Review

Management of Autoimmune Liver Diseases after Liver Transplantation

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Abstract: Autoimmune liver diseases are characterized by immune-mediated inflammation and eventual destruction of the hepatocytes and the biliary epithelial cells. They can progress to irreversible liver damage requiring liver transplantation. The post-liver transplant goals of treatment include improving the recipient's survival, preventing liver graft-failure, and decreasing the recurrence of the disease. The keystone in post-liver transplant management for autoimmune liver diseases relies on identifying which would be the most appropriate immunosuppressive maintenance therapy. The combination of a steroid and a calcineurin inhibitor is the current immunosuppressive regimen of choice for autoimmune hepatitis. A gradual withdrawal of glucocorticoids is also recommended. On the other hand, ursodeoxycholic acid should be initiated soon after liver transplant to prevent recurrence and improve graft and patient survival in primary biliary cholangitis recipients. Unlike the previously mentioned autoimmune diseases, there are not immunosuppressive or disease-modifying agents available for patients with primary sclerosing cholangitis. However, colectomy and annual colonoscopy are key components during the post-liver transplant period.

Keywords: autoimmune hepatitis; primary biliary cholangitis; primary sclerosing cholangitis

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1. Introduction

Autoimmune liver diseases (AILDs) are characterized by progressive immune-mediated inflammation and eventual destruction of the hepatocytes and the biliary epithelial cells. It mainly includes autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC), which may also occur as overlap syndromes [1]. A small proportion of AILDs is represented by immunoglobulin G (IgG4)-related hepatobiliary diseases that include IgG4-sclerosing cholangitis and IgG4-autoimmune hepatitis [2].

Liver transplantation (LT) is a therapeutic procedure for patients with irreversible liver damage. The indications for LT in patients with AILDs are similar for patients with other chronic liver diseases with certain particularities [3]. Collectively, these autoimmune hepatobiliary diseases account for approximately 24% of total LT, representing the third most common LT indication in most transplant centers [2,4].

The improvement in surgical techniques, patient selection, perioperative care, and immunosuppressive regimens helped increase post-LT patient and graft survival over the past decades in patients with AILDs [5,6]. Each autoimmune liver disease requires particular therapeutic strategies, but the goals of treatment are the same: to improve the recipient's survival, to prevent liver graft-failure, and to decrease the recurrence of the disease. Several considerations should be taken into account to meet these goals, such as identifying post-LT risk factors that correlate with liver graft-failure and disease recurrence,

finding the most appropriate immunosuppressive regimen, and implementing additional cancer surveillance depending on the LT indication [3].

The objective of this review is to provide the latest recommendations regarding post-LT management in patients with AILDs, including specific recommendations to each AILD, and general measures for bone health and metabolic syndrome after LT.

2. Autoimmune Hepatitis

AIH is a complex inflammatory liver disease of uncertain etiology that involves a combination of immunologic, genetic, and environmental factors. The prevalence of AIH among adults widely varies worldwide and ranges from 4 (Singapore) to 42.9 (Alaska) cases per 100,000 persons [7–9]. In the United States, a recent population-based national study reported an estimated prevalence of 31.2 cases per 100,000 persons [10]. Clinical presentation is quite heterogeneous. Patients can be asymptomatic, debut with acute symptoms (acute severe or acute liver failure), or in most cases, present mild symptoms that might become chronic. The diagnosis can be challenging and requires particular laboratory indicators such as elevated aminotransferase levels and increased total Immunoglobulin G; lymphoplasmacytic interface hepatitis on histology, a presence of autoantibodies in the serum (antinuclear antibodies, anti-smooth muscle antibody, and anti-liver kidney microsomal antibodies). Other liver diseases that may resemble AIH like viral hepatitis, Wilson's disease, hereditary or metabolic liver injuries should be excluded [11].

Despite continuous updates in AIH management guidelines for patients with AIH, a significant number of patients progress to end-stage liver disease and eventually require a LT. AIH accounts for 5% of the indications for LT performed in the United States [3]. Patient and graft survival rates at 5-years are 76% and 70.9%, respectively [12–14]. These rates are relatively satisfactory; nevertheless, there is still a higher risk for late acute rejection (9%), chronic rejection (16%), as well as for recurrent disease (36% to 68% at five years) when compared to other LT indications [2,11,14–17]. Challenges arise in the diagnosis of recurrent AIH (rAIH). Factors such as immunosuppressive therapy and the short duration of the disease make it difficult to differentiate rAIH from graft rejection. Features on the biopsy help to distinguish between these two entities [11]. Table 1 outlines the different rates and risk factors associated with rAIH.

Table 1. Frequency and risk factors for recurrence of Autoimmune Hepatitis after liver transplantation.

Reference	Sample Size	Frequency	Risk Factors for Recurrence
Wright et al. [18]	43	11 (25.6%)	HLA-DR3-positive recipient
Prados et al. [19]	27	9 (33%) 8% at 1 year 68% at 5 years	HLA-DR3-positive recipient
Ratzu et al. [20]	25	3 (20%)	NR
Milkiewicz et al. [16]	47	13 (28%)	Discontinuation of steroids HLA-DR3-positive recipient (n.s.)
Reich et al. [21]	32	6 (25%) at 15 ± 2 months	Re-transplantation for rAIH Transplantation for chronic AIH (patients transplanted for fulminant AIH seem to be protected from recurrence) (n.s.)
Ayata et al. [22]	14	5 (42%)	HLA-DR3-positive recipient High-grade inflammation of the native liver Tacrolimus-based immunosuppressive regimens
González-Koch et al. [23]	41	7 (17%) at 4.6 ± 1 years	HLA-DR3 or HLA-DR4 incidence in recipient
Renz et al. [24]	37	12 (32%) at 25 ± 22 months	NR
Yusoff et al. [25]	12	2 (17%)	NR
Molmenti et al. [26]	45	11 (20%)	NR
Duclos-Vallée et al. [27]	17	7 (41%) at 2.5 ± 1.7 years	HLA-DR3-positive recipient

Table 1. Cont.

