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Relapse of autoimmune diseases after liver transplantation

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Abstract

Background. *The recurrence of autoimmune liver diseases can lead to reduced survival of recipients and grafts.*

Aim. *To study the incidence and impact of the recurrence of autoimmune liver diseases on graft survival; the effect of maintenance immunosuppression on the recurrence of autoimmune diseases in liver transplant recipients*

Material and methods. *Transplantation outcomes in 111 recipients (21 recipients operated on for autoimmune hepatitis, 50 recipients operated on for primary biliary cirrhosis, and 40 recipients operated on for primary sclerosing cholangitis) were analyzed retrospectively.*

Results. *The recurrence of autoimmune hepatitis is observed in 5%, the recurrence of primary biliary cirrhosis is in 10%, and the recurrence of primary sclerosing cholangitis is in 17% of cases. Among patients with recurrence of autoimmune diseases, men accounted for 54%, while for only 31% in the subgroup of patients without relapse (p=0.004). The follow-up for recipients with relapse (64.5 (42.8; 82.0) months) was comparable to the follow-up for recipients without relapse (46.5 (17.9;103.5) months, p=0.54). A ten-year graft survival was significantly*

higher in the group of recipients with recurrent autoimmune diseases compared with recipients without autoimmune diseases recurrence (p<0.0001).

Conclusions. *The recurrence of autoimmune diseases leads to a decrease in graft survival. The effect of immunosuppression components on the risk of recurrence of autoimmune diseases in the graft has not been established.*

Keywords: liver transplantation, primary sclerosing cholangitis, primary biliary cholangitis, primary biliary cirrhosis, autoimmune hepatitis, recurrence of liver diseases

Conflict of interests Authors declare no conflict of interest

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ASMA, anti-smooth muscle antibodies

AIH, autoimmune hepatitis

ALD, autoimmune liver disease

ALT, alanine aminotransferase

AMA, antimitochondrial antibodies

ANA, antinuclear antibodies

Anti-LKM, anti-liver kidney microsomal antibodies

AZA, azathioprine

CI, confidence interval

CNI, calcineurin inhibitor

CYC, cyclosporine

EVE, everolimus

GCS, glucocorticosteroid

GD, graft dysfunction

GT, graft cirrhosis

HA, hepatic artery

LT, liver transplantation

MPA, mycophenolic acid

OR, odds ratio

PBCh, primary biliary cholangitis

PBCi, primary biliary cirrhosis

PS, prednisolone

PSC, primary sclerosing cholangitis

PTLD, post-transplant lymphoproliferative disease

re-LT, liver retransplantation

TAC, tacrolimus

UDCA, ursodeoxycholic acid

Introduction

Liver transplantation (LT) is the only definitive treatment for end-stage liver disease caused by autoimmune hepatitis (AIH), primary biliary cholangitis (PBCh, formerly called primary biliary cirrhosis (PBCi)) and primary sclerosing cholangitis (PSC). These diseases are referred to as autoimmune liver diseases (ALDs), although autoimmunity does not fully explain the pathogenesis of these diseases. Autoimmune hepatitis is a classic autoimmune disease with a significant female-to-male predominance (7:1), hypergammaglobulinemia, an almost invariable presence of autoantibodies in the blood, other autoimmune comorbidities, and good clinical, serological, and histological responses to anti-inflammatory drugs such as corticosteroids and azathioprine. Another disease, PBCh/PBCi, has some features of autoimmune diseases, including the reactivity to specific mitochondrial autoantigens (the E2 component of the pyruvate dehydrogenase complex [PDC-E2]), the presence of anti-mitochondrial antibodies (AMA) in more than 90% of patients, the predominance of women (10:1), and is often associated with

other autoimmune diseases. Despite this, PBCh does not respond to any anti-inflammatory or immunosuppressive drugs. Finally, of the three liver diseases mentioned, PSC is the least common autoimmune disease. This disease is characterized by a male-to-female predominance (2:1), the absence of disease-specific autoantibodies, and a complete lack of response to anti-inflammatory and immunosuppressive drugs. In PSC patients, non-specific perinuclear antibodies against neutrophil cytoplasm (pANCA) are sometimes detected; and in 80% of patients there is an association with inflammatory bowel diseases. In addition, overexpression of genes involved in innate and acquired immune responses has been demonstrated in genome-wide association studies (GWAS).

