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TOPIC HIGHLIGHT

Pietro Invernizzi, MD; Ian R Mackay, MD, *Series Editors*

Transplantation in autoimmune liver diseases

Marcus Mottershead, James Neuberger

Marcus Mottershead, James Neuberger, Liver Unit, Queen Elizabeth Hospital, Birmingham B15 2TH, United Kingdom
Correspondence to: James Neuberger, MD, Liver Unit, Queen Elizabeth Hospital, Birmingham B15 2TH, United Kingdom. j.m.neuberger@bham.ac.uk
Telephone: +44-6-272414 Fax: +44-6-272449
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Abstract

Liver transplantation remains an effective treatment for those with end-stage disease and with intractable liver-related symptoms. The shortage of organs for transplantation has resulted in the need for rationing. A variety of approaches to selection and allocation have been developed and vary from country to country. The shortage of donors has meant that new approaches have to be adopted to make maximal use of the available organs; these include splitting grafts, use of extended criteria livers, livers from non-heart-beating donors and from living donors. Post transplantation, most patients will need life-long immunosuppression, although a small proportion can have immunosuppression successfully withdrawn. Newer immunosuppressive drugs and different strategies may allow a more targeted approach with a reduction in side-effects and so improve the patient and graft survival. For autoimmune diseases, transplantation is associated with significant improvement in the quality and length of life. Disease may recur after transplantation and may affect patient and graft survival.

Key words: Liver transplantation; Autoimmune disease; Recurrence; Immunosuppression

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INTRODUCTION

The three major autoimmune liver diseases that may require liver transplantation are primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC) and autoimmune hepatitis (AIH). In this review, we will discuss the role, timing and outcome of transplantation for these indications.

Criteria for liver transplantation for patients with autoimmune diseases are relatively well defined[1]. As with other indications, liver transplantation is indicated either to relive intractable symptoms of liver disease (such as pruritus or encephalopathy which do not respond to conventional therapy) or to prolong life. Life after transplantation is normally excellent but is never normal. Furthermore, survival is reduced when compared to an age and sex-matched population[2]. Reasons for the reduction in survival include the mortality of the procedure itself, the risks of recurrent disease and the consequences of immunosuppression which may be class related (such as an increased risk of sepsis and some malignancies) or more-specifically related to the individual drugs used (such as renal failure and cerebro- and cardio-vascular death). Thus, for most patients with chronic liver disease, timing of transplantation has to be done with consideration of the risks and balance of remaining with the native liver and of the procedure.

Some guidance is given by prognostic models, of which the most commonly used is the model for end-stage liver disease (MELD) formula[3]. MELD, initially used to predict short-term survival after stent insertion has been shown to be accurate in prediction of most patients with chronic liver disease. The score, which is derived from serum bilirubin, creatinine and prothrombin time, is useful; for the average patient, there is a survival benefit when transplanted with a score of 16 or more. Addition of other analytes to the formula, such as serum sodium, may increase the accuracy[4]. In some situations, the model does not predict outcome. For example, in those with a liver cell cancer where the prognosis without transplant is dependent on the cancer rather than parenchymal function. Other exceptions occur with hepatopulmonary syndromes, for example. There are several recent reviews of the general indications and contra-indications (see for example[5,6]).

There is an increasing gap between the number of patients who would benefit from a transplant and the availability of suitable organs for transplantation. In order to fulfil demand, differing strategies have been utilized: this includes use of split livers, non-heart beating donors, marginal donors and to a lesser extent,

living donor programmes. These strategies have, to some extent, masked the shortage of organs. Extended criteria or marginal livers are being utilized in greater numbers, (these are grafts where there is concerns that their use might impact on the outcome of the patient). These include those grafts where there is a greater risk of non-function (characterized by steatosis in the graft, older donors and prolonged cold ischemia times), technical problems (such as the use of split, partial or reduced grafts) or those grafts that carry a risk of transmission of viral infection or malignancy.

Living donor transplantation accounts for around 2%-5% of transplants in Europe and North America but for almost all transplants carried out in Asia, where donation rates from deceased donors are very low. Limitations on living donation focus on the risk to the donor: too much liver volume removed from donor may induce liver failure in the donor, too little may cause recipient graft failure. The mortality for the donor in left lobe is 0.05% rising to 0.4%-0.5% in right lobe transplants and donor morbidity is 20% with long-term outcomes unknown[7].