Reference	Sample Size	Frequency	Risk Factors for Recurrence
Balan et al. [28]	NR	NR	HLA-DR locus mismatching
Montano-Loza et al. [29]	46	11 (24%) 18% at 5 years 32% at 10 years	Concomitant autoimmune disease Abnormal pre-LT AST, ALT, IgG Moderate to severe hepatic inflammation in the liver explants
Krishnamoorthy et al. [30]	73	5 (7%) 6% at 5 years 11% at 10 years	NR

HLA—human leukocyte antigen; rAIH—recurrent autoimmune hepatitis; NR—not reported; n.s.—no significance.

The keystone in post-LT management for AIH relies on identifying which would be the most appropriate immunosuppressive maintenance therapy. Transplant centers adopt new immunosuppressive protocols to balance their potential effects on the long-term morbidity and mortality of AIH patients after LT. Several systematic reviews and meta-analyses have reported post-LT outcomes in patients with AIH [2,31]. However, conclusions about the management continue to be limited, making it challenging to draw management recommendations with high-quality evidence.

2.1. The Role of Steroids

Most of the transplant centers still continue having a conservative approach with long-term steroid maintenance, despite the new recommendation from the 2019 American Association for the Study of Liver Diseases (AASLD) guidelines to gradually discontinue steroids. As part of post-LT management in non-AILDs, steroid withdrawal improves metabolic profile (lower incidence of hypertension, hyperlipidemia, and diabetes mellitus) without increasing the risk for liver graft failure. However, concerns arise about the likelihood of recurrence of primary disease in AIH post-LT patients [2].

Milkiewicz et al. reported that halting steroids in post-LT patients showed an increased rate of recurrent AIH (rAIH) [16]. Based on this observation, they changed their immunosuppression regimen for long-term corticosteroid use. Later, Krishnamoorthy et al. showed that steroid use (prednisolone 5–10 mg) after LT for AIH was safe and decreased the incidence of rAIH without increasing the risk of infections and osteoporosis [31].

Recent studies suggest that corticosteroid withdrawal does not influence disease recurrence [32], neither increases the risk of infections or metabolic complications [33]. A recent systematic review and meta-analysis compared withdrawal versus continuation of steroids in patients with AIH after LT [34]. The study concluded there was no difference in AIH recurrence (OR 0.62, 95% CI: 0.19–1.96), acute cellular rejection, graft loss, or death. Gradual withdrawal of steroids showed more benefits and decreased costs, yet similar feasibility, accessibility, and equity [11]. Therefore, the AASLD suggests that a gradual withdrawal of glucocorticoids should be considered after LT.

2.2. Immunosuppression Therapy

Patients may need an individually tailored immunosuppression regimen to balance their risks and benefits. The goals of immunosuppression therapy in AIH recipients of LT are to three: decrease the risk of acute cellular rejection, prevent the recurrence, and improve graft and patient survival.

The combination of a steroid and a calcineurin inhibitor (CNI), such as tacrolimus or cyclosporine A (CsA), are the current immunosuppressive regimen of choice for LT [11,35]. However, other centers opt to initiate with other combinations, either with a CNI alone or adding an antimetabolite drug as mycophenolate or azathioprine (triple immunosuppression) [11,35,36]. Inconclusive data exists about how the immunosuppressive regimen changes impact the rAIH and graft survival rates. For instance, Doycheva et al. found no significant difference in rates of rAIH among the calcineurin inhibitors cyclosporine and tacrolimus [24,27,30]. Another study showed no prevention of rAIH with cyclophos-

phamide or azathioprine ($p = \text{NS}$) [27]. A single-center retrospective European study found that the use of dual immunosuppression with CNI and steroids have a higher risk of AIH recurrence compared to triple immunosuppressive therapy with CNI, steroids, and antimetabolite (OR 1.47, $p = 0.018$) [37]. In contrast, another study showed that the proportion of patients on triple therapy (steroid, azathioprine/mycophenolate, tacrolimus) was similar between patients with and without rAIH [38].

Large multicenter prospective studies are required to confirm which immunosuppressive regimen (single, dual, or triple) is more beneficial in AIH patients after LT.

3. Primary Biliary Cholangitis

PBC is a chronic autoimmune disease that mainly targets biliary epithelial cells. It is more predominant in women, and its complex etiology involves an interaction between genetic susceptibility and environmental factors [39].

After introducing ursodeoxycholic acid as part of the PBC treatment, PBC showed a global increased prevalence rate with heterogeneous geographic and sex ratio distribution. Prevalence ranges from 19.1 (Australia) to 40.2 (Minnesota, USA) cases per million persons. The latest report from the United States estimated a 12-year prevalence of 293 cases per million population, with a mean age at diagnosis of 60 years and a female: male ratio of 4:1 [40]. Despite that PBC is less frequent in men, the course of the disease is poorer than in women, with higher transplant and mortality rates [41].

PBC usually has a chronic course with a diverse clinical presentation. At diagnosis, most patients are asymptomatic (50%) but can progress from developing disabling symptoms, such as unbearable pruritus or fatigue, to ultimately end liver failure and the need for a LT [42]. Patients may also present certain dermatologic signs such as xanthelasma, hyperpigmentation, jaundice, and other autoimmune features as thyroid disorders or Sjogren's syndrome [43].

According to the most recent AASLD guidelines, diagnosis of PBC is established when two of the following three findings are present: (a) elevated serum alkaline phosphatase (ALP); (b) presence of antimitochondrial antibody (AMA) or other autoantibodies (anti-sp100 or anti-gp210) if AMA is negative; (c) liver biopsy showing nonsuppurative biliary ductal destruction. The diagnosis also requires excluding alternative causes of chronic cholestasis such as drug reactions, biliary obstructions, and other autoimmune pathologies [44].

