Recurrence of autoimmune liver diseases after liver transplantation: clinical aspects

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Abstract Autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis are autoimmune liver diseases characterized by progressive immune-mediated inflammation leading to the destruction of the hepatocytes and the biliary epithelial cells, and eventually to cirrhosis and liver failure. The ultimate treatment of these diseases, upon the establishment of end-stage liver disease, includes liver transplantation (LT). Recurrence of autoimmune liver diseases after LT is an entity increasingly recognized in the last few decades. The mechanisms driving recurrence remain poorly understood. The accurate diagnosis of the recurrence and the proper management of the affected patients remains a clinical challenge. This review discusses clinical aspects related to the recurrence of autoimmune liver diseases after LT. The main goals of this review are to discuss the reasons explaining the variability of the incidence rates of recurrent autoimmune disease and the outcome and risk factors for recurrent disease. We discuss in detail the diagnostic criteria and the treatment options of these disorders.

Keywords Autoimmune liver disease · Liver transplantation · Recurrence · Autoimmune hepatitis · Primary biliary cirrhosis · Primary sclerosing cholangitis

Introduction

Recurrence of the primary disease after liver transplantation (LT) has become a major focus for clinicians and researchers. The ultimate goal of the management of these patients is first, to tailor immunosuppression and second, to avoid graft dysfunction and recurrence of the original disease in order to maximize graft survival. Though disease recurrence can be expected to a certain degree for diseases such as viral hepatitides, for others it can be largely unpredictable. This review discusses clinical aspects related to the recurrence of autoimmune liver diseases.

Incidence rates of recurrent autoimmune disease

Recurrence rates of autoimmune disease after LT are variable in different series, which is partly explained by several differences: (a) methods for the assessment of recurrent disease, (b) criteria used to establish the diagnosis of recurrent disease, (c) use of immunosuppressive regimen and (d) duration of follow-up. It should also be noted that reported rates of recurrence depend on whether routine protocol biopsies are performed, since recurrence disease may be present without abnormal liver function tests.
Regarding autoimmune hepatitis (AIH), previous studies have reported that recurrent AIH (rAIH) ranges from 20 to 42 % after LT [1, 2], while a recent review [3] estimated a prevalence rate of 23 % after a median of 26.4 months after LT and a weighted recurrence rate was calculated to be 22 %. Recurrence of PSC (rPSC) ranges from 9 to 47 % [4], but in the above-mentioned literature review [3], it was estimated that 161 (17 %) of 940 patients had rPSC, and the weighted recurrence rate was calculated as 11 %. Finally, recurrent PBC (rPBC) has been reported to be approximately 10–35 % at 5 years [5], but its incidence increases with time and in recipients with living donor LT, compared to recipients of cadaveric donor LT [6]. In a recent review [3], an incidence of 16 % was found after a median post-LT follow-up of 69 months and the weighted recurrence rate was 18 % (Table 1).

Outcome and risk factors for recurrent disease

Primary biliary cirrhosis

The consequences of rPBC appear to be relatively small, since the course of the disease is often, but not always, slow. Generally, rPBC is not considered a major clinical problem [7]. As a result, even in studies with long follow-up, there was no difference in graft survival between recipients with and those without rPBC. For example, in a series of 485 PBC transplant recipients, recurrent PBC was the cause of re-LT in only 3 (0.6 %) patients [8] and in a recent study including 52 patients with rPBC and extended follow-up after LT to 20 years, it was found that rPBC had no impact in patient or graft survival. Although patients with rPBC may have developed more advanced fibrosis, compared to patients transplanted for other liver diseases, it is unclear whether this is clinically relevant. Interestingly, in another cohort, none of 17 patients with rPBC developed cirrhosis after a mean follow-up of 4.7 years [9]. Risk factors for rPBC have not elucidated, but advanced donor age, recipients’ characteristics and peri-operative factors have been implicated [10]. Regarding immunosuppression, the data in the literature remains controversial, but some evidence suggests that cyclosporine-, compared to tacrolimus-based regimen, is associated with reduced rate of rPBC and slower progression [8, 11, 12]. These reports did not control for the use of azathioprine often combined with cyclosporine and used less often with tacrolimus. In addition, a recent review was not able to confirm that either cyclosporine- or tacrolimus-based immunosuppression were different with respect to long-term survival for PBC patients who had LT [3]. Interestingly, some reports have suggested that steroids may prevent rPBC, but their long-term use is associated with higher rates of hypertension, diabetes mellitus and dyslipidemia.