The shortage of grafts means that rationing must occur: the competing interests of equity, justice and utility have to be recognised. Thus, criteria for selection (that is admission to the list) and allocation (identification of the recipient for a graft) need to be agreed. Different health care systems have adopted different principles. Conflict may exist where transplantation is considered for some indications, such as liver disease from alcohol where the medical views are not in accordance with those of the public[8]. The immunological processes that operate in an allografted liver are complex, since the immune system of the host can react against alloantigens, human leucocyte antigen (HLA) molecules and "minor" transplantation antigens of the donor. Concurrently, passenger leucocytes of the donor may react against HLA or other antigens of the host, resulting in "two-way" immune responsiveness. The liver above all other organs has a propensity to generate a state of intra-hepatic immune tolerance that limits harmful immune reactivities, sometimes to the degree that immunosuppressant drugs become dispensable after a liver transplant. The immunological issues involved, which are beyond the scope of this article, are discussed informatively in several reviews[9,10].

Post transplant, most patients will need life-long immunosuppression. However, in the last decade there have been developments in the management of immunosuppression. In the early days of liver transplantation, the principles of immunosuppression after liver transplant were extrapolated from renal transplant programmes. However, there are some major differences: early acute rejection after liver transplantation is not associated with an adverse outcome; the requirement of immunosuppression is less and sometimes, as mentioned, it is even possible to withdraw immunosuppression completely. It is not possible reliably to identify those patients in whom immunosuppression can be safely withdrawn: however, those with good graft function at 5 years and with minimal inflammation on histology and were not transplanted for autoimmune diseases are most likely to benefit from a planned withdrawal of immunosuppression[11,12].

Tailoring immunosuppression to the individual is a much discussed but little practiced approach. For instance, those grafted for hepatitis C virus infection need to be protected against rejection since major changes in corticosteroids will increase the consequences of viral re-infection. The advent of newer biological agents including humanized monoclonal antibodies such as Campath-1H (alemtuzumab), antibodies to interleukin-2 receptor (IL-2R), and CLTA-4Ig, may permit more selective approaches to immunosuppression. Campath-1H is a humanized monoclonal antibody against CD52, a molecule expressed on the surface of human B and T lymphocytes. Antibodies to the IL2Ra chain target the CD25 molecule on activated T lymphocytes. Cytolytic T-lymphocyte-associated antigen 4 (CTLA-4) Ig is an immunoglobulin fusion protein with CTLA-4, a natural down-regulatory molecule expressed by T lymphocytes. There are other biologicals under investigation. Induction of full tolerance has long been the goal of solid organ transplantation but, despite advances in the laboratory, this goal has so far remained elusive in the human. The adoption of approaches allowing for early immunological engagement (the Window of Opportunity for Immunological Engagement) as suggested by Calne[13] or use of Campath-1 or other biologicals may offer a new and effective approach[14].

AIH

AIH is a relatively uncommon indication for liver transplantation, currently accounting for no more than 5% of cases[15]. As with cirrhosis from other causes, liver transplantation is indicated in those with end-stage disease characterized by a MELD score > 16, signs of decompensation on treatment such as hepatic encephalopathy, ascites or variceal haemorrhage or, rarely, with hepatocellular carcinoma development. In those who present with acute or fulminant liver failure, liver transplantation should be considered early in the course. Outcomes are good with 1 year and 5 years patient survival rates of about 87% and 80%-90%. Graft survival rates at 1 year and 5 years are 84% and 74%-76%[16-18].