One-third of PBC patients may require LT [45]. However, the indication of PBC for LT has decreased during the last years—2% of all LT in 2018 according to the Organ Procurement and Transplantation Network [43]. This trend may reflect the benefits of early treatment with ursodeoxycholic acid and the availability of emerging alternatives for refractory disease. The indications for LT in PBC are similar to those seen in other end-stage liver diseases with the addition of intractable pruritus [44,46,47]. Compared to other liver diseases, PBC has more favorable post-LT outcomes, with an overall five-year graft and patient survival of 94% and 90%, respectively [48]. Therefore, a small proportion of patients would require a second liver transplant—the cumulative incidence of early retransplantation is about 3.6% [5].

The main concerns in post-LT PBC patients are acute cellular rejection and disease recurrence. Acute cellular rejection after LT rates ranges from 21.7% to 83.3% [49–51], and can increase risk of graft failure, decrease patient and graft survival, and can play a role in the development of recurrence [49,52]. Recurrent PBC (rPBC) is frequent, with rates that range between 14 to 42% [45,53]. A recent study demonstrated that disease recurrence might negatively impact the overall graft and patient survival after LT [48]. For this reason, interventions that prevent the recurrence of the disease may play a role in improving post-transplant outcomes. Table 2 summarizes the rates and risk factors associated with rPBC.

Table 2. Frequency and risk factors for recurrence of Primary Biliary Cholangitis after liver transplantation.

Reference	Sample Size	Frequency	Risk Factors for Recurrence
Wong et al. [54]	2	2 (100%)	Tacrolimus-based immunosuppression
Dmitrewski et al. [55]	27	8 (30%)	Tacrolimus-based immunosuppression
Liermann Garcia et al. [56]	400	68 (17%) at 36 months	Younger age at transplant Tacrolimus-based immunosuppression
Hashimoto et al. [57]	6	2 (33%)	Tacrolimus-based immunosuppression
Khettry et al. [58]	43	8 (18.6%)	Not significant results
Levitsky et al. [59]	46	7 (15%) at 78 months	Not significant results
Sylvestre et al. [60]	100	17 (17%) at 4.7 years	NR
Sanchez et al. [61]	156	17 (10.9%) at 72.1 months	Used of tacrolimus rather than cyclosporine
Neuberger et al. [62]	485	114 (23%)	Recipient's age Use of tacrolimus
Guy et al. [63]	48	17 (35%)	Not significant results
Jacob et al. [50]	100	14 (14%)	Tacrolimus-based immunosuppression
Morioka et al. [64]	50	9 (18%)	Average trough level of Tacrolimus within 1-year LDLT HLA-DR locus mismatching
Charatcharoenwittaya et al. [65]	164	52 (32%) at 3.5 years	Older recipient age at transplant Male gender Tacrolimus-based immunosuppression
Montano-Loza et al. [66]	108	28 (26%) 13% at 5 years 29% at 10 years	Tacrolimus-based immunosuppression Use of mycophenolate mofetil
Bosch et al. [67]	90	48 (53%) 27% at 5 years 47% at 10 years	No significant factors
Egawa et al. [68]	444	65 (14%) 9.6% at 5 years 20.6% at 10 years	Younger age at transplant (<48 years) IgM > 554 mg/dL Gender mismatch Use of Cyclosporin A as initial immunosuppression
Kogiso et al. [69]	330	58 (14.0%) at 4.6 (0.8–14.5) years	Younger recipient age Higher serum IgM Donor sex mismatch Human leukocyte antigen B60 and DR8 Initial treatment with cyclosporine A
Montano-Loza et al. [48]	785	173(22%) at 5 years 283(36%) at 10 years	Biochemical cholestasis within the first 6 months Tacrolimus use
Corpechot et al. [70]	780	233 (30%) 18% at 5 years 31% at 10 years	Exposure to tacrolimus

HLA—human leukocyte antigen; NR—not reported.

Adequate post-LT management in PBC decreases the risk of disease recurrence, graft loss, liver-related death, and all-cause death. After LT, the management relies on the use of immunosuppressants and the use of ursodeoxycholic acid (the most beneficial disease-modifying drug).

3.1. The Role of Ursodeoxycholic Acid

Numerous studies and guidelines have suggested that ursodeoxycholic acid (UDCA) as prophylaxis may decrease the risk of recurrence in LT patients with PBC. The Global PBC Study Group published the most extensive international study of post-LT PBC patients.

The group found that UDCA's preventive administration to post-LT patients was associated with reduced PBC recurrence risk, graft loss, liver-related death, and all-cause mortality. Furthermore, a regimen combining cyclosporine and preventive UDCA was associated with the lowest PBC recurrence risk and mortality [70]. Two meta-analyses confirmed these findings. The first one by Pedersen et al. examined UDCA's effect after LT. They included 12 studies that comprised 1727 patients. They showed that UDCA prophylaxis decreased the rate of rPBC (13.3%, CI: 7.2–19.4%) compared to not using prophylactic UDCA (33.8%, CI: 28.7–38.9%) [71]. The second meta-analysis by Li et al. evaluated the role of prophylactic UDCA as a potential risk factor for PBC recurrence. The use of preventive UDCA significantly reduced the risk of rPBC (HR of 0.40, 95% CI: 0.28–0.57, $p < 0.001$, $I^2 = 0\%$) [72].

UDCA's preventive administration (10–15 mg/kg/d) should be initiated soon after LT to prevent PBC recurrence and improve graft and patient survival [67,70]. Further studies are required to determine if second-line therapies would also represent an option for post-LT PBC patients.

