Post-Transplant Management and Complications of Autoimmune Hepatitis, Primary Biliary Cholangitis, and Primary Sclerosing Cholangitis including Disease Recurrence

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KEYWORDS

• Liver transplantation • Primary sclerosing cholangitis • Primary biliary cholangitis
• Autoimmune hepatitis • Rejection • Recurrent disease • Immunosuppression

KEY POINTS

- Transplant recipients with autoimmune liver diseases are at increased risk for rejection compared to other indications for transplant.
- Autoimmune liver diseases can recur post-transplant and increase the risk of graft loss and mortality, particularly in primary sclerosing cholangitis.
- These complications have in some cases been linked to immunosuppressive agents, though there is generally insufficient evidence to recommend specific regimens, and this warrants further study.

INTRODUCTION

Autoimmune liver diseases including autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) are the indication for approximately 15% of liver transplants in the US (4% AIH, 4% PSC, 5% PBC) and 25% in Europe.[1–3] These conditions have been increasing in incidence and prevalence, and, in some European countries, autoimmune liver diseases are or are projected to

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soon be the leading indication for transplant.[3,4] Understanding the post-transplant care of these patients is therefore important.

The post-transplant outcomes of patients with autoimmune liver diseases are generally good, with survival rates around 90% at 1 year and 70% at 5 years, though the post-transplant course can present some unique complications (**Table 1**).[5] In addition to rejection, which these patients may be at increased risk for, recurrent disease can also occur and adversely impact graft and patient survival. There are also other disease-specific complications that may require management, including persistent symptoms such as fatigue in PBC and inflammatory bowel disease (IBD) in PSC. This review will provide an overview of post-transplant complications in autoimmune liver diseases and the post-transplant management of these patients.

POST-TRANSPLANT COMPLICATIONS: REJECTION

Patients with autoimmune liver disease are generally considered to be at higher risk for rejection, though the reported incidence has varied over time with evolving immunosuppression strategies, practices regarding protocol biopsies, and, to a lesser extent, histologic definitions.[6–14] Several series have reported a higher risk of early T-cell-mediated rejection (TCMR), late TCMR, and chronic rejection in transplant recipients with AIH.[9–11,15] In early studies, the observed risk was as high as over 80% for early TCMR and 30% for late TCMR, though in more recent data these have been more similar to non-immune liver diseases at 20% to 40% and 10%, respectively (see **Table 1**).[2,10,11,13,16] This change over time may reflect recommendations for augmented immunosuppression in these patients due these early data, though this is uncertain.[17,18] The risk of chronic rejection in recipients with AIH (15%) is also higher than other etiologies of liver disease and may be increased in younger recipients.[9]

Transplant recipients with PBC and PSC have also been found to have an increased risk of early (40%–83%) and late (13%–28%) TCMR, while chronic rejection (5%–8%) may be more similar to non-immune liver diseases (see **Table 1**).[2,6–9,15,16,19] In contrast to AIH, no guidelines have recommended increased immunosuppression in these patients, and the increased risk of TCMR has persisted in more recent studies.[2,16] In PSC, younger age and IBD have been associated with a higher risk of TCMR, though the data for IBD is somewhat conflicting.[7,20,21] Further research on

Table 1
Post-transplant complications in autoimmune liver disease

	AIH	PBC	PSC
Rejection	• Early TCMR: 20%–88% • Late TCMR: 10%–33% • Chronic rejection: 15%	• Early TCMR: 59%–83% • Late TCMR: 13%–26% • Chronic rejection: 8%	• Early TCMR: 39%–71% • Late TCMR: 13%–28% • Chronic rejection: 5%–8%
Recurrence	• 20%–30% at 5 y	• 20%–30% at 10 y	• 20%–25% at 5 y
Other Potential Complications	• Early infection, particularly fungal infections	• Persistent fatigue • Persistent sicca symptoms • Osteoporosis (early)	• Inflammatory bowel disease • Colorectal cancer • Pancreatic cancer • Persistent fatigue • Osteoporosis (early)

the clinical factors, including immunosuppression regimens, associated with rejection in patients with autoimmune liver diseases is needed.