Meanwhile, LT for the indications such as autoimmune liver diseases has promising outcomes. Outcomes after LT performed for autoimmune diseases are satisfactory. One-year and 5-year recipient survival rates are about 90% and 70%, respectively [1]. ALD recurrence has been reported by various research teams to be between 10% and 50% of patients with AIH, PBCh, and PSC [2]. This large variation in ALD recurrence rates may be due to differences in protocol-based liver biopsy practices at different transplant centers. The ALD recurrence may adversely affect the graft and recipient survivals.

Prospective studies investigating factors that may influence the ALD relapse are lacking because there is a small number of such patients at each center, and different institution use different immunosuppression regimens. In addition, such studies can obviously only be observational, and not interventional in nature.

Over the past two decades, risk factors for the recurrence of autoimmune graft diseases have been studied in numerous single-center and several multicenter retrospective studies. There is a great variability

in reported risk factors across studies due to differences in patient populations, sample sizes, factors studied, and statistical methods.

The aim of our study was to investigate the incidence of recurrent ALDs and their impact on graft survival, as well as the impact of maintenance immunosuppressive therapy regimens on the recurrence of autoimmune diseases in the liver graft.

Material and methods

From September 2000 to July 2021, 136 LT from a post-mortem donor for the end-stages of ALD were performed in the Department for Liver Transplantation of the N.V. Sklifosovsky Research Institute for Emergency Medicine. We retrospectively analyzed transplant outcomes in 111 recipients. Excluded from the analysis were the following: 14 recipients who died in the early post-transplant period; 4 recipients who discontinued follow-up in the Liver Transplantation Unit; 6 recipients who had been followed-up at the time of analysis for less than 6 months; and a recipient whose immunosuppressive therapy was changed during the follow-up. The final analysis included 21 recipients operated on for AIH, 50 recipients operated on for PBCh/PBCi, and 40 recipients operated on for PSC.

Statistical processing of digital values was performed using the *Statistica 8.0* software. When comparing frequencies, a two-tailed Fisher's exact test was used. To compare two groups by quantitative characteristics, the Mann-Whitney test was used. Results are presented as median and interquartile range. Survival analysis was performed using the Kaplan–Meier estimator of multiplied probabilities. Intergroup comparisons were made basing on the log-rank test. Differences between the compared parameters were considered statistically significant if the error probability was less than 0.05 ($p<0.05$).

Results

The recurrence of ALD in the graft was observed in 13 of 111 recipients (11.7%): in 1 (4.7%) with AIH; in 5 (10%) who had PBCh; and in 7 recipients (17.5%) with PSC. The diagnosis of recurrent AIH and recurrent PBCh/PBCi was verified histologically in all patients. The PSC recurrence for the recipients was verified cholangiographically; in 4 of them the histological verification was also performed.

Table 1. The incidence of the recurrence of autoimmune diseases in liver transplant recipients with regard to gender and the maintenance immunosuppression scheme

