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REVIEW

Autoimmune liver diseases and recurrence after orthotopic liver transplantation: what have we learned so far?

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Summary

Primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH) may all recur after liver transplant. Diagnosis of rPBC is defined by histology; rAIH by serology, biochemistry and histology; rPSC by histology and/or imaging of the biliary tree and exclusion of other causes of nonanastomotic biliary strictures. Criteria for recurrent disease (RD) may differ from those used in similar disease in the native liver: frequent use of immunosuppressive therapy changes the pattern and natural history of RD and can co-exist with other transplant-related causes of graft damage. RD may occur in the presence of normal liver tests; the reported incidence will depend on the way in which diagnostic tests (especially protocol biopsies) are applied. The risk of RD increases with time, but does not correlate with the rate of graft loss. Treatment is largely unproven: ursodeoxycholic acid will improve serology and may slow progression of rPSC and rPBC; introduction or increased dose of corticosteroids may reduce progression of rAIH. Risk factors for rPBC include use of tacrolimus compared with cyclosporine; for rPSC include absence of colon peri-transplantation and for rAIH possible associations with some HLA haplotypes have been suggested.

Introduction

Liver transplantation remains a well-accepted treatment modality for end-stage liver disease with most patients returning to a lengthy and excellent quality of life. Outcomes are improving and, as the early mortality has been dramatically reduced, the clinical focus of attention has shifted to long-term outcomes. Amongst the many factors affecting long-term graft survival, recurrent disease is the most commonly recognized cause of late graft dysfunction and graft failure [1]. Although recurrent infection with the Hepatitis C virus (HCV) has the most severe impact on graft survival, recurrence of autoimmune disease is also important and can result in graft loss, which may be preventable with appropriate treatment. Furthermore, understanding factors that affect recurrence may provide insight into the mechanisms of autoimmune disease in the native liver.

Incidence of recurrent disease

Histological evidence of recurrent primary biliary cirrhosis (PBC) in the liver allograft was first reported in 1982 and, although greeted with some scepticism, has now become accepted [2]. Shortly after, case reports of recurrent autoimmune hepatitis (AIH) (in 1984) [3] and primary sclerosing cholangitis (PSC) [4] were published and these isolated case reports were followed by larger series [1,5–7]. Incidence rates are variable in different series, which have drawn varying conclusions (Table 1); this variation can be explained, at least in part, by a number of factors – these include different methods for

Table 1. Overview of published scientific data on recurrent autoimmune liver disease.

	AIH	PSC	PBC
Recurrence rate	22%	11–37%	18%
Graft loss from recurrent disease	++	+++	+
Risk factors	HLA-DR3 pos recipient, severe necro-inflammation in native liver	ACR, prolonged use steroids	Unknown, possible use of TAC
Pathogenesis	Type 2: cytochrome P450D6 antigen, type 1 unknown	Unknown	Unknown
Histology	Plasma cell-rich inflammation in ortal tracts and the liver parenchyma, interface hepatitis, confluent/bridging necrosis (in more severe cases)	Fibrous cholangitis with bile duct obliteration, ductopenia, secondary features of chronic cholestasis	Granulomatous bile duct destruction, plasma cell rich portal inflammatory infiltrate, ductopenia, secondary features of chronic cholestasis
Possible risk factors for recurrence	Lack of corticosteroids	Intact colon	Use of TAC rather than cyclosporine
Possible treatment	Add/increase corticosteroids	UDCA	UDCA

ACR, acute cellular rejection; TAC, tacrolimus; UDCA, ursodeoxycholic acid.

the assessment of recurrent disease (for example whether protocol or event-driven biopsies are undertaken), inconsistent criteria to diagnose recurrent autoimmune disease, changes in immunosuppression and duration of follow up.

Over 15 publications [8–14] focussing on incidence in recurrent AIH have been published. After analysing all available data, Gautam *et al.* [6] reported a calculated prevalence rate of 3% and weighted recurrence rate 22%. In PBC, a similar number of original studies [15–21] have reported recurrence with calculated prevalence and recurrence rates of 13% and 18%. In PSC, the calculated prevalence is similar to the recurrence rates approximately 10% as reported in 15 published articles [22–29].

Clinical and serological features

Criteria for the diagnosis of recurrent autoimmune disease in the allograft may not be the same as those developed for use in the native liver (Table 2). For example, the International Autoimmune Hepatitis Group criteria [30] were developed primarily for research purposes, to ensure that all studies in patients with AIH used similar cohorts of patients. It may not be appropriate to apply the same scoring system to the liver transplant patient, who will already be receiving immunosuppression, will probably have a graft with nonidentical HLA and other antigens, and may have a number of transplant-related causes for graft damage, that do not occur in the native liver.