Primary sclerosing cholangitis

Similarly to PBC, long-term (more than 5 years) patient survival seems to be similar in patients with or without rPSC [13, 14]. However, patients with rPSC underwent more frequently to re-LT due to recurrent disease. Indeed, rPSC is second only to recurrent HCV in terms of recurrent disease after LT. In addition, PSC graft survival is reduced compared to PBC, which may be related to the slower progression of PBC, compared with PSC. Interestingly, Rowe et al. [15] found that graft loss to be highest in rPSC with a hazard ratio of 6.0 compared to those with rPBC in a large cohort of patients surviving more than 90 days after LT. Thus, longer follow-up beyond 10 years may be required to assess the impact of rPSC on survival. Recurrence of PSC has been associated with many factors, such as steroid-resistant rejection, OKT3 use, preservation injury, ABO incompatibility, cytomegalovirus infection, male recipient gender, donor–recipient gender mismatch [16–20] and absence of ulcerative colitis. However, an important issue is the difference in exclusion/inclusion criteria and methods of rPSC diagnosis, which may be the reason for the discrepancies among studies regarding the incidence and the risk factors associated with rPSC [3]. Interestingly, the absence of UC after LT (due to pre-LT colectomy or not) has been found to be an important factor preventing rPSC. In addition, a recent study showed that the presence of severe or de novo UC after LT is a risk

| Table 1 Diagnostic criteria for recurrent primary biliary cirrhosis (PBC) after liver transplantation (LT) |
|---------------------------------------------------------------|
| Diagnostic criteria for recurrent PBC                           |
| LT performed for PBC                                          |
| Persistence of AMA or anti-M2 antibody                        |
| Characteristic portal triad lesions on a liver biopsy \*        |
| - Epithelioid granulomas                                      |
| - Mononuclear inflammatory infiltrate                         |
| - Lymphoid aggregates                                         |
| - Bile duct damage                                            |
| Absence of other pathology/disorders, including:               |
| - Acute and chronic rejection                                 |
| - Graft versus host disease                                   |
| - Biliary obstruction                                         |
| - Vascular abnormalities                                      |
| - Cholangitis and other infections                            |
| - Viral hepatitis                                              |
| - Drug toxicity                                               |

\* Three of the four portal tract lesions need to be present, and at least three portal fields
factor for rPSC [14]. This explains the finding that maintenance steroids (>3 months) (which was the only independent factor for rPSC) was given for activity of UC [14]. These findings give support to the hypotheses that UC and PSC have common pathogenesis [21].

Autoimmune hepatitis

The course of rAIH has not been elucidated. Although rAIH appears to follow a protracted course with reasonable long-term survival [22], it may be a significant cause of graft loss [15]. These findings have led many centres to suggest long-term immunosuppression with prednisolone at a relatively low dose (about 5–10 mg/day) for at least 1 year post-LT [23]. However, a recent study has suggested that early steroid withdrawal does not influence the incidence of rAIH, and most patients with rAIH can be managed without re-LT [24]. No consistent risk factors for rAIH have been identified, but there are reports that high-grade inflammation in the native liver before LT [25] and HLA-DR3 haplotype are independently associated with higher rate of recurrence [26]. The role of immunosuppression is still controversial, but a recent systematic review by Gautam et al. found no difference in recurrence rates between recipients on tacrolimus or cyclosporine-based regimen [22, 27].

Diagnosis of recurrent disease

Clinical and serological features

The diagnosis of recurrent autoimmune disease cannot be based on the same criteria as those in the pre-LT setting. For example, it may not reasonable to apply the same scoring system to a LT recipient with suspected recurrent disease, who is under immunosuppression, since many other transplant-related causes may be responsible for the graft dysfunction. On the other hand, the diagnosis of recurrent disease should be based on a combination of biochemical, serological and histological (or radiological) findings. However, abnormal liver tests, detection of auto-antibodies and high levels of serum immunoglobulins (IGs) may follow histological changes [28–30]. For example, it is estimated that only half of the patients with rPBC will have abnormal liver tests [9] and the latter may remain normal several years after histological diagnosis of recurrence disease. In addition, auto-antibodies and IGs levels are not useful to establish the diagnosis of recurrence liver disease [2, 31]. This is true not only for antimitochondrial antibodies (AMA) in rPBC, but also for other auto-antibodies in patients transplanted for AIH [30], since the latter have been detected in patients with rejection and in those transplanted for causes other than AIH [30, 32–34].