Recurrence after transplantation

Diagnostic criteria for recurrent AIH (rAIH) have been developed and are summarised in Table 1. The reported recurrence rate of AIH following transplantation is variable 17%-42% at 5 years[19,20]. Table 2 shows the reports of recurrent AIH. Gautam`s systematic review of 13 papers concluded disease recurrence occurred in 22% of recipients at a median interval of 26.4 mo[21]. Czaja suggested that a loss of self-tolerance and molecular mimicry would explain the repopulation of the allograft with recipient antigen-presenting cells and that the already primed promiscuous recipient cytotoxic

Table 1 Criteria for the diagnosis of recurrent AIH

Criteria
Liver transplant for autoimmune hepatitis
Auto-antibodies in significant titre (> 1:40)
Sustained rise in serum aminotransferase activity (> 2 times normal)
Elevated serum immunoglobulins
Compatible liver histology (infiltration of portal tracts by plasma cells, piecemeal necrosis and bridging necrosis[21])
Corticosteroid dependency
Exclusion of other causes of graft dysfunction (such as rejection and HCV infection)

T cells are likely factors for recurrent disease[22].

Many studies have been published in the literature, but most include relatively small numbers, use different criteria for the diagnosis and are retrospective. Reich retrospectively reviewed 24 AIH transplant recipients; 6 patients developed biopsy proven recurrence at 15 mo, 3 proceeded to regrafting and 2 of these patients developed recurrent AIH in the second graft. No patient transplanted for fulminant hepatic failure developed recurrence compared to 1/3 of those with chronic disease[15]. Duclos-Vallee performed protocol biopsies and demonstrated histological recurrence preceded biochemical abnormality by 1-5 years in 23.5%[25]. There was no difference in survival or recurrence between the three sub-types of AIH. Rates of rejection were high both in the control and AIH groups but greater in those grafted for AIH. (50% and 88%)[27]. No patient required re-transplant because of recurrent disease and there was no difference in patient survival or graft survival[18].

There are no consistent risk factors for recurrence identified. Pre-transplant disease duration, donor/recipient gender distribution, HLA studies, and rejection episodes did not correlate with AIH recurrence but the degree of necro-inflammation in the native liver was significantly greater in those with recurrence in one study[24]. The choice of immunosuppression is controversial but a recent systematic review by Gautam found no difference in recurrence rates between recipients on tacrolimus (31%) or cyclosporin[21].

Khalaf reported a histological recurrence in 18.7% (median follow up of 530 d) which was successfully treated by optimizing immunosuppression. Steroid withdrawal failed in all recipients and was always accompanied by almost immediate elevation of liver enzymes[28]. A case of AIH recurrence 6 years after a living donor related liver transplant, in the absence of autoantibodies was reported. The patient had steroids discontinued 1 year post orthotopic liver transplant (OLT) whilst maintained on tacrolimus but became antinuclear antibody (ANA) positive again 3 years later, 2 years prior to the histological diagnosis but in the absence of abnormal LFTs[29].

De novo AIH

De novo AIH has features of a steroid responsive AIH in patients transplanted for other non-immune indications and is characterized by a biochemical hepatitis, circulating auto-antibodies, elevated immunoglobulins and an inflammatory infiltration with interface hepatitis. The first report of de novo AIH was in 7 children at a median of 2 years post-transplant[30]. Children are more at risk than adults but the condition is still relatively uncommon with an incidence of around 3%. There is usually a good response to additional immunosuppression with corticosteroids, but in some cases there is progression to cirrhosis and subsequent graft failure[31]. Whether this is truly a de novo autoimmune phenomenon or merely a form of rejection is not certain: early studies suggesting an immune response to graft antigens are controversial[32] and studies suggesting an immune response to graft isoforms of glutathione-S transferase remain unconfirmed.

Table 2 Reports of recurrent autoimmune hepatitis

Author	Follow up (mo)	*n*	Recurrence	Period recurrence occurred	Re-OLT/ Cirrhosis
Milkiewicz 1999[23]	29	47	13/47	29 mo	3/47
Ayata 2000[24]	67	12	5/12	35-280 d	2/12
Reich 2000[15]	27	24	6/12	At 15 mo	3/24
Molmenti 2002[18]	29	55	11/55	At end	
Duclos-Vallee2003[25]	120	17	7/17	2.5 yr[1]	2/17
Núñez-Martínez 2003[26]	38	15	1/15	At end	
Vogel 2004[27]	24	28	9/28	5 yr	4/28
Gautam 2006[21]			23%	2.4 mo[2]	

[1]Mean; [2]Median.