Table 2. Criteria for the diagnosis of recurrent AIH, PSC and PBC.

Recurrent autoimmune hepatitis (AIH)
Liver transplant for AIH
Auto-antibodies in significant titre
Sustained rise in serum aminotransferase activity (>twice normal)
Elevated serum immunoglobulins
Diagnostic or compatible liver histology (see Table 1)
Corticosteroid dependency
Exclusion of other causes of graft dysfunction (e.g. rejection, HCV infection)
Recurrent primary sclerosing cholangitis (PSC)
Liver transplant for PSC
Multiple nonanastomotic biliary strictures
Exclusion of other causes (including rejection, infection, ischaemia)
Diagnostic or compatible liver histology (see Table 1)
Recurrent primary biliary cirrhosis (PBC)
Liver transplant for PBC
Diagnostic or compatible liver histology (see Table 1)

Deterioration of liver enzymes after transplant raises the suspicion of recurrence and will usually lead to further investigations. However, histological (or radiological) features of disease recurrence may be seen in the presence of normal liver tests [31,32].

Serology is of limited help in making the diagnosis of recurrent disease. In PBC, titres of antimitochondrial antibodies (AMA), thought to be diagnostic and possibly pathognomonic in the native liver, may show a transient fall and then return to or exceed levels seen pretransplan-

tation irrespective of histological features of PBC in the graft [15,33]. Serum immunoglobulins (Igs) (in particular IgM) may be elevated, but have not been correlated with recurrence [34]. Other clinical factors, such as development of associated symptoms of PBC (such as itching or lethargy) or associated diseases (such as thyroid disease or sicca syndrome) are not helpful establishing the exact diagnosis [18].

In AIH, criteria for the diagnosis of recurrent disease have been proposed by Manns *et al.* [35] (Table 2). Individually, none of the features is specific for recurrent AIH and the diagnosis should therefore be based on a combination of serological, biochemical and histological findings. The presence of auto-antibodies and increased Igs may be preceded by histological changes [9]; this suggests that protocol biopsies may be indicated in those grafted for AIH. Conclusions of published articles concerning auto-antibodies are variable, but in general, similar to those seen in PBC, antibodies persist but at a lower level than before transplant [32,36]. However, the presence of auto-antibodies is not specific to recurrent autoimmune disease as several reports have demonstrated the existence of auto-antibodies *de novo* in patients with rejection [37,38] and in those transplanted for other causes than AIH [39,40].

Nonorgan-specific auto-antibodies (such as anti-nuclear and anti-actin) are seen not infrequently after transplantation and their significance remains uncertain. Our own studies have suggested that the combination of auto-antibodies and chronic hepatitis in the allograft may be indicative of a subgroup of those with chronic hepatitis who will progress to a cirrhosis [41]. However, these conclusions are tentative and the significance of chronic hepatitis and its possible association with rejection, remains beyond the scope of this review.

For recurrent PSC, the diagnosis can be made either by the classical histological features of peri-ductal fibrosis (see below) or by radiological demonstration of multiple nonanastomotic strictures. Most liver allograft recipients, grafted for PSC, will have a Roux loop so the diagnosis of recurrent disease must be made on imaging the biliary tree, either by magnetic resonance imaging or percutaneous cholangiography. The former is used more commonly but there are few data on the sensitivity and specificity. The greatest problem lies in the differentiation between recurrent PSC and secondary causes of sclerosing cholangitis. The latter usually have an ischaemic basis, for which there are several possible causes, including ischaemia, rejection and infection [42,43]. Ischaemic biliary complications are typically seen in between 2 and 6 months after transplantation, in contrast with recurrent PSC, which is usually diagnosed more than 12 months post-transplant [23].

Histological features of recurrence

Because of the low sensitivity and specificity of auto-antibodies for disease recurrence, considerable emphasis has been placed on histological findings in establishing the diagnosis of recurrent AIH and PBC. However, as discussed above, there are problems in applying conventional diagnostic criteria for AIH and PBC in the native liver to the liver allograft. These include the variable effects of immunosuppression in modifying histological features and interactions with other causes of graft dysfunction, which may include common targets for immune-mediated damage. Furthermore, there may be histological similarities between recurrent disease and other graft complications, particularly acute and chronic rejection.