Group		Gender (m/f)	CNI (TAC/ CYC)	EVE	MPA	GCS	AZA	CNI+ MPA or CNI +GCS	CNI + MPA + GCS
All (n=111)	Recurrence (n=13)	**7/6‡**	**7 ‡**	1 (7.6%)	3 (23%)	7 (54%)	2 (15%)	6 (46%)	3 (23%)
	No recurrence (n=98)	**23/75 ‡**	**81/17 ‡**	13 (13%)	42 (43%)	59 (60%)	9 (9%)	44 (45%)	32 (33%)
AIH (n=21)	Recurrence (n=1)	0/1	0/1	0	0	0	0	0	0
	No recurrence (n=20)	1/19	16 /4	2 (10%)	7 (35%)	15 (75%)	0	12 (60%)	5 (25%)
PBCh/PBCi (n=50)	Recurrence (n=5)	1/4	**1/4‡**	0	2 (40%)	1 (20%)	0	3 (60%)	0
	No recurrence (n=45)	1/44	**34/11‡**	6 (13%)	22 (49%)	21 (47%)	3 (7%)	21 (47%)	12 (27%)
PSC (n=40)	Recurrence (n=7)	6/1	5/2	1 (14%)	1 (14%)	6 (86%)	2 (29%)	3 (43%)	3 (43%)
	No recurrence (n=33)	21/12	31/2	5 (15%)	13 (39%)	23 (70%)	6 (18%)	11 (33 %)	15 (45%)

Notes: ‡ $p < 0.05$; CNI, calcineurin inhibitor; TAC, tacrolimus; CYC, cyclosporine; MPA, mycophenolic acid; PS, prednisolone; EVE, everolimus, AZA, azathioprine; GCS, glucocorticosteroid

When analyzing the entire group of recipients, we found that the ALD recurrence was more often observed in men than in women. Among patients with recurrent ALD, men accounted for 54%, while in the subgroup of patients without ALD recurrence, men accounted only for

23% ($p<0.05$). In addition, the risk of recurrent ALD developing was higher in the recipients receiving cyclosporine than tacrolimus (29% vs. 7%, $p=0.007$). A relationship between cyclosporine and the risk of ALD recurrence was seen in the PBCh but not PSC group.

No relationship of other components of immunosuppressive therapy or their combinations to the risk of ALD recurrence in the graft have been established (Table 1).

Table 2. Characteristics of liver transplant recipients with recurrence of autoimmune graft disease

No	Full name	ALD	Gender	Age at the time of LT	Maintenance immunosuppression at the time of ALD recurrence	Follow-up duration, months	Outcome at last follow-up exam
1	LSA	AIH	f	22	CYC	166	Alive, no GC
2	ZhZH	PBCh	f	32	CYC	6	Re-LT, death
3	MMR	PBCh	m	46	CYC/PS	6 before and 62 after re-LT	Re-LT, alive
4	DTA	PBCh	f	48	CYC/MPA	75 before and 91 after re-LT	Re-LT, alive
5	SST	PBCh	f	51	CYC/ MPA	147	Re-LT, death
6	KLV	PBCh	f	64	TAC	52	GC, death
7	BKG	PSC	m	17	TAC/PS	15	Re-LT, alive
8	BKG	PSC	m	19	TAC/PS/AZA	64	Death of PTLD, no GC
9	DDN	PSC	m	26	TAC/MPA/PS	79	Alive, no GC
10	ZhNG	PSC	f	28	CYC	202	GC, alive
11	BSA	PSC	m	20	CYC/PS/AZA	42	No GC, cholangitis, sepsis, death
12	GDA	PSC	m	43	TAC/PS	92	Alive, no GC
13	FNA	PSC	m		TAC/EVE/PS	50	Death, no GC

Notes: GCT, graft cirrhosis; TAC, tacrolimus; CYC, cyclosporine; MPA, mycophenolic acid; PS, prednisolone; EVE, everolimus; AZA, azathioprine; re-LT, liver retransplantation, PTLD, post-transplantation lymphoproliferative disease

Clinical characteristics of liver transplant recipients who suffered the ALD recurrence are shown in Table. 2.

The follow-up period of recipients with ALD recurrence (64.5 (42.8;82.0) months) was comparable to the follow-up period for recipients without recurrence (46.5 (17.9;103.5) months, p=0.54).

Ten-year graft survival was significantly lower in the group of recipients with ALD recurrence compared to those without ALD recurrence after LT (p<0.0001) (Figure).