Conclusion

The outcome for OLT in AIH is good and is merited in those with chronic disease and a much smaller cohort will have an acute or fulminating course the prognosis of which is relatively unaffected by corticosteroids. Recurrence of disease is relatively common in the allograft and may be detected on protocol biopsy at an asymptomatic stage before biochemical or clinical clues. Generally recurrent AIH responds well to increases in immunosuppression or addition of corticosteroids. This should be taken into account when considering long term immunosuppression and especially on reduction should be in conjunction with immunoglobulins, autoantibody profile and histology. Most data are retrospective with relatively small numbers and studies are lacking in long term reduction and withdrawal of immunosuppression and further controlled studies are required.

PBC

Indications

Indications for transplantation are listed in Table 3. Unlike pruritus, which is rapidly reversed after transplantation, lethargy is not an indication since often

Table 3 Indications for transplantation in PBC

Indications
Symptom based
Intractable pruritus refractory to medical therapy
Hepatic encephalopathy
End-stage liver disease
Recurrent variceal haemorrhage
Episode of spontaneous bacterial peritonitis
Pulmonary hypertension
Hepato-pulmonary syndrome
Diuretic resistant ascites
Progressive osteopaenia
Muscle-wasting
Hepatoma (Milan criteria)
Biochemistry
Serum bilirubin > 150 μmol/L
Serum albumin < 25 g/L

Table 4 Criteria for the diagnosis of recurrent PBC

Criteria
Transplantation for PBC
Characteristic histological features of PBC
Mononuclear inflammatory infiltrates
Lymphoid aggregates
Epithelioid granulomas
Bile duct damage
Persistence of anti-mitochondrial antibodies
Elevated immunoglobulins
Exclusion of other causes of graft damage

Definite recurrent PBC is made when all 4 of these criteria are present, and in the presence of at least 3 of the 4 histological features. Probable recurrence when only 2 histological features are present[40].

it does not improve with transplantation[33]. The need for transplantation for PBC is falling (United Network for Organ Sharing (UNOS) data shows, of 2391 cadaveric liver transplants in 1991, 18% were for cholestatic liver disease compared with 10% of 4579 in 2000 and was the second most common indication for transplantation) and the impact of ursodeoxycholic acid (UDCA) is a tempting but controversial explanation.

Timing of transplantation

A variety of disease-specific prognostic models have been developed but for short term survival a MELD score is effective and a score > 16 indicates a survival benefit from transplantation. Serum bilirubin > 100 μmol/L[34] as well as significant poor liver function with length of life attributed to disease limited to 1 year are indicators for transplantation assessment[35]. A Mayo risk score > 7.8 has also been validated to indicate survival in the absence of transplantation[36,37].

Survival after OLT

The 1, 3 and 5 year actuarial patient and graft survival was 94%, 91%, and 82%, and 89%, 83%, and 75%, respectively in a series of 301 PBC transplant recipients in the UK[38] which is comparable to European transplant registry data. The commonest indication for re-transplantation in the first year is chronic rejection[39]. Survival rates remain consistently better than other indications, even after adjusting for case-mix and other risk factors. Immunosuppression is usually a standard triple regimen of calcineurin inhibitor (tacrolimus or cyclosporin), corticosteroids (withdrawn over 3 mo) and azathioprine or mycophenolate mofetil.

Recurrent disease

Recurrent disease (Table 4) is diagnosed by characteristic histology and absence of other causes of graft damage. The histology of recurrence is comparable to pre-transplant PBC[40]. Patients with anti-mitochondrial antibodies and normal liver function tests in the presence of normal histology may develop recurrence with hallmark granulomatous cholangitis[41]. Elevated serum immunoglobulins and persisting anti-mitochondrial antibodies do not in themselves indicate recurrent disease. Recurrent PBC is seen in 17% of patients at a mean of 36 mo[42] rising to 30% at 10 years. Recurrence rates on biopsy as high as 35% at 1 year have been reported[43]. The reported median time to recurrence is between 3.7 and 5 years[44,45]. Recurrence may not be diagnosed unless a protocol biopsy is taken as the liver tests may be normal[42]; indeed only half will have biochemical abnormality[44]. Liver tests may remain normal for 5 years after histological diagnosis[45].