Histological features of a plasma cell-rich mononuclear cell portal infiltrate with interface hepatitis are still helpful in the diagnosis of recurrent AIH [9,12,44,45]. Histological features of recurrent AIH may differ from those of AIH in the native liver – for instance, presentation with features of acute lobular hepatitis appears to occur more frequently in recurrent AIH [8,46]. The histological finding of a predominantly mononuclear portal inflammatory infiltrate compatible with a diagnosis of chronic autoimmune hepatitis should not be regarded by itself as diagnostic of recurrent AIH, as there are a number of other possible causes of chronic hepatitis in the liver allograft. These include viral infection (recurrent or acquired with known or unidentified viral agents), *de novo* AIH or late cellular rejection with autoimmune/hepatitic features [41,47–51]. Likewise zone 3 necro-inflammatory lesions (central perivenulitis) have been recognized to occur as manifestation of recurrent AIH [8,46], but can also be seen in late cellular rejection [52] and in *de novo* AIH [53,54]. However, distinction between these entities is more of theoretical than practical importance as all suggest that increased immunosuppression is indicated.

As with PBC and PSC in the native liver, classical bile duct lesions are rarely seen in liver allograft biopsies. The diagnosis of recurrent PBC or PSC may thus be made on the basis of compatible histological findings such as bile duct loss and features of chronic cholestasis – these include ductular reaction and periportal fibrosis and changes of cholate stasis including periportal deposits of copper-associated protein.

De novo AIH

First described in children in 1998 [40], *de novo* AIH occurs in patients transplanted for indications other than AIH, in general nonimmune mediated diseases. It resembles AIH in the native liver with elevated transaminases and Igs, organ nonspecific auto-antibodies and

histological features of portal inflammation with interface hepatitis. Since then, many authors have reported *de novo* AIH [39,55–63]. A higher prevalence has been observed in children compared with adults, possibly reflecting immunosuppressive drugs interfering with normal T-cell maturation in the immature immune system [64]. Some cases may present histologically with isolated or predominant features of central perivenulitis before subsequently developing typical portal tract changes [58,60].

In recent studies, a number of patients treated with pegylated-interferon for chronic HCV infection have been described who developed graft dysfunction with serological and histological features suggestive of *de novo* AIH [65–67]. As interferon therapy has also been implicated as a risk factor for late rejection in HCV-positive individuals [68,69], these observations raise further questions regarding the relationship between rejection and so-called *de novo* AIH.

The pathogenesis of *de novo* AIH has not yet been clarified. Salcedo *et al.* [58] demonstrated the occurrence of concomitant viral infection (cytomegalovirus, Epstein Barr virus, Parvovirus or HCV) in all patients, thereby suggesting molecular mimicry may be a possible pathophysiological mechanism. Viral infections can also precipitate autoimmunity through polyclonal stimulation, enhancement and induction of membrane expression of MHC class I and II antigens and interference with immunoregulatory cells. In animal models, the use of calcineurin inhibitors leads to autoimmunity through the interference with maturity of T-cells and function of regulatory T-cells [70–73]. In HCV, treatment with pegylated interferon is known to induce autoimmunity [74] through its immunomodulatory effect and molecular mimicry by the virus itself.

As antibodies are directed against graft antigens rather than self antigens (i.e. an alloimmune response) it has been suggested that so-called *de novo* AIH may represent a form of late cellular rejection. This suggestion is supported by the finding of auto-antibodies arising transiently *de novo* following in association with otherwise typical episodes of acute rejection [37,38] and by the observation that acute rejection is a risk factor for the development of *de novo* AIH [61,75]. Auto-antibodies have also been seen in children developing chronic rejection with features of central perivenulitis [76]. In support of the suggestion that *de novo* AIH may represent a form of rejection, recent reports have shown that antibodies to Glutathione S-Transferase T1 (GSST1) develop in 80% of GSST1-negative recipients of GSST1-positive donors, including in all patients who developed *de novo* AIH [59,60,63,77].

Thus, it may be that there is an immune response to this recipient antigen, which is present in 20% of Caucasians [60,78]. HLA-constitution susceptible for the development of AIH (HLA-DR3 and 4) in the donor might be a risk factor [40,57,58].

Treatment is similar to that commonly used in classical AIH usually resulting in excellent graft- and patient survival [58]. However, occasional cases have progressed to graft failure.