3.2. Immunosuppression Therapy

In Europe and the USA, the primary maintenance immunosuppressants used after LT are CNIs. Among all CNIs, tacrolimus constitutes the drug of choice. Nonetheless, CNIs have numerous adverse events, particularly those related to renal toxicity. For that reason, there is an increasing trend to use antimetabolites such as mycophenolate mofetil (MMF) due to its more acceptable safety profile [73–75]. However, these recommendations might vary when PBC is the LT indication.

Most of the studies are inconsistent in describing the impact of immunosuppressors after LT in PBC patients. The Global PBC Study Group published two consecutive multicenter international studies. The first study included a database of 789 patients with PBC who underwent LT. Results showed that tacrolimus (HR 2.31, 95% CI 1.72–3.10, $p < 0.001$) was associated with a higher risk of PBC recurrence. Likewise, mycophenolate mofetil (HR 1.56, 95% CI: 1.19–2.04; $p = 0.001$) and cyclosporine (HR 0.62, 95% CI: 0.46–0.82; $p = 0.001$) were weakly associated with the recurrence of PBC [48]. The second one, the largest multicenter cohort study published so far, reaffirmed the previous results showing that tacrolimus exposure increased the risk of rPBC (HR 2.06, 95% CI: 1.44–2.94, $p < 0.0001$) and supported the use of cyclosporine A in post-LT PBC patients [70].

Two meta-analyses published in 2020 also explored the relationship between immunosuppressive therapy and the risk of recurrence of the disease. One found that the use of mycophenolate mofetil, azathioprine, tacrolimus, or cyclosporin was not a significant risk factor for rPBC after LT [76]. Additionally, when analyzing “tacrolimus vs. cyclosporine A,” no significance was found. The second study evaluated the risk factors for recurrence in PBC patients. The authors included six studies with a total of 3184 PBC patients, where 935 (29%) developed recurrence of the disease. The study concluded that tacrolimus increased the risk of PBC recurrence (HR 2.62, 95% CI: 1.35, 5.09) [72].

An immunosuppression protocol that meets all LT recipients' needs is currently unavailable, and actual therapeutic regimens seem to vary depending on the LT indication. Based on the available evidence, cyclosporine A reduces PBC recurrence; therefore, it should be considered over tacrolimus as the primary immunosuppressant after LT.

4. Primary Sclerosing Cholangitis

PSC is a chronic, immune-mediated cholestatic liver disease that mainly affects intra- and extrahepatic bile ducts, causing progressive inflammation and obliterative fibrosis, promoting multiple strictures [15,77–80]. The etiology remains unclear, and it may be triggered by toxic or infectious agents in individuals with an immunogenetic predisposition. PSC has a strong association with inflammatory bowel disease (IBD); up to 75% of cases are ulcerative colitis (UC) and occurs mainly in men [81,82]. This association increases the risk of liver disease progression when compared to Crohn's disease [83,84].

The prevalence of this rare disease is low but is more commonly seen in northern countries. The global incidence of PSC is 0.77 per 100,000 persons at risk. In a recent population-based epidemiologic US study, the incidence was 1.11 per 100,000 persons, and the prevalence 23.99 per 100,000 persons in 2018 [85]. PSC has a higher prevalence among men with a mean age of diagnosis at 37 years old [83].

Clinical presentation is highly variable. Over half of patients are asymptomatic at diagnosis, and most of them present abnormal liver function tests for an extended period [79,86]. Symptomatic patients present most commonly with fatigue, upper quadrant abdominal pain, and pruritus [85]. Recent studies showed that fatigue might persist after LT in female recipients [87]. A more aggressive presentation of the disease is characterized by recurrent episodes of biliary tract obstruction and subsequent cholangitis that may progress to cirrhosis, liver failure, or develop hepatobiliary malignancies [77,80].

PSC diagnosis encircles a combination of clinical, laboratory, imaging, and histological findings. Abnormal cholestatic liver tests (particularly alkaline phosphatase elevation) are present. Magnetic resonance cholangiography (MRCP) is the current gold standard diagnostic method, where the presence of multifocal strictures in the intra- and extra-hepatic bile ducts are usually sufficient for the diagnosis of PSC. Liver biopsy with the pathognomonic “onion skin” fibrosis is rarely found and unnecessary to establish the diagnosis. Nevertheless, biopsy helps to exclude secondary causes of sclerosing cholangitis and identify overlapping syndromes [80,88].

No immunosuppressive or disease-modifying agents are currently available to prevent PSC patients from progressing to end-stage liver disease [89]. Liver transplant is the only proven treatment to prolong survival among PSC patients with end-stage liver disease [90]. Recently, the International PSC Study Group (IPSCSG) showed that 36.7% of PSC patients progress to liver transplantation or death during a median follow-up of 14.5 years [83]. Based on the United Network for Organ Sharing (UNOS) database, PSC has been the leading indication for LT among AILDs and has increased over the last years. From 2008 to 2016, PSC patients accounted for 48% of total liver transplants for autoimmune diseases and accounted for 4.5% of all LT indications [5]. Post-LT outcomes are favorable, with five-year graft and patient survival of 85.4% and 85.5%, respectively, and only 3.6% of patients requiring retransplantation [91]. After LT, the main causes of graft failure are acute and chronic cellular rejection, hepatic artery thrombosis, biliary strictures, and disease recurrence [92]. PSC is now the most common disease to recur after liver transplantation [79]. The recurrence of the disease occurs in up to 20% of LT recipients within five years, increasing up to four times the risk of graft failure or mortality [93]. Table 3 describes the different rates and risk factors associated with rAIH.

Table 3. Frequency and risk factors for recurrence of Primary Sclerosing Cholangitis after Liver transplantation.