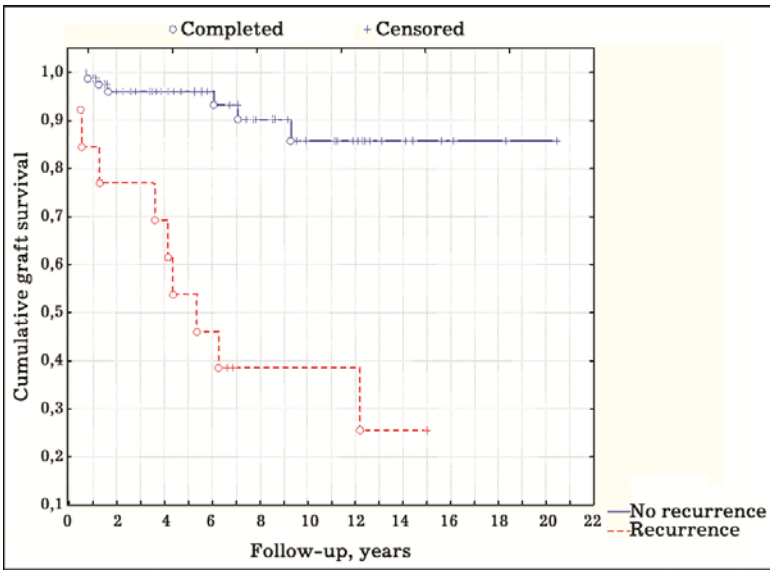

Figure. Graft survival in liver transplant recipients operated on for autoimmune liver disease as a function of the autoimmune liver disease recurrence (p<0.0001)

Discussion

To identify the recurrent ALD in a transplanted liver, the histological or cholangiographic (for PSC) verification of the diagnosis is necessary. The progression of recurrent PBCh and PSC is basically characterized by the loss of small bile ducts or ductopenia. Unfortunately, this sign is not pathognomonic, and can occur in a number of other graft diseases from ischemic cholangiopathy to a chronic rejection. Liver transplant recipients may also experience a combination of alloreactivity and disease recurrence. The recurrence of AIH, PBCh, and PSC may be

associated with an increased incidence of chronic rejection, with loss of more than 50% of bile ducts from the portal tracts, and arteriopathy. This presents additional difficulties for the correct diagnosis of the recurrent autoimmune diseases in the graft.

Various research teams have proposed some diagnostic criteria to recognize the ALD recurrence in the graft. The diagnostic criteria most commonly used in clinical practice are summarized in Table 3.

Table 3 Criteria for the diagnosis of recurrent autoimmune diseases in liver transplant recipients

	Recurrent PBCh/PBCi [3, 4]	**Recurrent AIH [5]**	**Recurrent PSC [6]**
Diagnostic criteria			
Indication for transplantation	PBCh/PBCi	AIH	PSC
Histological signs	• Lymphoplasmacytic infiltrate in the portal tract • Lymphoid collections • Epithelioid granulomas • Bile duct injury	• Interstitial hepatitis • Perivenular lymphoplasmacytic infiltrate • Pseudorosettes of hepatocytes	• Fibrous cholangitis/fibroobliterating lesions with or without ductopenia • Biliary fibrosis/cirrhosis
Cholangiographic signs			Intrahepatic and/or extrahepatic bile duct strictures, moniliform duct deformity and irregularity > 90 days after LT
Other signs	Increase in IgM AMA-M2	Increased ALT IgG increase ANA, ASMA, anti-LKM1	
Exclusion criteria			
	Other causes of GD	Other causes of GD	• Thrombosis/stenosis of the HA • Chronic rejection • Strictures only in the area of anastomoses • Strictures outside the anastomoses up to 90 days after LT • ABO incompatibility between donor and recipient
Criteria required for diagnosis			
		All criteria	Sufficient are histological OR cholangiographic criteria and all exclusion criteria
Likely	All criteria plus 2 of 4 histological criteria		
Definite	All criteria		

Notes: ALT, alanine aminotransferase; ANA, antinuclear antibodies; anti-LKM, anti-liver kidney microsomal antibodies; GD, graft dysfunction; HA, hepatic artery; ASMA, anti- smooth muscle antibodies

Of particular difficulty is the determination of the timing of the ALD recurrence after the LT. Biochemical parameters are not reliable, since abnormal liver function tests are observed in liver transplant recipients due to a variety of causes: from statuses to inadequate immunosuppression, and cannot serve as a correct criterion for the timing of the ALD relapse onset. To some extent, the answer could be obtained by performing annual protocol liver biopsies or non-invasive cholangiography (for the diagnosis of PSC).