Primary biliary cirrhosis

Recurrent PBC after LT was first reported in 1982 [35]. Although there was some initial controversy, recurrence of PBC after LT is now well recognized and its diagnosis is based on well-accepted criteria (Table 2) [36]. The diagnosis of rPBC should be suspected in patients transplanted for PBC and who develop a cholestatic pattern of abnormal hepatic tests or in the presence of typical histopathologic findings during post-LT surveillance. However, histological features of rPBC are often present without abnormal biochemical indices. Thus, a liver biopsy performed only when symptoms or abnormal serum liver tests are present underestimates the rate of rPBC. Thus, many centres perform protocol liver biopsy in order to identify earlier, the patients with rPBC. AMA and anti-M2 are not reliable markers for the presence of rPBC, as they often persist or may only have a transient fall with reappearance after LT without recurrence of PBC. Presumably, they reflect the persistence of the basic abnormality that is associated with development of the disease [28–30, 37]. The gold standard for diagnosing rPBC is the liver biopsy, demonstrating the characteristic histologic features with granulomatous bile duct destruction with or without plasma cell infiltrate. However, it is important to exclude other processes that can lead to graft dysfunction with similar histologic findings, such as acute or chronic rejection.

Primary sclerosing cholangitis

The first case report suggesting disease recurrence in PSC patients after LT was published in 1988 [38]. The diagnosis

| Table 2 | Diagnostic criteria for recurrent primary sclerosing cholangitis (PSC) after liver transplantation (LT) |
| --- | --- |
| Diagnostic criteria for recurrent PSC | |
| Liver transplantation for PSC | |
| Cholangiography showing non-anastomotic biliary strictures of the intrahepatic and/or extrahepatic biliary system, with irregularities more than 90 days after LT | |
| Liver biopsy specimens showing fibrous cholangitis and/or fibroobliterative lesions with or without ductopenia | |
| Absence of other pathology/disorders, including: | |
| Recurrent biliary infection | |
| Hepatic artery stenosis or thrombosis | |
| Chronic rejection | |
| Donor/recipient ABO incompatibility | |
| Non-anastomotic stricture developed during the first 90 days after LT | |
of rPSC is based on clinical, laboratory, histological, and, mainly, cholangiographic findings, but none of these are specific for rPSC. In addition, a helpful diagnostic serum marker in the pre-LT setting, anti-pANCA is not useful post-LT [39]. The diagnosis is complicated by the fact that other potential causes after LT leading to bile duct lesions suggesting PSC have to be excluded, such as recurrent biliary infection, hepatic artery stenosis or thrombosis, chronic rejection, donor/recipient ABO incompatibility and ischemic cholangiopathy and/or non-anastomotic strictures developed during the first 90 days after LT, which may mimic PSC in the post-LT setting [39–41]. Day 90 has been chosen in an attempt to eliminate cases of ischemic type biliary stricture related to reperfusion or preservation injury during surgery or quality of the donor graft particularly form non-heart beating donors, which typically develop within that time period [42]. Indeed, rPSC is considered to be a diagnosis of exclusion [13, 43] and strict cholangiographic and/or histological criteria diagnostic of rPSC have been adopted (Table 3) [42]. However, some studies have based the diagnosis of rPSC only on histological findings [44], but it is known that liver biopsy is inaccurate for the diagnosis of PSC due to sampling problems, while other causes, such as ABO incompatibility between donor and recipient and hepatic arterial occlusion, lead to histological lesions that can mimic rPSC. Other studies have been mainly based on radiological demonstration of rPSC with the presence of multiple non-anastomotic strictures seen by magnetic resonance imaging or percutaneous or retrograde cholangiography [45, 46], without considering the fact that ischaemic biliary complications are usually seen up to 6 months post-LT, in contrast with recurrent PSC, which is usually diagnosed more than 12 months after LT. Thus, because of the lack of a diagnostic gold standard, the diagnosis of rPSC after LT remains difficult, and well-defined cholangiographic and histological criteria are mandatory [3, 40, 42].

### Autoimmune hepatitis

The diagnosis of rAIH is based on increased serum transaminases, and serum IgG and importantly on appropriate histology showing destruction of liver parenchyma, significant plasma cell infiltration and varying degrees of fibrosis [2]. Alternative diagnoses, such as hepatitis B and C, and chronic and acute rejection, should be considered before AIH recurrence is diagnosed (Table 4) [22, 47].

### Histological features of recurrence

Histological findings are considered very important, particularly in establishing early the diagnosis of recurrent AIH and PBC. However, the diagnostic criteria for AIH and PBC in the native liver cannot be applied to the liver allograft due to the variable effects of immunosuppression. In addition, there may be histological similarities between recurrent disease and other graft complications, particularly acute and chronic rejection. In rAIH, histological features of a plasma cell-rich mononuclear cell portal infiltrate with interface hepatitis are helpful [48, 49], while the presence of acute lobular hepatitis appears to occur more frequently in rAIH. However, these histological findings should be differentiated from other causes, such as viral infection, de novo AIH or late cellular rejection with AIH features [48, 50, 51].