No association between antibody-mediated rejection and autoimmune liver disease has been reported.[22,23] The entity previously considered *de novo* AIH though has recently been renamed plasma cell-rich rejection, as this appears to be a manifestation of allograft rejection.[24–26] This occurs in 3% to 5% of adult liver transplant recipients with non-AIH diseases.[24]

POST-TRANSPLANT COMPLICATIONS: RECURRENT DISEASE

Recurrent Autoimmune Hepatitis

Recurrent AIH occurs in 20% to 30% of recipients at 5 years, with some variability depending on whether biopsies were clinically indicated or obtained by protocol.[5,27–29] This is diagnosed similarly to AIH pre-transplant, with positive autoantibodies, elevated immunoglobulin G (IgG), and typical histologic features, including the presence of lymphoplasmacytic portal inflammation with interface hepatitis, pseudorosettes, and lobular collapse and necrosis in severe cases.[27,30,31] Recurrent AIH has been found on protocol biopsies in the absence of abnormal liver tests. It can be difficult to distinguish from alloimmune rejection, though the features typical for rejection, including endotheliitis and bile duct damage, are usually not present.[31] Recurrent AIH is associated with increased mortality and had reduced graft survival of 12.2 years versus 24.0 years in a large multicenter study.[27]

Several risk factors for recurrent AIH have been reported, including younger age, greater inflammation pre-transplant (higher IgG, high transaminases, moderate/severe inflammation in explant), donor-recipient sex mismatch, use of mycophenolate mofetil (MMF), and the discontinuation of steroids (**Table 2**).[27,29,32–37] The role of immunosuppression regimens is controversial. The link to MMF was identified in a large multicenter study, though some have argued that this may reflect an "era effect" in which other factors from the time period in which MMF was used less commonly underlie this finding.[27] Data on prolonged steroids has also been conflicting, and a systematic review did not find conclusive evidence of a protective effect.[38,39]

Recurrent Primary Biliary Cholangitis

Recurrence of PBC occurs in 20% to 30% of recipients at 10 years.[5,28,40] Diagnosis can be challenging as antimitochondrial antibody and immunoglobulin M (IgM) often persist post-transplant, and cholestasis can be seen in other clinical scenarios.[41] Liver biopsy is therefore typically required. Histopathologic findings are consistent with PBC prior to transplant, with mononuclear cell portal tract infiltrate, portal granulomas, bile duct damage and disappearance, and bile ductular proliferation, though this needs to be distinguished from immune-mediated injury of small bile ducts due to rejection. Until recently, recurrent PBC was not thought to have a significant impact on graft or patient survival, accounting for only 1.3% of graft loss.[42] Yet, more recent data from a large cohort with long-term follow-up found that recurrent disease does confer a slightly increased risk of graft failure and mortality.[43,44]

Reported risk factors for recurrent PBC include younger age, early cholestasis post-transplant, tacrolimus, and MMF, while cyclosporine has been associated with a decreased risk (see **Table 2**).[43–50] The role of ursodeoxycholic acid (UDCA) post-transplant had been uncertain, with early studies demonstrating improvement in cholestasis but not other outcomes.[51] More recent data though has shown a role for UDCA in preventing the development of recurrent PBC as well as improving graft and patient survival.[44,47,52,53] In a large cohort, preventative UDCA was associated

Table 2
Risk factors for recurrent disease post-transplant in autoimmune liver diseases