Recurrent AIH after LT is observed in 17–42% of patients [7, 8]. Autoantibodies in the recipient's blood serum usually persist for a long time after LT. The histological presentation of AIH resembles that of an acute cellular rejection; the treatment for both diseases involves increased immunosuppression. We observed AIH recurrence in only 1 of 21 recipients, which does not allow for any statistical subgroup analysis. Our patient is alive, her hepatitis activity is well controlled with glucocorticosteroids. A large retrospective study ranks the AIH recurrence as the third most common cause (after recurrent hepatitis C and PSC) of graft loss among all recurrent liver diseases. [9][1]. Moreover, AIH recurrence suggested the shortest time to graft loss (median 525 days). Of particular interest is the recurrence of AIH in the second graft of retransplant patients, which was seen in 50–67% of cases [2]. Further studies are needed to clarify the impact of AIH recurrence on the graft and recipient survivals.

It has not been established that any immunosuppressive regimen is better suited for the long-term management of patients undergoing

[1] At present, due to the widespread use of direct-acting antiviral drugs, hepatitis C has ceased to be a problem affecting the prognosis of recipients.

transplantation for AIH. A recently published systematic review and meta-analysis found no effect of including low-dose corticosteroids into maintenance immunosuppression regimens on the incidence of AIH recurrence after liver transplantation (odds ratio (OR) 0.27; 95% confidence interval (CI) 0.01–7.25). Continuing steroid therapy does not prevent relapse after transplant [10].

The PSC recurrence occurs in 50% of liver transplant recipients within 5 years of LT and may result in graft loss in 25% within 5 years. Recurrent PSC is associated with more than 4-fold increased risk of death (OR 4.71, 95% CI 3.39–6.56) with 1-, 5-, and 10-year graft survival rates of 98%, 84%, and 56%, respectively compared to 95%, 88% and 72% in patients who did not develop PSC in the graft [11].

In 1999, the Mayo Clinic proposed criteria that currently serve as the gold standard for diagnosing PSC recurrence [6] (Table 3). PSC recurrence should be differentiated from ischemic bile duct injury resulting from thrombosis or stenosis of the hepatic artery. Magnetic resonance cholangiography and arteriography allow the examination of the graft biliary tree and graft vessels. The results of histological examination of the liver tissue are of secondary importance.

There is no effective way to prevent PSC recurrence in transplanted liver. The benefit of ursodeoxycholic acid (UDCA) at a dose of 10–15 mg/kg/day has not been proven, but this drug has been widely used by doctors in the development of cholestasis in liver transplant recipients. The results of a recent meta-analysis suggest that the use of cyclosporine reduces the risk of recurrent PSC in the graft (OR 0.69; 95% CI 0.49–0.97), while the use of mycophenolate mofetil (MMF) increases it (OR 1.46; 95% CI 1.00–2.12). We were unable to identify the effect of any immunosuppressive drugs or their combinations on the risk of PSC recurrence. Notably, one of our patients also had a recurrence of PSC in

the liver obtained after retransplantation. This patient lived after liver retransplantation for more than 5 years and died of PTLD.

The PBCh relapse was first described by J. Neuberger et al. in 1982 [12]. The incidence of PBCh recurrence after LT is 21 to 37% at 10 years and approximately 40% at 15 years [13].

