Liver Transplantation (LT) for Paediatric Autoimmune Liver Disease

The purpose of this guide is to outline the management issues related to LT and should be read in conjunction with the ESPGHAN Clinical Advice Guides on Autoimmune Hepatitis (AIH) and Autoimmune Sclerosing Cholangitis (ASC).

LT is a treatment option for AIH and ASC patients with end-stage chronic liver disease, hepatic malignancy, or intractable symptoms, as well as for AIH patients presenting with severe acute liver failure (ALF) unresponsive to steroid treatment.

FACTS & STATS

AIH accounts for 2% to 5% of paediatric LTs performed in Europe and the United States.

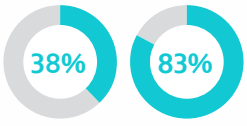
Sclerosing cholangitis accounts for 2% to 3% of LTs performed in paediatric-aged patients, only some of whom have ASC in the US.

The transplant rate for AIH is variable, ranging from 9% to 55% and the interval between presentation and transplantation ranges from days (in the case of fulminant presentation) to several years after diagnosis.

Overall, LT rate for sclerosing cholangitis ranges between 15% and 45%, and the interval between diagnosis and LT ranges from 6 to 12 years.

Recurrence of Autoimmune Hepatitis after Liver Transplantation

AIH can recur in the allograft despite immunosuppression. Recurrent disease, particularly if not diagnosed and not treated promptly, may have serious consequences on graft function – requiring re-transplantation. As histologic evidence can precede clinical evidence of recurrence, it might be useful to include a follow-up liver biopsy in the protocol for the management of patients transplanted for AIH.



The reported recurrence rate in children is variable from 38-83% and depends on the criteria used for diagnosis, the immunosuppressive regimen, length of follow-up, and performance of "per protocol" biopsies.

The mean time from LT to recurrence is 5 years but it may occur as early as 35 days after transplantation.

IDENTIFYING A RECURRENCE

The diagnosis of recurrent AIH is based on the reappearance of clinical symptoms and signs, elevation of transaminase and IgG levels, autoantibodies, and interface hepatitis, along with response to prednisolone and azathioprine. Recurrent AIH is reported to develop less frequently in patients transplanted for ALF compared to those with a chronic presentation.

These criteria are essentitally those included in the International Autoimmune Hepatitis Group (IAIHG) scoring systems used to diagnose AIH in the native liver. While not tested systematically for the diagnosis of recurrent AIH, they may provide a useful diagnostic tool in view of the similarity between AIH in the native liver and recurrent disease in the allograft.

Features reported to be associated with recurrence of AIH after LT are:

- possession of either human leukocyte antigen (HLA)– D-related antigen 3 (DR3) or –D-related antigen 4 (DR4) by the recipient
- discontinuation of corticosteroids after transplantation (therefore caution should be exercised in weaning patients off immunosuppression)
- the severity of necroinflammatory activity in the native liver at the time of LT

Although early studies pointed to an association between tacrolimus-based immunosuppression and the risk of AIH recurrence, a subsequent systematic review reported that primary immunosuppression with either cyclosporine or tacrolimus did not influence the risk of recurrence.

Treatment

Most transplant recipients with recurrent AIH respond to reintroduction or an increase in the dose of corticosteroids and azathioprine, which should be implemented as soon as the diagnosis is made.

If treatment fails, alternatives include addition of mycophenolate mofetil (MMF) in lieu of azathioprine to the standard therapeutic regimen, replacement of tacrolimus with cyclosporine, and replacement of calcineurin inhibitors with sirolimus.

Recurrence of Sclerosing Cholangitis after Liver Transplantation

Recurrence of sclerosing cholangitis after paediatric LT has been reported in 10% to 50% of recipients and the risk for recurrence increases over time. In paediatrics, recurrent disease, particularly in the context of ASC, is associated with seriously compromised graft survival.

Diagnosis of recurrence

The diagnosis of recurrent sclerosing cholangitis is advised by the histological and/or cholangiographic findings of bile duct disease, including presence of fibrous cholangitis, fibro-obliterative lesions with or without ductopaenia, fibrosis or cirrhosis, and/or interface hepatitis, whereas the cholangiography generally shows diffuse biliary structuring.

Other causes of non-anastomotic biliary strictures in the graft should be carefully excluded, including ischemic biliary insults (e.g. as consequence of hepatic artery thrombosis), ABO incompatibility between donor and recipient, bacterial or fungal cholangitis, and chronic ductopaenic rejection.

Possible risk factors of recurrence

Paediatric studies point to an association between active IBD after LT and the development of recurrent disease, and a study in adult patients shows that persistent ulcerative colitis, requiring maintenance steroids, is associated with an increased risk of developing recurrent disease in the graft. However, colectomy before or during LT may provide protection against the development of recurrent disease.

Treatment

There is no established treatment for recurrent sclerosing cholangitis after paediatric LT. If dominant strictures are present, they should be dilated by interventional cholangiographic means whenever possible. Ursodeoxycholic acid treatment has been advocated in the setting of transplanted adult PSC patients because it seems to improve biochemical indices of liver disease, but it remains unknown whether it has an impact on outcomes.

De novo Autoimmune Hepatitis after Paediatric Liver Transplantation

De novo AIH after LT affects patients transplanted for disorders other than autoimmune liver disease. Although nonspecific development of autoantibodies over time after liver transplantation is common, affecting >70% of recipients, the prevalence of de novo AIH in children ranges from 2% to 6%.

Treatment

Studies have shown that patients develop a form of graft dysfunction with features identical to those of classical AIH, namely, high transaminase levels, hypergammaglobulinemia, positivity for autoantibodies—ANA, SMA, typical and atypical anti-LKM-1 (i.e., staining renal tubules only), and histological features of chronic hepatitis with portal/periportal inflammation and centrilobular necrosis. Patients with de novo AIH do not respond to conventional anti-rejection treatment, but only to the classical treatment of AIH.

Diagnosis

De novo AIH has been described as a complication of living donor LT recipients and rejection and steroid dependence have been identified as risk factors for the development of this complication. In a paediatric series, the most common histological feature of de novo AIH was lobular hepatitis, often without interface necroinflammatory activity or prominent plasma cell infiltrates.

Advice on use of steroids

Treatment with prednisolone alone or in combination with azathioprine or MMF is successful in de novo AIH and has led to excellent graft and patient survival.

Children should be given a starting dose of 1 to 2 mg/kg of predniso(lo)ne, without exceeding a daily dose of 60 mg, in combination with azathioprine (1–2 mg/kg); the steroids should then be tapered for 4 to 8 weeks, to reach a maintenance dose of 5 to 10 mg/day. In the absence of response, azathioprine should be replaced by MMF.

CASE STUDY

The importance of maintenance therapy with steroids in de novo AIH was shown in a study comparing treatment with and without steroids; all steroid-untreated patients developed cirrhosis and either died or required re-transplantation; none of the steroid-treated patients had progressive disease.

This advice guide is produced and published by the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and authored by members of the society's Hepatology Committee. Full references for the advice within this guide can be found within the following paper, which this guide is based upon: Mieli-Vergani, Giorgina, et al. "Diagnosis and Management of Pediatric Autoimmune Liver Disease: ESPGHAN Hepatology Committee Position Statement." Journal of Pediatric Gastroenterology and Nutrition 66.2 (2018): 345-360.

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