Reference	Sample Size	Frequency	Risk Factors for Recurrence
Goss et al. [94]	127	11 (8.6%)	NR
Jeyarajah et al. [95]	100	18 (18%) at 21 months	Younger recipient age CMV infection IBD presence
Graziadei et al. [92]	150	30 (20%) at 55 months	NR
Vera et al. [96]	152	56 (37%) at 36 months	Male gender
Khettry et al. [97]	51	6 (14%)	Donor-recipient gender mismatch
Kugelman et al. [98]	71	15 (21.1%)	Use of orthoclone (OKT3)
Brandsaeter et al. [99]	61	19 (39%)	Steroid-resistant rejection
Balan et al. [29]	NR	NR	HLA-A locus mismatching
Cholongitas et al. [100]	69	7 (13.5%) at 6 months	Ulcerative colitis requiring maintenance steroids
Campsen et al. [101]	130	22 (16.9%) at 60 months	Presence of cholangiocarcinoma before transplantation

Table 3. Cont.

Reference	Sample Size	Frequency	Risk Factors for Recurrence
Alexander et al. [102]	69	7 (10%) at 68 months	Presence of HLA-DRB1*08 ACR Steroid-resistant ACR
Alabraba et al. [103]	230	54 (23.5%) at 4.6 years	Presence of intact colon after transplant
Egawa et al. [104]	30	11 (37%)	CMV diseases Related donor
Kashyap et al. [105]	58	11 (19%) at 41.5 months	NR
Moncrief et al. [106]	59	15 (25%) at 40.2 months 21% at 5 years 37% at 10 years	Acute cellular rejection Cytomegalovirus mismatch
Mason et al. [107]	92	NR	Cholestasis at 3 months
Gelley et al. [108]		6 (12%)	Active IBD in the colon
Ravikumar et al. [109]	679	81 (14.3%) at 9 years	Younger age Presence of UC after LT
Hildebrand et al. [110]	335	62 (20.3%) at 4.6 years	IBD Older donor age Higher INR at the time of LT
Gordon et al. [111]	306	34 (11%) 8.7% at 5 years 22.4% at 10 years	Biliary complication Higher donor age Pre-transplant cholangiocarcinoma
Ueda et al. [112]	45	16 (40%) at 30 months 39.3% at 5 years 45.8% at 10 years	Active IBD after LT
Lindström et al. [113]	440	85 (19%)	Treatment with tacrolimus
Bajer et al. [114]	47	21 (44.7%) at 63 months	De novo colitis after LT History of ACR

HLA—Human leukocyte antigen; IBD—Inflammatory bowel disease; CMV—Cytomegalovirus; NR—not reported; LT—Liver transplant; ACR—Acute cellular rejection; INR—International normalized ratio.

Patients with PSC have unique characteristics related to IBDs and a higher risk of gastrointestinal malignancies after LT that may lead to additional management strategies aside from the general measures due to other LT indications. Three strategies are essential: the immunosuppression therapy, the management of colitis and colonoscopy surveillance through the transplant process. Both strategies are directed to improve post-LT outcomes.

4.1. Immunosuppression Therapy

The immunosuppression regimen after LT in PSC patients consists of a CNI, mainly tacrolimus, either with corticosteroids as dual therapy or with the addition of an antimetabolite as a triple regimen. Like for the other autoimmune indications, the regimen intends to prevent disease recurrence and improve graft survival. Data regarding the impact of the immunosuppression type on the PSC recurrence rate is inconclusive. For instance, two different European large multicenter studies tested the influence of CNI types on rPSC after LT. One of them in the UK, within 679 patients, found a trend for more rPSC in the cyclosporine group; however, it did not reach statistical significance (HR 2.07, 95% CI: 0.97–4.44) [109]. The second was a German study that included 335 patients and did not find a significant influence of either tacrolimus or cyclosporine on rPSC (HR 1.17, 95% CI: 0.68–1.99, $p = 0.58$ and HR 0.71, 95% CI: 0.43–1.18, $p = 0.19$, respectively) on rPSC [110]. In contrast, a multicenter nordic study that included 440 transplanted PSC patients showed that tacrolimus was associated with an increased risk of rPSC (HR of 1.81; 95% CI 1.15–2.82; $p = 0.10$) [113]. A meta-analysis by Chen et al. also explored the relationship between the

immunosuppressant type and the rPSC risk. They include only two studies and comprised 775 patients. They found that cyclosporine A decreased the risk of rPSC after LT, whereas tacrolimus did not (HR 0.69, 95% CI: 0.49–0.97, $p = 0.03$ and HR 1.48, 95% CI: 0.98–2.24, $p = 0.06$, respectively) [76].

One special consideration that may influence the choice of immunosuppressive therapy in patients with PSC is the underlying IBD activity. In this regard, several studies have coincided that both tacrolimus and its combination with mycophenolate mofetil increase the risk of IBD relapse after LT [115].

Large multicenter prospective studies are required to confirm which immunosuppressive regimen is more beneficial in PSC patients after LT.

4.2. Role of Colectomy before LT on Post-LT Outcomes

The presence of active ulcerative colitis after LT increases the risk of disease recurrence [100]. Previous publications showed that colectomy was carried out at lower or equal rates in LT recipients with rPSC compared to the non-recurrence group [116]. Some authors suggested that colectomy before LT may prevent recurrence of the disease and colon cancer. Recent studies suggested that the gut microbiome can play a role in the protective effect of colectomy; however, data is still inconclusive. Also, inconsistency exists whether colectomy should be performed prior, at, or after LT [2]. A Nordic cohort study of 440 PSC patients who underwent LT between 1984 and 2007 showed that colectomy before or at LT decreases the disease's recurrence at almost half of it (HR 0.49, 95% CI: 0.26–0.94, $p = 0.033$) [113]. Another study also revealed that compared to ileal pouch-anal anastomosis or no colectomy, colectomy with end-ileostomy improved graft survival and decreased disease recurrence [117].

Two recent meta-analyses confirmed that colectomy prior to LT indeed decreases the risk of recurrence of PSC. One of these studies by Steenstraten et al. demonstrated that colectomy before LT reduced the risk for rPSC with marginal significance (HR 0.65, 95% CI: 0.42–0.99) [118]. Likewise, a meta-analysis by Chen et al. found a significant inverse correlation between colectomy before LT and rPSC (HR 0.59, 95% CI: 0.37–0.96) [76].