The role of UDCA in the treatment or prevention of recurrent PBC remains uncertain. A retrospective review of 154 PBC liver transplant recipients followed at the Mayo Clinic for least 1 year reported that recurrent PBC was not associated with death or liver re-transplantation. 38 patients with recurrent PBC received UDCA at an average dose of 12 mg/kg per day for a mean duration of 55 mo. Over a 36-mo period, an estimated 52% of UDCA-treated patients experienced normalization of serum alkaline phosphatase and alanine aminotransferase compared to 22% of untreated patients but no significant difference in the rate of histological progression was noted between subgroups. UDCA did not influence patient and graft survival[46]. It should be noted that this experience does not concord with our own unpublished data where graft loss from recurrent PBC is 4%.

Should all those transplanted for PBC be offered UDCA? The agent is safe and improves all serological parameters and may retard progression so, even in the absence of clear evidence, we would advocate its routine use.

Risk factors for recurrence

Many studies have evaluated risk factors for recurrence. The literature is mixed concerning donor and recipient age as well as cold and warm ischaemia time[42,43,47,48]. The type of immunosuppression used is also controversial[45,49]. In a study of 485 recipients followed up over 79 mo, the recurrence rate with tacrolimus was 23% with OR 2.73 and time to recurrence 62 mo compared to 123 mo on cyclosporin ($P < 0.001$)[47]. Guy found similar results with OR 2.5 for tacrolimus[43]. No differences between cyclosporin and tacrolimus were

seen in other trials, though protocol liver biopsies were not performed or were only done in the context of graft dysfunction[50,51]. Sanchez reported a 156 patient cohort using protocol biopsies at 1, 2, 5, 10 and 15 year intervals with recurrence in 8.4% of recipients taking cyclosporin, azathioprine and steroids, compared with 12.2% of those receiving cyclosporin and steroids alone and 16.7% of patients taking tacrolimus and steroids ($P = 0.11$)[52]. Thus the evidence does suggest that cyclosporin is, compared with tacrolimus, associated with a slower rate of progression of recurrent disease. Whether this indicates that those grafted for PBC should be offered cyclosporin-based immunosuppression rather than that based on tacrolimus, and whether those with recurrent PBC should be switched from tacrolimus to cyclosporin is uncertain.

Implications of recurrence

The consequences of recurrent disease appear to be relatively small[53]. In our series of 486 PBC transplant recipients, 3 were re-grafted as a consequence of recurrent disease, all of whom have recurrence in the re-graft[54].

Quality of life issues

Pruritus may resolve within days of transplantation. Fatigue persists and does not appear to improve post liver transplant[33] although there is a great improvement in quality of life[55]. Gross studied 157 adult patients with PBC or PSC before and 1 year after liver transplantation. The quality of life following transplantation was significantly better than before transplantation in all aspects but at 1-year follow-up, was not predictable by the pre-transplant subjective health status or clinical factors[56].

PSC

Survival after transplantation

Indications for transplantation are as for other end-stage liver disease complications. European data show patient survival at 1, 3, 5 and 10 years was 86%, 79%, 76% and 66% respectively from Jan 1988-June 2006 (www.eltr.org).

PSC recurrence

Recurrent PSC (Table 5) must be distinguished from secondary sclerosing cholangitis; Characteristic histological features are not always present so the diagnosis may be made on imaging the biliary tree. PSC recurrence is relatively common with figures of 37% at 36 mo and 60 % at 5 years[57,58] Gautam's systematic review of 14 reports revealed a recurrence rate of 17% but was unable to comment upon possible risk factors[21]. Sheng studied the prevalence of stricturing disease in 100 patients who underwent transplantation for PSC and 543 controls without PSC. 27% PSC liver recipients compared to 13% of controls showed intra-hepatic strictures by cholangiography. Intra-hepatic and non-anastomotic extra-hepatic strictures were significantly more frequent in the PSC group[59]. In a small cohort who underwent living donor liver transplantation with a median follow up of 3.5 years, half developed recurrent PSC with the mean time to recurrence 3.3 years (1.1-5.4 years).There was no direct comparison to their cadaveric cohort[60]. Khettry retrospectively analysed 51 PSC patients with a follow-up of 2 to 14 years. Of the remaining 42 patients, 6 had recurrent PSC with typical histological and cholangiographic findings, 12 had autoimmune liver disease that was not otherwise specified with histology of AIH/overlap syndrome, 3 had chronic rejection, 4 had ischemic cholangiopathy, and 17 had no recurrence. Post-transplant malignancies were significantly more common in the non-recurrent cases compared with all others combined ($P = 0.031$) and caused death in four. The majority of deaths (11/13) in other groups were due to sepsis. In conclusion, allograft autoimmune liver disease was seen in 18 (43%) of 42 long-term post-LT PSC patients, with progression in 5 of 18 patients. Features of PSC were seen in 6 (33%) of 18[61].

