OPEN

Outcomes of Liver Transplant Recipients With Autoimmune Liver Disease Using Long-Term Dual Immunosuppression Regimen Without Corticosteroid

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Background. Liver transplant (LT) recipients with autoimmune liver disease (primary sclerosing cholangitis, primary biliary cholangitis, autoimmune hepatitis) are at increased risk of developing acute cellular rejection (ACR), and in many cases graft failure due to recurrent disease. We describe our experience with dual immunosuppression without steroid maintenance and analyze its effect on disease recurrence; ACR; patient and graft survivals; and complications, such as sepsis and de novo malignancy. **Methods.** We included 74 consecutive LT recipients (April 2006 to April 2013) with autoimmune liver disease (primary sclerosing cholangitis, 20; primary biliary cholangitis, 23; autoimmune hepatitis, 31) from a single transplant center. Immunosuppression protocol included rabbit antithymocyte globulin for induction and mycophenolate mofetil with tacrolimus or sirolimus/everolimus indefinitely for maintenance. **Results.** Overall 1-, 3-, 5-, and 7-year patient survival was 95.9%, 90.4%, 82,2% and 74.9%, re–graft-free survival was 93.2%, 86.3%, 79.9%, and 72.8%, respectively (median follow-up, 5.5 years). In a multivariate Cox regression analysis, sepsis during post-LT period ($P = 0.040$; hazard ratio [HR], 2.52; 95% confidence interval [CI], 1.04-6.11), steroid use for ACR ($P = 0.037$; HR, 2.60; 95% CI, 1.06-6.34), and younger age (<40 years) at LT ($P = 0.038$; HR, 2.53; 95% CI, 1.05-6.10) predicted graft survival, whereas steroid use for ACR was the only variable that was predictive of overall patient survival ($P = 0.004$; HR, 4.10; 95% CI, 1.59-10.52). Overall, 34 biopsy-proven ACR was noted in 22 LT recipients (30%), 13 (17.5%) had disease recurrence, and 34 episodes of sepsis occurred in 19 patients. **Conclusions.** Dual immunosuppression protocol in LT recipients with autoimmune liver disease without corticosteroid maintenance had acceptable rates of survival and ACR without predisposing patients to the adverse effects of long-term steroid therapy.

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Liver transplantation (LT) remains the most effective treatment for patients with end-stage liver disease from autoimmune processes including primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC), and autoimmune hepatitis (AIH). Overall, autoimmune liver diseases account for approximately one fourth of LT performed in Europe and the United States,[1] with a 5-year post-LT survival rate of around 85%.[2] Unfortunately, autoimmune liver diseases recur in a sizable proportion of the patients leading to graft failure and other complications. Published studies have

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reported a wide variance in the rates of recurrence. The exact rates of recurrence are somewhat obscured by inconsistencies in diagnostic criteria and approaches. Despite reports of efficacy and safety by proponents of long-term corticosteroid use after LT to reduce the risk of rejection and recurrence of AIH,[3] the deleterious effects of long-term use of corticosteroid after LT is well reported. Treatment with glucocorticosteroids induces bone loss and may lead to cardiovascular risk factors including hypertension, hyperlipidemia, obesity, and glucose intolerance.[4] Avoidance of glucocorticosteroids may reduce this excess morbidity without influencing graft loss.[5] A recent Cochrane meta-analysis has compared benefits and harms of glucocorticosteroid avoidance (excluding intraoperative use) or withdrawal versus glucocorticosteroid-containing immunosuppression after LT, and noted glucocorticosteroid avoidance or withdrawal appears to reduce diabetes mellitus and hypertension while increasing acute rejection, glucocorticosteroid-resistant rejection, and renal impairment.[4] The analysis further reported, glucocorticosteroid avoidance or withdrawal may be of benefit in selected patients, especially those at low risk of rejection and high risk of hypertension or diabetes mellitus. We have recently published our experience in the largest series of OLT recipients using a steroid-free protocol with rabbit antithymocyte globulin (RATG) induction demonstrating excellent outcomes, low complication rates, and preservation of renal function with rejection occurring in 22.8% patients, 6.6% patients requiring steroids.[6] In the current study, we describe our experience with dual immunosuppression use in a steroid-free protocol and analyze its effect on autoimmune liver disease recurrence rates, incidence of acute cellular rejection (ACR) post-LT, overall and regraft-free survival, and the incidence of complications in terms of sepsis and risk for posttransplant malignancy.

MATERIALS AND METHODS

A retrospective chart review of electronic medical records of all patients who underwent LT for AIH between April 2006 and April 2013 was conducted. The original diagnosis of PSC, PBC, and AIH in the native liver was made based on appropriate clinical, biochemical, and compatible histological dataset and the exclusion of other competing etiologies. Post-LT data were collected on patient demographics, serum liver biochemistry, immunosuppressive regimens, explant histology, episodes of acute and chronic rejection, recurrence of the disease in the allograft, death or regraft, immunosuppression-related complications—particularly sepsis and malignancy. Sepsis data were defined as an infection that required hospitalization regardless of duration, or resulted in significant morbidity or mortality.