Accordingly, better control of inflammatory activity should be adopted since it protects against rPSC. Moreover, a lower threshold for colectomy should be considered in PSC-IBD patients who need LT [76,118].

4.3. Colonoscopy Surveillance after Liver Transplantation

Liver transplantation guidelines recommend routine annual colonoscopies in the pre-LT setting as part of colorectal cancer surveillance in PSC patients. However, patients with normal colonoscopies before LT can have CRC diagnosed within the first two years after LT [119,120].

IBD is well established as a predisposition to colorectal cancer (CRC). The risk increases when patients have concomitant PSC. Interestingly, the risk for CRC does not resolve after LT [121]. Based on several studies, CRC seems to be four times higher in PSC patients after liver transplantation when compared to non-PSC patients. The risk increases to up to ten times in the subset of PSC-IBD patients [119,122,123]. Potential contributors to the increased risk of CRC might be the immunosuppressive regimen, and a more aggressive IBD course after LT. Furthermore, some PSC-related mechanisms may also contribute to the carcinogenesis, such as an alteration in bile acids pool, an increased concentration of secondary bile acids, microbiome dysbiosis, farnesoid X receptor downregulation, and colonic mucosal inflammation [82,100,123–125].

Despite limited data about CRC prevention, the AASLD guidelines for LT management recommend post-transplant annual colonoscopy with mucosal biopsy for PSC recipients in case they have UC [120]. For non-IBD PSC patients we recommend to repeat colonoscopies every 5 years. However, further studies should be done to prove whether annual surveillance would be beneficial in this population [126].

5. Bone Maintenance

Bone diseases are a serious complication during the peri-transplant period. It increases the risk of fractures and negatively impacts morbidity and mortality in post-LT patients. Regardless of their pre-LT bone mineral density, patients have an accelerated bone loss rate during the first three to six months after LT. For instance, PBC and PSC patients can have up to 18% of bone loss during the first post-LT semester [75,127–130]. After this period, bone mass loss decreases, especially in patients with a normal graft function [120]. The importance of bone loss timing is important; the higher bone loss during the first semester correlates with the higher incidence of fractures during the first year [131]. The prevalence of bone fractures in the first year after liver transplant ranges from 20% to 43% [128,130,132].

Among metabolic bone diseases, osteoporosis and osteopenia are the most frequently encountered. Osteoporosis is defined as bone mineral density (BMD) ≥ 2.5 standard deviations below the mean value for the young adult population (T-score) on dual X-ray absorptiometry (DXA). A score between 1 and 2.5 standard deviations below the average is known as osteopenia [128,133].

The underlying autoimmune condition plays a role in the pathophysiology of bone loss. Cholestasis syndromes such as PBC and PSC are prone to increase bone mass loss due to malabsorption of lipid-soluble vitamins and impaired hepatic 25-hydroxylation. AIH patients have an increased risk of osteoporosis primarily due to corticosteroid use. Regardless of the etiology, liver transplantation is a risk factor due to numerous factors: undernutrition, immobilization, or use of immunosuppression [134–136].

There are three essential components that should be considered in each transplant patient to ensure an adequate bone health after LT: the prevention, early detection and treatment of osteoporosis.

5.1. Prevention of Osteoporosis

One essential component consists of bone loss. Some of the key measures to prevent bone loss are the following: early mobilization after transplantation, alcohol and smoking cessation, regular weight-bearing exercises, avoidance of drugs that have a negative impact on bone metabolism, and a balanced diet that ensures adequate levels of calcium and vitamin D [137].

Vitamin D deficiency is common in patients with liver diseases, with rates up to 91% in the LT waiting list and 84% in patients after LT [138]. Although some studies have failed to demonstrate that vitamin D and calcium improve BMD or reduce the risk of fracture, other benefits were proven. A recent retrospective cohort of 528 post-LT transplant patients concluded that sufficient vitamin D levels improved survival and decreased the risk of ACR (HR 0.31, 95% CI: 1.38–8.68, $p < 0.01$ and sHR 0.09, 95% CI: 0.01–0.72, $p = 0.02$, respectively) [139].

Patients with autoimmune liver disease have a risk of vitamin D deficiency that differs slightly between them. In patients with AIH, vitamin D insufficiency (serum 25-hydroxyvitamin D level, ≤ 29 ng/mL) and severe vitamin D deficiency (serum 25-hydroxyvitamin D level, ≤ 7 ng/mL) occur in 68%–81% and 20% of the cases, respectively [11]. A retrospective study that evaluated 209 AIH patients found that vitamin D increased five times more the risk of liver-related mortality or requirement for liver transplantation (HR 5.26, 95% CI: 1.54–18.0, $p = 0.008$) [140]. These findings justify assessing serum 25-hydroxyvitamin D levels in all AIH patients at diagnosis and supplementing vitamin D as clinically indicated.

Data regarding vitamin D levels in PBC patients is contradictory. Some authors found a decreased calcium absorption and serum vitamin D levels in PBC patients compared to controls [141,142]. Others found normal levels of vitamin D [143]. However, when vitamin D deficiency is present, it is more prevalent in patients with advanced-stage PBC compared to early-stage PBC patients [144–146]. Furthermore, vitamin levels in PBC patients are lower among those who suffered death or transplant ($p = 0.023$).

In patients with PSC, many suffer from inflammatory bowel disease, which increases the risk of bone disease. Also, glucocorticoid treatment increases the rate of bone loss and risk of fracture. Post-LT PSC patients are prone to develop fractures, even in the absence of metabolic bone disease, due to immobilization and concomitant therapy with glucocorticoids [147].