To diagnose the recurrent graft PBCh, the criteria proposed by J. Neuberger et al. (2003) are commonly used (Table 3). AMAs represent a poor marker of recurrence because the correlation between serum AMA levels and recurrent PBCh is not significant. Despite the trend towards decrease in AMA concentrations after LT, the total AMA level remains elevated after LT in most patients. On the contrary, it has been shown that with the PBCh recurrence, the total IgM is increased compared to patients without recurrence. This laboratory value can be used to select recipients in whom diagnostic liver biopsy is indicated [3].

A number of authors report cases of graft loss and recipients death from the development of lethal graft cirrhosis. P. Manousou et al. (2010) report the mean time of 6.7 years from PBCh recurrence to decompensation [14]. I.A. Rowe et al. (2008) noted that the mean time to graft loss due to disease recurrence makes 7.8 years. However, the authors found no significant difference in survival between relapsed and non-relapsed patients [9]. We observed a recurrence of PBCh in 5 recipients, in all 5 cases there was a graft loss.

The search for links between immunosuppression regimens and the incidence of ALD revealed a single statistically significant association: 4 (80%) of our 5 patients with PBCh recurrence and only 11 (24%) of 45 recipients without PBCh recurrence in the graft received cyclosporine (Table 1). The statistical significance of these differences persisted with increasing power of analysis (analysis of all ALD patients as a single group). According to the literature, the effect of CNI on the risk of PBCh

recurrence is not unambiguous. Some studies failed to find a relationship between CNI and PBCh recurrence, others concluded that tacrolimus-based immunosuppression is associated with an increased risk of PBCh recurrence compared to cyclosporine-based therapy [15, 16]. According to the study results obtained by J. Neuberger et al. (2004), median time to PBCh recurrence was 10.2 years in the cyclosporine-treated liver transplant group and 5.1 years in the tacrolimus-treated recipient group. [17]. More recent studies (including a systematic review of 16 studies) have failed to confirm the positive effect of cyclosporine, as well as the negative effect of tacrolimus on the risk of PBCh recurrence in the graft [14, 18].

In a meta-analysis (2021) in the patients transplanted for PBCh, the prophylactic use of UDCA reduced the PBCh recurrence rate (13.3%, CI 7.2–19.4%) compared to no prophylactic use of UDCA (33.8%, CI 28.7–38.9%) [19]. The positive effect of UDCA at a dose of 10–15 mg/kg/day on the outcome of the disease does not have a sufficient evidence base, but the safety of using this drug can be considered reasonable.

An important advantage of our work is the relatively long follow-up period for recipients, which in some cases reached 20 years or more.

One of the shortcomings of our study is the lack of a separate subgroup of recipients transplanted for overlapping syndromes. We observed at least one of the relapses of this syndrome (AIH/PSC) after LT. This patient was analyzed in a subgroup of patients with PSC. Overlapping syndromes are the ALDs in which there are signs of AIH and PBCi or PSC concurrently. Because overlapping syndromes are relatively rare, randomized, controlled trials have not been conducted, and the treatment is often empirical by nature and aims at treating both autoimmune diseases. At the same time, a significant proportion of patients with overlapping syndromes develop a progressive disease

requiring LT. After LT, the disease recurrence is manifested by either one or both of the original AIH manifestations and hepatobiliary disease. Moreover, patients with overlapping syndromes are reported to have earlier relapses and higher relapse rates compared with patients undergoing LT for either AIH, PBCi, or PSC [1].

Conclusions

1. Recurrence of autoimmune liver disease in the graft confirmed histological or cholangiographically occurs in 5% of autoimmune hepatitis cases, 10% of primary biliary cholangitis/primary biliary cirrhosis cases, and 17% of primary sclerosing cholangitis.

2. The recurrence of autoimmune liver diseases significantly worsens the prognosis, reducing the graft survival.

3. An impact of calcineurin inhibitors, mycophenolic acid agents and azathioprine, as well as glucocorticosteroids, on the risk of recurrence of autoimmune liver diseases in the graft has not been established. Perhaps an exception is the subgroup of patients who underwent liver transplantation for primary biliary cholangitis/primary biliary cirrhosis. In this case, a relationship was found between administering cyclosporine and the risk of recurrence.

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