Table 5 Criteria for the diagnosis of recurrent primary sclerosing cholangitis[72]

Criteria
Transplant for PSC
Multiple non-anastomotic strictures, headings and irregularity more than 90 d post OLT
Characteristic liver histology (fibrous cholangitis and/or fibro-obliterative lesions) with or without ductopenia, biliary fibrosis or biliary cirrhosis may be seen (but absence of characteristic features does not exclude the diagnosis).
Exclusion of other causes of secondary sclerosing cholangitis & stricturing (due to surgery, trauma, ischaemia, hepatic artery stenosis/thrombosis, established ductopaenic rejection, blood type ABO incompatibility and infections)
Cholestatic liver tests

Many factors have been associated with recurrence including steroid-resistant rejection, OKT3 use, preservation injury, ABO incompatibility, cytomegalovirus infection, male sex, donor-recipient gender mismatch and steroid resistant rejection but not specific calcineurin inhibitor use or frequency of rejection[61-67].

Although there is some controversy as to the effect of pre-transplant colectomy on the recurrence rate, our own data consistently show that colectomy either before or during transplant is not associated with recurrent disease whereas the incidence of recurrence in those who had a colectomy post transplant is no different to those with an intact colon. Overall, recurrence of PSC leads to patient and graft loss.

Colitis and colonic neoplasia after transplantation

Evidence linking immunosuppression with inflammatory bowel disease-free survival is mixed[68,69]. Colitis is variable and may present *de novo* after transplantation, with an incidence of 6% at 1 year and 20% at 5 years[70]. In a study of 20 PSC transplant recipients with coexisting ulcerative colitis followed over a median period of 11.9 years before OLT and 4.4 years after OLT, there was a significantly higher relapse rate after OLT than pre-transplant. 35% of recipients went onto colectomy after OLT (3 for disease severity and 4 for neoplasia/

dysplasia)[71]. These results were mirrored in a study from Birmingham which looked at 152 patients with PSC (100 with coexisting IBD). The incidence of colorectal cancer after transplant was 5.3% compared with 0.6% in non-PSC cases. All cancers in the PSC group were in patients with IBD and an intact colon. The cumulative risk of developing cancer in the 83 patients with an intact colon and IBD was 14% and 17% after 5 and 10 years, respectively. The multivariate analysis identified colonic dysplasia after transplant ($P < 0.0003$), duration of colitis more than 10 years ($P < 0.002$), and pancolitis ($P < 0.004$) as risk factors[69]. Colonoscopy is thus recommended annually following transplant.

FUTURE PROSPECTS

Over the last three decades, liver transplantation has evolved from an experimental, high risk procedure to a routine operation with a high success rate. Indications have widened and contra-indications decreased. Currently, the major limitation remains the shortage of organs so that not everyone who might benefit from the procedure can receive a graft and surgeons have to use extended criteria organs. The use of stem cell therapy and liver cell transplants, remain in their infancy. There still remain considerable challenges ahead: major causes of graft loss include recurrent disease, especially Hepatitis C but also autoimmune diseases, and the side-effects and complications of immunosuppression. The goal of achieving tolerance remains elusive but the development of new agents, especially biologicals, may allow for more effective strategies. The stimulus and challenges of liver transplantation have advanced our understanding of the mechanisms of alloantigen immune recognition and target cell damage and helped introduce new immune-modifying agents and strategies. They have also helped our understanding of the anatomy, physiology and pathophysiology of the liver. However, the long-term goal of clinical research must be the treatment of disease in the native liver so that transplantation becomes redundant.

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