Due to the high risk of vitamin D deficiency, patients with AILDs require nutritional counseling and vitamin D and calcium supplementation after LT. We follow the AASLD guidelines. In patients with AIH, we recommend daily supplementation of elemental calcium and vitamin D at 1000–1200 mg and 400–800 IU, respectively. In patients with PBC, we recommend daily supplementation with calcium and vitamin D at 1500 mg and 1000 IU, respectively. In patients with PSC, we recommend a mandatory daily supplementation of calcium 1000–1200 mg and vitamin D 400 IU (10 µg) [120,148].

5.2. Early Detection of Osteoporosis

The second component to ensure a healthy bone after LT consists in the early detection of osteoporosis through the assessment of the bone mineral density (BMD). BMD screening is done by using a Dual Energy X-ray Absorptiometry (DEXA) scan. The screening frequency of BMD is similar among all AILDs [11,44,115,120]. Patients with osteopenia require annual BMD screening in the first years after LT. Patients with normal BMD require screening every 2 to 3 years. The frequency of the subsequent BMD screening is assessed on an individual basis and depends upon the progression of the underlying disease or the presence of different risk factors (e.g., glucocorticoids use, postmenopausal status, history of low-trauma fracture, elderly age) [120,137].

5.3. Treatment of Osteoporosis

The third component are specific measures to treat osteoporosis. Bisphosphonates are the most common medications used to treat osteoporosis and its use might be the most appropriate to manage LT populations with high risk of fractures [149]. Bisphosphonates include: etidronate, alendronate, risedronate, pamidronate, ibandronate and zoledronic acid. After LT, they are indicated in recipients with osteoporosis or osteopenia with high risk of fracture. Route and dosing can be either by weekly dose of oral agents (alendronate or risedronate), or by monthly dose of intravenous bisphosphonates (pamidronate or ibandronate). Previous studies demonstrated that either oral or intravenous agents can improve BMD after LT, but they lack conclusive data about the effects on fracture prevention after LT [149,150].

A randomized, double-blind, placebo-controlled trial tested the effect of zoledronic acid on bone loss in patients with chronic liver disease that underwent LT. 62 patients were randomly assigned to receive either infusions of zoledronic acid, or saline, and it was given within 7 days of transplantation, and at month 1, 3, 6, and 9 after LT. All patients received supplementation with calcium carbonate and ergocalciferol. The results showed that zoledronic acid improved BMD over placebo after 3 months. However, the study did not have enough power to assess the effect of zoledronic acid on fractures [151].

Another prospective, randomized controlled trial tested the effects of weekly alendronate (70 mg) on bone mineral density after liver transplantation. 98 LT patients were randomized to receive either alendronate 70 mg weekly or placebo; daily calcium and calcitriol were also provided to all patients. The alendronate group had a significant increment in BMD of the lumbar spine ($5.1 \pm 3.9\%$ vs. $0.4 \pm 4.2\%$, $p < 0.05$), femoral neck ($4.3 \pm 3.8\%$ vs. $-1.1 \pm 3.1\%$, $p < 0.05$) and total femur ($3.6 \pm 3.8\%$ vs. $-0.6 \pm 4.0\%$, $p < 0.05$) at 12 months when compared with calcium and calcitriol alone. However, alendronate failed to decrease the risk of fractures after LT ($p > 0.05$) [152].

Later on, a randomized controlled trial compared an intravenous bisphosphonate (zoledronic acid, single 5 mg infusion) with oral alendronate (70 mg weekly). Results showed that BMD increased by 3.6% in the alendronate group (95% CI, 1.5 to 5.7%; $p = 0.017$), and 2.7% in the zoledronic acid group (95% CI: 0.5 to 4.8%, $p = 0.02$). The

between-group comparison showed that both interventions had similar efficacy to prevent bone loss at the hip during the first year after LT (-0.7% , 95% CI: -3.2 to 1.8% , $p = 0.58$) [153]. The lack of clinical benefit in the prevention of fractures after LT brings out the need for further studies. Figure 1 summarizes all the post-LT strategies for each autoimmune liver disease, and the management of osteoporosis after LT.

Figure 1. Post-liver transplant algorithm management. LT—liver transplant; AILD—autoimmune liver disease; AIH—autoimmune hepatitis; PBC—primary biliary cholangitis; PSC—primary sclerosing cholangitis; CNI—calcineurin inhibitors; UDCA—ursodeoxycholic acid; IBD—inflammatory bowel disease; BMD—bone mineral density.

In conclusion, the AASLD recommends starting with weekly oral alendronate (70 mg). However, other oral agents as risedronate (35 mg) may be equally effective. In cases of oral intolerance, intravenous agents as zoledronic acid or ibandronate may be used [120].

6. Metabolic Syndrome

Metabolic syndrome is a cluster of lipid and non-lipid factors that aim to identify patients at high risk for cardiovascular diseases outside the common cardiac risk factors. It is highly prevalent in liver transplant patients (40–60%), and its increasing prevalence correlates with an increased incidence of cardiovascular diseases [154,155]. A large retrospective cohort of patients who underwent LT showed that metabolic syndrome was almost two times more prevalent in patients who developed cardiovascular events compared to those who did not (61% vs. 37%, $p < 0.001$). In addition, cardiovascular diseases constitute the second most common non-hepatic cause of mortality in patients after liver

transplantation [156,157]. For this reason, management of metabolic syndrome constitutes a matter of uttermost importance [158].

According to the 2001 guidelines of the National Cholesterol Education Program Adult Treatment Panel III (ATP III), the diagnosis of metabolic syndrome is made by the presence of three or more of the following risk factors: blood pressure $\geq 130/85$ mm Hg, abdominal obesity (abdominal circumference >102 cm for men and >90 cm for women), fasting blood glucose levels ≥ 110 mg/dL, plasma triglycerides ≥ 150 mg/dL, and low plasma concentrations of HDL cholesterol (<40 mg/dL for men and <50 mg/dL for women) [159]. The management of this condition consists of lifestyle modifications, direct therapies against each component of the metabolic syndrome, and glucocorticoid or immunosuppressive regimens modification.