	AIH	PBC	PSC
Patient Factors	• Younger age[27] • Concomitant autoimmune disease[29] • Black race[32] • High IgG[27,29] • High AST, ALT[27] • More severe inflammation in explant[29,34] • HLA-DR3 or -DR4[33]	• Younger age[43] • Elevated IgM[45]	• Younger age[57,62] • Male sex[68] • Recurrent cholangitis[55] • Higher MELD score[63,65,113] • IBD, especially UC[58,62,64–66] • HLA-DR8[108] • Cholangiocarcinoma[54,65,113]
Transplant Factors	• Donor/recipient sex mismatch[27] • HLA locus mismatching[32]	• Donor/recipient sex mismatch[45] • HLA locus mismatching[46] • Older donor age[46]	• Donor/recipient sex mismatch[114] • Older donor age[58,65,71,113] • Extended criteria donor[67] • CMV donor/ recipient mismatch[115] • Living donor first-degree relative[63,116]
Post-Transplant Factors	• MMF[27] • Discontinuation of steroids[35,36,38,39] • Lack of antimetabolite[37]	• Increased cholestasis early post-transplant[43] • Tacrolimus[47,48] • Cyclosporine (↓)[43,45,48,49] • Azathioprine (↓)[49] • UDCA (↓)[44,47,52,53] • Antiretroviral therapy (↓)[50]	• IBD activity[69] • Colectomy(↓)[57,65,67,68] • Biliary complication[63,113] • CMV infection[63] • TCMR: any episode,[65,108,115] multiple episodes,[55,65] steroid resistant[19] • Antithymocyte globulin[64] • Tacrolimus[57] • Cyclosporine (mixed)[61,70] • Prolonged steroids[66] • Single agent or no immunosuppression at 1 year[71]

with 2.26 years of life gained over 20 years, and the best outcomes were observed for the combination of UDCA and cyclosporine.[44]

Recurrent Primary Sclerosing Cholangitis

PSC recurs in 20% to 25% of transplant recipients at 5 years.[54–58] It typically presents with cholestasis and multifocal non-anastomotic biliary strictures greater than 90 days post-transplant and must be differentiated from ischemia, ABO incompatibility, and chronic rejection, which can be challenging.[59–61] Histologic findings are similar to PSC pre-transplant and may include fibrous cholangitis and/or fibro-obliterative lesions with or without ductopenia, biliary fibrosis, or biliary cirrhosis.[59] Ductopenia can also be seen in chronic rejection, so the diagnosis of recurrent PSC should be made based on a combination of clinical and histopathologic findings. Recurrent PSC is also associated with increased graft loss and mortality.[56,58,62,63] This is

typically more clinically significant than recurrent AIH and PBC, with nearly half progressing to graft failure in some series.[62]

Risk factors for recurrent PSC are shown in **Table 2**. In several studies, the presence of IBD, particularly ulcerative colitis (UC), and increased IBD activity post-transplant have been associated with an increased risk of recurrent PSC, while a colectomy has been protective.[57,58,62,64–69] These findings suggest that intestinal inflammation may increase the risk of recurrent PSC. Immunosuppression regimens have also been linked to recurrent PSC. Use of steroid-free antithymocyte globulin induction protocols, tacrolimus, and prolonged steroids have been associated with recurrent PSC in some studies, while cyclosporine has been mixed.[57,61,64,66,70] Reduced immunosuppression with one agent or no immunosuppression after 1 year has also been linked to recurrent PSC.[71] The seemingly mixed association between both more and less immunosuppression being linked to recurrent PSC may reflect underlying individual differences in recurrence risk and immunosuppression needs.

OTHER POST-TRANSPLANT COMPLICATIONS

Infection

Though all patients post-transplant are at risk for infection, patients with AIH are at higher risk for fatal infections in the early post-transplant period (particularly fungal infections), and this contributes to inferior outcomes relative to PSC and PBC.[13,72,73] Surprisingly, based on limited data, this risk does not appear to be related to immunosuppression strategy either before or after transplant, including prolonged use of steroids, though it could be related to spontaneous immunosuppression in patients with AIH.[13,74,75]

Osteoporosis

All transplant recipients experience accelerated bone loss in the immediate post-transplant period, likely related to high doses of steroids and possibly calcineurin inhibitors.[76,77] Patients with cholestatic liver diseases may have decreased bone density post-transplant relative to other etiologies, but this typically improves after 4 to 6 months.[76–79] In patients maintained on long-term steroids, this risk may persist, though a single-center cohort of patients with AIH found that the proportion who developed osteoporosis was similar to published rates for other transplant recipients.[36,76,80]

