody; PBC, primary biliary cirrhosis

a relationship between HLA-mismatching, particularly DR-locus mismatch, and recurrent PBC (173,192). In contrast, Jacob *et al.* (178) found that no HLA-B match had significantly more disease recurrence. However, many other studies have failed to find any relevance between HLA-mismatch and recurrent disease both in DDLT and LDLT cohorts (169,171,174,180,193).

Many reports have described that tacrolimus-based immunosuppression correlates with an increased risk of recurrent PBC and a reduced time to recurrence after liver transplantation when compared with cyclosporine (14,172,174,178,179,194-196). In contrast, recent meta-analysis by Gautam *et al.* (197), evaluating 16 studies of 1,241 patients, could not find a significant difference between cyclosporine and tacrolimus in terms of recurrence, while there was a trend toward more recurrence in patients with tacrolimus. There is no clear explanation for these findings, but the beneficial effect of cyclosporine for native PBC or recent overall less-potent immunosuppression with tacrolimus may have some impact on recurrence of PBC (16).

Other immunosuppressive agents, including steroids, azathioprine, and mycophenolate mofetil have also been investigated for association with recurrent disease. So far no study has found an association between steroid administration and recurrence (14,169,170,176). Given the recent trend of steroid tapering in conjunction with near-exclusive use of tacrolimus, discriminating for the effect of each agent on recurrent disease seems difficult in the absence of a controlled clinical trial. Recent studies, at least, validate that a tailored steroid regimen for recipients of PBC is unnecessary. Manousou *et al.* (180) recently reported that neither cyclosporine nor tacrolimus alone had any impact on recurrent PBC, while cyclosporin in combination with azathioprine resulted in the lowest rates of recurrence. Sanchez *et al.* (169) found no difference in recurrence rate between patients with mycophenolate mofetil and those with azathioprine when used in conjunction with cyclosporine and steroids. Yet, no other study has found a correlation between recurrent PBC and azathioprine/mycophenolate mofetil (170-172,198).

Other donor and recipient factors have been scarcely investigated. Among those, an older age

of both recipient and donor could be a debate in the future, considering the increasing number of PBC patients receiving liver transplants at older ages and the increasing use of older deceased donor livers, although the available studies at present are conflicting (14,174). Few studies investigated graft quality, suggesting that poor qualities of graft such as ischemic time (14,174) and graft histology (fibrosis and steatosis) (177) were risk factors for disease recurrence.

3.7. Disease progression and treatment

As shown in Table 1, graft or patient loss due to progression of recurrent disease is extremely rare, representing no effect on long-term outcomes in all studies. Two leading institutes of liver transplantation, the Mayo and Birmingham groups, have reported 3 out of 485 and 2 out of 154 cases required retransplantation, respectively (172,174). The Mayo group also reported the result of sequential protocol biopsies of definitely recurrent PBC, revealing that periportal fibrosis was present in 8 of 17 (47%) with a mean follow-up of 5.9 years and that 2 of them further developed septal fibrosis during an additional 3 years of follow-up (182). The Birmingham group recently reported that the rate of graft loss due to recurrent disease was 5.4% among 541 liver transplants for PBC with a median time from the diagnosis of recurrence to graft loss of 7.8 years, which was significantly lower than those of other etiologies (199). With a longer follow-up, recurrence of disease could have an impact on patient and graft survival.

To date no standard guideline exists for treatment of recurrent PBC. The modification of immunosuppression has not been formally reported as an interventional study. Based on the aforementioned possible beneficial effect of UDCA and its widespread use in PBC patients, and given nearly all recurrent PBC is diagnosed at an early stage, many authors have pointed out the potential role of UDCA for recurrent PBC after liver transplantation (14,169,171,174,178). However, in addition to the limitation of the small number of recurrent disease cases, normal or near normal serum liver biochemistries at initial diagnosis of most recurrent patients makes it challenging to assess the efficacy of UDCA. A recent report from the Mayo group found that 52% of patients with recurrent PBC treated with UDCA showed normalization of liver biochemistries, while the liver biochemistry normalization rate was 22% in untreated patients. However there was no significant difference in histologic progression between those with and without UDCA. Moreover, no long-term survival benefit was observed in patients treated with UDCA in the study (174). Whether UDCA treatment has an impact on the natural history of recurrent PBC needs to be further investigated in controlled trials with extended follow-up.

4. Conclusion

The clinical course of PBC has become notably benign with the use of UDCA at an early stage and the establishment of liver transplantation for end-stage disease. In addition to investigations for pathogenesis of this entity and new treatment for those without response to UDCA therapy, the following issues need randomized controlled trials; the actual survival benefit of UDCA in the natural course of PBC, and the impact of cyclosporine and UDCA for those with recurrent disease after liver transplantation.

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