Treatment

In recurrent PBC, no therapeutic options have been shown to halt progression of disease. Most centres offer their patients ursodeoxycholic acid (UDCA) 10–15 mg/kg/day, as recommended in native livers. While liver tests improve on this agent, there is no evidence as yet to show that there is any alteration in the natural history of recurrent disease [79]. There have been no prospective, controlled trials and, indeed, practical constraints make it very difficult to conduct such a study. Recurrence of PBC in patients receiving tacrolimus is reported to be more rapid than with cyclosporine. So switching to alternative regimes such as those based on mycophenolate or cyclosporine may be advisable although there is no evidence to date that such an approach will have any significant impact on the course of disease.

In recurrent PSC, no specific treatment has been shown to prevent or slow progression, although high dose UDCA (15–20 mg/kg/day) will be prescribed in the majority. Those with ulcerative colitis will benefit from UDCA in reducing the risk of colon adenoma and carcinoma [80]. Choice of immunosuppression has no influence on recurrence [26]. Although, as indicated below, there is some evidence that recurrent PSC is not found in those with no colon at the time of transplantation, there is no reason to undertake prophylactic colectomy in the absence of other indications.

In recurrent AIH, the general approach is to increase corticosteroids: some centres use prednisone up to 20 mg/day and in nonresponders (as evidenced by either serology or histology) switching from cyclosporine to tacrolimus-based regimes [81]. The addition of mycophenolate 2 g/day had been effective in some nonresponders. Treatment should be guided by the liver tests, levels of Igs and auto-antibodies and liver histology. However, not all patients respond to enhanced immunosuppression. Eventually, re-grafting may be required in some patients. In such cases, the use of higher doses of corticosteroids may be helpful but there are few data to confirm whether this is beneficial in practice.

Effect on recurrent disease on graft function and survival

Graft function and survival have been increased by improvements in surgical and anaesthetic approach as well as immunosuppressive medication and the allocation

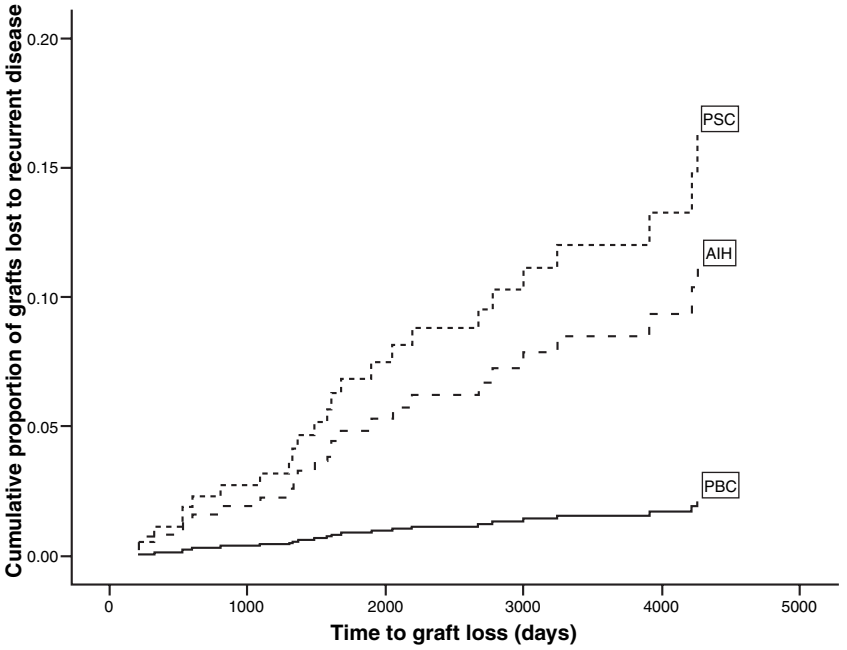

Figure 1 Proportion of all grafts lost after 90 postoperative days to disease recurrence by aetiology of liver disease (courtesy of Dr Ian Rowe).

and matching of liver recipients and donors. Although in specific nonmalignant hepatic conditions, graft failure, once recurrence occurred, has been significant. The reported recurrence rates vary because of the variation in the use of diagnostic criteria for disease recurrence. In particular, it should be stressed that the reported rates of recurrence will heavily depend on whether protocol biopsies are routinely performed.

Rowe *et al.* [1] evaluated the rate and impact of graft loss in a large cohort of patients surviving more than 90 days after transplant in a large-volume transplant centre. They found graft loss to be the highest in recurrent PSC with a hazard ratio of 6.0 compared to those with recurrent PBC (Fig. 1). Our own experience, based on relatively small numbers, suggests that the natural history of recurrent disease in the graft is not necessarily the same as in the re-graft, even when the indication for re-graft is recurrent disease.

Does recurrence shed light on disease pathogenesis?