Approximately one-third of patients with normal weight at the time of transplant become overweight or obese after the procedure [156]. Furthermore, only 24% of patients perform an adequate amount of at least 150 min of exercise per week [160]. Main lifestyle changes include weight reduction through a limited caloric intake with low proportions of simple or processed carbohydrates and increased physical activity [154]. Regular physical activity has beneficial effects on the prevention and management of dyslipidemia, reducing the risk of cardiovascular events [161]. Current guidelines do not include specific physical activity targets for liver transplant patients. Based on general recommendations as to the Physical Activity Guidelines for Americans, it seems adequate to encourage LT recipients 150 min a week of moderate-intensity aerobic activity along with 15 to 20 min of resistance exercise training twice per week [162,163].

Therapies against metabolic syndrome components include treating hypertension, dyslipidemia, and diabetes mellitus. Figure 2 describes the key points involved in the management of these pathologies in the post-LT setting.

Hypertension	Dyslipidemia	Diabetes mellitus
<ul style="list-style-type: none"> • Goal: BP $< 130/80$ mmHg • General measures: Sodium restriction, smoking cessation, alcohol avoidance, regular exercise, early tapering of steroids. • Pharmacotherapy: <ul style="list-style-type: none"> • First line: <ul style="list-style-type: none"> • Calcium channel blockers as amlodipine or felodipine. Avoid diltiazem and verapamil because of interaction with CNI. • Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, in the late post-transplantation period. • Second line: Cardioselective beta-blockers 	<ul style="list-style-type: none"> • Goal: LDL cholesterol < 100 mg/dL, triglycerides < 250 mg/dL • General measures: diet and lifestyles changes • Statins are safe in the posttransplant population and may be used as needed to treat dyslipidemia • Pravastatin and fluvastatin are not metabolized by CYP3A4 and do not increase the risk for statin-associated myopathy when used with a calcineurin inhibitor. • Add ezetimibe if target LDL is not achieved. • Try fish oil omega-3 (2000–4000 mg daily) if triglycerides levels do not respond to diet lifestyles changes • Fibrates with caution when combined with statins. 	<ul style="list-style-type: none"> • General measures: Lifestyle changes • Target HbA_{1c} $< 7.0\%$ • Try oral antidiabetics followed by insulin • First choice: Metformin <ul style="list-style-type: none"> • Not recommended in patients with GFR < 60 mL/min/1.73 m² (creatinine level < 1.5 mg/dL) • Choices follow recommendations from the general population, except for sodium-glucose cotransporters-2 inhibitors

Figure 2. Key points in the management of hypertension, dyslipidemia, and diabetes mellitus in post-liver transplant patients. BP—blood pressure; CNI—calcineurin inhibitors; LDL—low-density lipoprotein; CYP3A4—cytochrome P450 3A4; HbA_{1c}— hemoglobin A_{1c}; GFR—glomerular filtration rate.

Modification of immunosuppression regimens helps to decrease the risk of metabolic syndrome [164]. Calcineurin inhibitors (CNIs) such as cyclosporine or tacrolimus are associated with hyperlipidemia, hypertension, and diabetes mellitus. Within CNIs, cyclosporine is associated with an increased risk of hyperlipidemia in post-solid organ transplant pa-

tients compared to tacrolimus. In this setting, it seems appropriate to change cyclosporine to tacrolimus to decrease LDL and triglyceride levels. Prolong steroids after LT increase very-low-density lipoprotein (VLDL) secretion, and its conversion to low-density lipoprotein (LDL); contributes to obesity and diabetes, hence promoting hyperlipidemia and hypertension. Corticosteroids should be avoided, reduced to a minimum duration, or withdrawn to improve the metabolic profile after LT [165–170]. Mammalian target of rapamycin (mTOR) inhibitors such as rapamycin, sirolimus, or everolimus increase lipid serum levels, mostly triglycerides and LDL cholesterol. Unlike CNIs and steroids, mTOR inhibitors are not diabetogenic. Regimens using mTOR inhibitors should be avoided in recipients with serum triglyceride concentrations higher than 500 mg/dL, or LDL cholesterol higher than 250 mg/dL refractory to lifestyle changes and lipid-lowering agents [164,165,170–172]. Other strategies to minimize the use of CNIs and steroids, and reduce the subsequent risk of hyperlipidemia and diabetes, include the introduction or increase in the mycophenolate or azathioprine doses [154,165].

By preventing, diagnosing, and treating metabolic syndrome, we decrease the likelihood of CVD development among post-LT patients. Clinicians should assess for all features of metabolic syndrome before and after LT. The presence of metabolic syndrome requires aggressive management that includes targeted therapy, lifestyle modification, and optimization of immunosuppressive therapy. Any subsequent changes in the therapeutic regimens should consider the improvement of graft and patient survival while minimizing the risk of metabolic syndrome development.

7. Biopsy in the Diagnosis of Recurrence of AILDs

Post-transplant management do not include protocol liver biopsy for AILDs patients [120]. Hence, most centers relied on an event-driven biopsy instead of a routine screening for disease recurrence. Therefore, a liver biopsy should be performed when transplanted patients' liver function start to decline.

8. Conclusions

LT is the treatment of choice for patients with irreversible liver damage due to AILDs. Each AILD requires particular therapeutic strategies; however, they also share some common goals: to improve recipient's survival, to prevent liver graft-failure, and to decrease recurrence of the disease. Most of the studies are inconsistent regarding recommendations of steroids and immunosuppressors after LT. However, glucocorticoids and CNI remain the therapeutic strategies, as well as UDCA, particularly, in PBC patients. Post-transplant complications such as osteoporosis or metabolic syndrome can negatively impair on the quality of life of LT recipients, and they need to be addressed.

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