Fatigue and Other Symptoms

Fatigue is a burdensome symptom in cholestatic liver disease, especially PBC, and is associated with impaired quality of life.[81] Transplantation may improve fatigue in some patients with PBC, though nearly half still suffer from this symptom 2 years post-transplant, and fatigue may worsen in males.[82–84] In PSC, fatigue persists in one-third of patients, though, in contrast to PBC, improves in males.[85] Sicca symptoms in patients with PBC also persist post-transplant.[40]

Inflammatory Bowel Disease

Most patients with PSC have concomitant IBD, particularly UC. The presence of IBD and its degree of activity may increase the risk of rejection and recurrent PSC, as discussed above, though IBD alone does not appear to impact graft or patient survival.[86] IBD may, however, be associated with an increased risk of CMV infection.[86]

The natural history of IBD post-transplant is variable. The disease course can be quiescent or more aggressive, and *de novo* IBD develops in 20% at 5 years.[87–90] Up to 25% of recipients require the escalation of IBD therapy despite transplant-related immunosuppression, and immunosuppression regimens have also been linked to IBD outcomes.[88] Tacrolimus and MMF may be associated with increased disease

activity, while azathioprine and cyclosporine have been associated with an improved course.[88,90,91] Azathioprine may also protect against the development of *de novo* IBD, and MMF may increase this risk.[88,91] Combination biologic and antirejection therapy is associated with an increased risk of *Clostridium difficile*, though the overall rate of serious infections is similar to the general liver transplant population.[92]

Gastrointestinal Malignancy

Patients with PSC are at even higher risk for colorectal cancer (CRC) post-transplant, particularly with longer duration of IBD, extensive colitis, and moderate/severe IBD disease activity.[69,93–96] Recipients with PSC and IBD are more than twice as likely to develop CRC compared to PSC without IBD and four times as likely as IBD without PSC.[93,94] Individuals with prior colectomy and an ileoanal pouch may be at increased risk for dysplasia and malignancy in the pouch, though these data have been conflicting.[97,98] In addition to CRC, transplant recipients with PSC may also have an increased risk of pancreatic cancer.[94]

POST-TRANSPLANT MANAGEMENT

Post-transplant management of recipients with autoimmune liver disease must take into account these complications, including an increased risk of rejection, the potential for disease recurrence, and other disease-specific complications. Rejection and recurrent disease should be monitored for closely, as both have been found to impact graft and patient survival, though the optimal approach to this is uncertain.[2,43,44,56,58,62,63] In most cases, these complications will manifest with abnormal liver tests, though histologic disease can be present in the absence of other indicators.[37]

The role of surveillance biopsies in this population is uncertain, though over 25% of a cohort in a study demonstrating a benefit to an individualized approach to surveillance had autoimmune liver disease.[99] In addition, though some data has suggested links between immunosuppressants and these outcomes, in most cases, there is not convincing evidence to support a preferred regimen.[100] Potential strategies to reduce the risk of disease recurrence are shown in **Table 3**.

Autoimmune Hepatitis

Steroid maintenance therapy post-transplant in AIH is controversial.[101,102] Some data support a reduced risk of recurrent AIH, though the evidence has been

Table 3
Potential strategies to reduce the risk of recurrent disease post-transplant