The demonstration of recurrent disease and identification of risk factors may shed some light on the aetiology of the diseases. Common features of recurrent autoimmune liver diseases include the observation that recurrent disease is detected increasingly over time, and the natural history of disease in the graft is usually more rapid than in the native liver; furthermore, recurrence occurs in the presence of significant immunosuppression and may be affected by the immunosuppressive regime. Auto-antibodies, characteristic of autoimmune liver diseases, are non-organ-specific and even when the auto-antibody is disease-specific (such as for PBC), neither the presence nor the concentration of auto-antibody correlates with disease in the graft.

In PSC, several studies have focussed on predictors for recurrent disease. Male gender [27], gender mismatch between donor and recipient [25], presence of inflammatory bowel disease [82,83], presence of intact colon after liver transplant [27], clinically significant cytomegalovirus infection [24], recurrent acute cellular rejection (ACR) [24], steroid-resistant ACR [22], the presence of specific HLA-haplotypes (e.g. HLA-DRB1*08) [84] and possible treatment with the anti-T-lymphocyte preparation OKT3 [26] have been identified as possible risk factors. The lack of any consistent findings make it difficult to draw any firm conclusions about the aetiology of PSC: the observation that the disease does not recur in those with no colon after transplantation suggests the importance of back-wash ileitis in the pathogenesis of disease but it is not clear whether this suggests an immune mechanism or a toxic effect.

The presence of specific HLA and non-HLA-susceptibility alleles resulting in the production of pro-inflammatory cytokines and re-circulating gut-primed memory T-cells has been demonstrated [85,86]. Although not clarified in studies focussing on recurrence of PSC, as with AIH, a specific genetic predisposition might result in increased risk for reappearance. The existence of ACR has been found to be a risk factor in a number of studies [24,84]. It is possible that, following an episode of ACR

or ischaemic-reperfusion injury, autoimmune bile duct damage may be triggered by the appearance of autoimmune epitopes. Conversely, with recurrent disease, the sensitized immune system might lead to acute rejection.

The pathogenesis of AIH is unknown. Whether or not an autoimmune response will perpetuate depends on an individual's genetic susceptibility to present self or cross-reacting antigens [87], a sensibility to certain aetiological triggers (viruses or toxins) [88] and the constitution of the cytokine environment [89]. The presence of HLA-DR3, found in up to 70% of patients with recurrent AIH [10], may play an important role in presenting a variety of antigens to immunocytes with subsequent activation of T-lymphocyte subsets and in consequence the initiation of an immune response.

Antigen-presenting cells (APC) exist mainly outside the liver. Therefore, the activation of T-lymphocytes occurs according to several pathways, but through a common fashion named molecular mimicry. Aggressive and pre-primed recipient T-lymphocytes exhibit their activities against homologous donor-antigens. Second, the additional exposure of these cells to multiple donor-derived hepatic antigens will result in the development of a new immunological response and a third mechanism is the activation of recipient T-lymphocytes by APC derived from the donor. An extraordinary event is the reaction to MHC-II class alleles by recipient T-lymphocytes in the absence of antigenic peptides [8]. Possible gene polymorphisms or hormonal actions resulting in a change of the cytokine environment is the cause. Molecular mimicry might exist between yet unidentified viruses and self-antigens [90].

For recurrent PBC, few risk factors have been identified but include the use of tacrolimus rather than cyclosporine; the significance of this is unclear. Given the suggestion that xenobiotics and infectious agents may be implicated in triggering of PBC, differences in the intracellular impact of the two calcineurin inhibitors may help elucidate the mechanism of PBC: the observation by Van de Water [91] that the atypical distribution of E2 (the major auto-antigen of PBC) on biliary epithelial cells is seen in the allograft within a few days after transplant again suggests a factor, extrinsic to the liver, persists after transplantation.

Conclusion

Recurrent autoimmune disease is a significant cause of graft dysfunction and graft loss. The diagnosis of recurrent disease should be made on agreed criteria. Treatment, at present, has only a limited effect on modifying the course of recurrent disease. Implications for understanding the mechanism of autoimmune disease may be enhanced by identification of risk factors for recurrent disease. An important criterion in the definition of autoimmune disease is the loss of self-tolerance. Whether this can be applied to recurrent disease after liver transplantation is uncertain, as loss of tolerance may also be an important component of alloimmune responses in the liver allograft. Nevertheless, unraveling the present histological and immunological phenomena is of importance to gain more knowledge so that new therapeutic targets can be developed and reduce the number of patients in need for re-transplantation.

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