In both PBC and PSC, the classical bile duct lesions are not always seen in liver allograft biopsies. The diagnosis of recurrent PBC or PSC may be made on the basis of compatible histological findings, such as bile duct loss and features of chronic cholestasis. In PBC, the characteristic portal tract lesions include mononuclear inflammatory infiltrate, formation of lymphoid aggregates, epithelioid granulomas and bile duct damage, but it is important to examine a sufficient number of portal tracts.

### Table 3 Criteria for the diagnosis of recurrent autoimmune hepatitis (AIH)

| Diagnostic criteria for recurrent Autoimmune Hepatitis (AIH) |
|-------------------------------------------------------------|
| Liver transplantation for AIH                                |
| Serological findings including                              |
| Sustained rise in serum aminotransferase activity (×2 normal) |
| Auto-antibodies in significant titre                        |
| Elevated serum immunoglobulins                              |
| Diagnostic or compatible liver histology (e.g. plasma cell-rich mononuclear cell portal infiltrate with interface hepatitis) |
| Absence of other pathology/disorders (e.g. HCV, rejection)   |

### Table 4 Characteristics of recurrent autoimmune diseases after liver transplantation

|                | PBC  | PSC  | AIH  |
|----------------|------|------|------|
| Recurrence rate| 10–35 % | 9–47 % | 20–42 % |
| Outcome        | No effect | Moderate effect | Mild effect |
| Risk factors   | Advanced donor age, recipient's factors | Steroid-resistant rejection, OKT3 use, cytomegalovirus infection, male recipient gender, intact colon |
|                | Tacrolimus | High-grade inflammation in the native liver, HLA-DR3 haplotype |
Treatment

Although no standard approach exists for the treatment of rPBC, most centres offer patients ursodiol (UDCA) 10–15 mg/kg/day, as recommended in the pre-LT setting, because of its favourable side-effect profile and efficacy to improve liver biochemistries. In addition, UDCA could delay histologic progression, but its influence on the natural history of recurrent disease requires further study with randomized controlled trials [52]. For example, in one study, 3 (43 %) of 7 patients treated with UDCA for rPBC, had improvement in liver biochemical tests, while in another study, 13 (75 %) of 17 patients with rPBC treated with UDCA showed a marked decrease in serum alkaline phosphatase. However, it is unknown whether the biochemical improvement correlated with a histologic improvement [5], and there have been no prospective, controlled trial. Indeed, the precise benefit of UDCA in this setting remains unknown. On the other hand, since the incidence of colon cancer increases after LT, similarly to PSC, UDCA may reduce the risk of dysplasia and thus colon cancer. The benefit of using UDCA in combination with corticosteroids (such as budesonide, which has an 90 % first-pass metabolism by the liver) has not elucidated in the post-LT setting [53]. Although optimal immunosuppression to prevent PBC recurrence remains controversial, it has been reported that recurrence of PBC in patients receiving tacrolimus is more rapid than with cyclosporine, but the use of azathioprine was not controlled in this analysis. Switching to alternative regimes (e.g. those based on azathioprine, mycophenolate or cyclosporine) may be an option if recurrence appears to progress rapidly.

In the pre-LT setting, no specific treatment has been shown to prevent or slow progression of PSC. High dose of UDCA (15–20 mg/kg/day) may be detrimental [54]. Particularly, UDCA might benefit more those patients with PSC and UC by reducing the risk of dysplasia leading to colon adenoma and carcinoma. Based on these data and the safety of UDCA, UDCA is often used in rPSC, while the choice of immunosuppression does not seem to have any influence on recurrence.

In rAIH, the general approach is similar to that of AIH pre-LT, i.e. to increase corticosteroids up to 20 mg/day (with or without azathioprine) and in non-responders switching from a cyclosporine to tacrolimus-based regimen[55]. The addition of mycophenolate 2 g/day had been effective in some non-responders. The calcineurin inhibitors (CNIs) and mycophenolate have been used to treat AIH in the native liver, and may be effective in the graft. Treatment should be guided by the liver tests, levels of IgG, auto-antibodies and liver histology. However, not all patients respond to enhanced immunosuppression. Eventually, re-LT may be required in some patients. Transplantation centres commonly maintain AIH patients on prednisone and/or higher dose immunosuppression than non-AIH patients after LT in order to reduce rejection and recurrence rates, but the usefulness of this approach requires further evaluation.

Conflict of interest None.

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