	AIH	PBC	PSC
Pre-Transplant	• Treatment to reduce IgG, AST, ALT		• Treatment to control IBD • Consider colectomy if difficult to control IBD
Post-Transplant	• Adequate maintenance immunosuppression with the consideration of long-term, low-dose corticosteroids vs withdrawal	• Preventative UDCA • Consideration of switching from tacrolimus to cyclosporine after early post-transplant period	• Maintain IBD remission • Consider colectomy if difficult to control IBD

mixed.[16,35,36,38,39] Earlier guidelines from the American Association for the Study of Liver Diseases suggested the use of long-term, low-dose corticosteroids for recipients with AIH, though the more recent guidelines instead suggest gradual withdrawal be considered given the lack of data.[17,31] The International Liver Transplantation Society suggests considering maintaining low-dose steroids or adding MMF or azathioprine to facilitate steroid weaning.[103] An individualized approach accounting for the patient's risk of recurrent disease and rejection, balanced with the effects of long-term steroids, is likely the optimal approach. In addition, though MMF has also been recently implicated as a potential risk factor for recurrent AIH, further research is needed to confirm this finding.[27]

When recurrent disease does develop, immunosuppression should be increased, with the reintroduction of steroids, followed by the addition of azathioprine or MMF if needed, while continuing the calcineurin inhibitor.[31] If there is a lack of response, the antimetabolite or calcineurin inhibitor can be switched, and rapamycin has also been used in patients who did not respond to these regimens.[31,104] In some cases, recurrent disease may progress to graft failure, and retransplantation was needed in 13% to 50% of patients in small series.[35,105]

Primary Biliary Cholangitis

There are no guideline recommendations on immunosuppression regimens in PBC post-transplant, though some centers report changing from tacrolimus to cyclosporine after 3 months to balance the risk of TCMR with disease recurrence.[100] Use of UDCA post-transplant has also not been specifically recommended, though the published guidelines preceded some of the more recent data supporting reduced recurrent PBC, graft loss, and recipient mortality.[40,44,47,52,53,106] Some centers administer preventative UDCA at 10 to 15 mg/kg/d to reduce the risk of these complications.[100] If recurrent PBC develops, UDCA improves cholestasis and may delay histologic progression.[51] Recurrent PBC is now recognized to slightly increase the risk of graft failure, though this rarely requires retransplantation.[43]

Primary Sclerosing Cholangitis

There is also insufficient evidence to suggest a preferred immunosuppression regimen for PSC based on existing data. The potential relationship between immunosuppressive agents and IBD disease course may influence this decision, particularly as IBD activity is associated with recurrent PSC.[69] If recurrent PSC develops, unfortunately no effective treatment exists to slow progression. Some centers use UDCA, though there are no data supporting improved outcomes.[60,107] Up to one-third with recurrent disease may progress to require retransplantation, and outcomes in selected patients may be similar to first-time transplant.[54,108,109]

With regards to the management of IBD, studies have demonstrated the safety and effectiveness of anti-TNF agents and vedolizumab.[110,111] There are no data on the use of newer IBD agents post-transplant, though the thrombosis risk with JAK inhibitors could be a potential concern.[112]

Patients with PSC remain at higher risk for CRC and should continue to undergo yearly colonoscopies.[69,93–95] Recipients with a pouch should also have yearly surveillance, though data to support this practice has been conflicting.[97,98]

SUMMARY

In conclusion, autoimmune liver diseases have unique post-transplant considerations. These recipients are at increased risk of rejection, and recurrent disease may also

develop, which can progress to graft loss and increase mortality. Vigilantly monitoring for and managing these complications is therefore important, though data on associated risk factors and immunosuppression strategies has in most cases been mixed. The immunologic complications must be balanced against the complications of immunosuppressive therapy. There are also other disease-specific complications that require management and may impact these decisions, including IBD in PSC. Further work to better understand the optimal management strategies for these post-transplant complications is needed, and the future may involve a more personalized approach with tailored surveillance and immunosuppression strategies.[99]

CLINICS CARE POINTS

- Transplant recipients with autoimmune liver diseases are more likely to experience rejection.
- Transplant recipients with AIH are at increased risk of early infections, particularly fungal infections.
- Fatigue persists in many patients with PBC and PSC post-transplant.
- Management of IBD in PSC is important as this has been associated with both an increased risk of rejection and recurrent disease post-transplant.

CONFLICTS OF INTEREST

No relevant conflicts of interest.

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