Disease recurrence was determined based on compatible clinical, biochemical, and histological findings, and exclusion of alternate causes. The following criteria were used: (1) AIH recurrence was only made 6 months after transplantation to exclude other etiologies of liver dysfunction that predominate in this early period; (2) PBC recurrence was defined by original indication for LT and histopathology suggestive for recurrent PBC and exclusion of other causes[7,8]; (3) PSC recurrence was based on a confirmed diagnosis of PSC at transplantation in the explanted liver, histopathology, and/or cholangiogram evidence for PSC showing nonanastomotic biliary strictures of the intrahepatic biliary tree with beading and irregularity occurring at least 90 days posttransplantation to exclude ischemia- or reperfusion-induced injury. When defining each recurrent liver disease, alternate etiologies were ruled out, including the absence of other pathology and disorders.[9] Of note, protocol biopsies were performed at 1, 3, and 5 years at our center, whenever feasible. Acute and chronic cellular rejections were defined based on Banff schema for grading liver allograft rejection.[9]

Our center has been using a corticosteroid-free immunosuppression protocol,[6] which consists of induction immunosuppression with RATG given in 2 doses of 1.5 mg/kg. The first dose is given during the anhepatic phase; and the second dose is given on posttransplant day 2. A single dose of 500 mg intravenous (IV) methylprednisolone is administered as premedication before the first dose of RATG to minimize cytokine release syndrome. Mycophenolate mofetil (MMF) or mycophenolic acid is initiated on posttransplant day 1 and is continued for a total of 3 months and then discontinued unless the patient's disease is PSC, PBC, or AIH. Mycophenolate dose and administration frequency is adjusted based on side effect profile. The initiation of tacrolimus is delayed for a minimum of 3 days and a maximum of 7 days; and started when the serum creatinine is less than 2.0 mg/dL. Primary mammalian target of rapamycin inhibitor (mTor) is used in lieu of tacrolimus if the recipient's creatinine level remained over 2.0 mg/dL beyond posttransplant day 7. Goal trough levels for tacrolimus and sirolimus during the first 3 months postoperatively were 6 to 8 ng/dL and 8 to 10 ng/dL, respectively.

The University of Tennessee Health Sciences Center Institutional Review Board approved the study a priori.

Statistical Analyses

Demographic factors were reported as means with standard deviation or as a number with percentages, as applicable. Kaplan-Meier curves were produced for the range of outcomes, particularly overall and regraft-free survival. In each case, patients were censored at the end of follow-up, if the event of interest had not occurred. For outcomes not relating to mortality, patients were also censored at death, where there was no evidence that the event of interest had occurred now. Univariate and multivariate logistic regression analyses were performed to assess predictors of disease recurrence. Predictive variables for graft and patient survivals were assessed using univariate and multivariate Cox regression analyses. In view of the probable differential outcome of the included patients based on the etiology of the underlying liver disease, a stratified Cox regression analysis was used. For multivariable analysis, we followed the "10 event per covariate" recommendation[10,11] to determine the predictors supported in such models. All analyses were performed using (SAS 9.4, Cary, NC). Cases with missing data were excluded on a per-analysis basis.

RESULTS

Patient Demographics

The study sample included 75 patients who underwent transplantation for autoimmune liver disease (PSC, PBC, and AIH) from April 2006 to April 2013 at our center. One patient who was retransplanted for recurrent PSC (with history of remote LT for PSC) was excluded. This patient also had hepatitis B virus coinfection and expired due to graft loss

within 90 days. All patients received whole liver allografts from deceased donors (donation after brain death [DBD], 72 [97.30], donation after cardiac death [DCD] = 2 [2.70]). The demographic data for the 74 patients are presented in Table 1.

Posttransplant Immunosuppression

Per our protocol, the autoimmune disease group continued with dual immunosuppression beyond 90 days, whenever tolerated. After excluding for patients who died or were lost to follow up (2 relocated to another transplant center by 6 month, 5 expired by 12 months), 70 (95.9%) patients remained on dual immunosuppression regimen at 6 months, and 61 (91.04%) at 1 year. Three patients discontinued their mycophenolate by 6 months for leukopenia per physician recommendation. At 6 months after LT, 57 (78.1%) were on tacrolimus/mycophenolate, 7 (9.6%) on sirolimus/mycophenolate, and 6 (8.2%) on tacrolimus/sirolimus. At the end of 1 year, 48 (71.6%) were on tacrolimus/mycophenolate, 7 (10.5%) on sirolimus/mycophenolate, 6 (9%) on tacrolimus/sirolimus, and 6 (9%) patients were on monotherapy with tacrolimus. At their last follow-up (excluding single patient with primary nonfunction [PNF]), 67 (91.8%) patients were maintained on a dual immunosuppression regimen, 54 (74%) were on tacrolimus/mycophenolate, 5 (6.9%) on sirolimus/mycophenolate, 7 (9.6%) on tacrolimus/sirolimus, 1 (1.4%) on everolimus/mycophenolate, and 6 (8.2%) were on monotherapy. All patients remained "steroid-free" at their last follow-up.

Long-Term Survival

The follow-up period of each of the 3 categories of the autoimmune liver diseases are similar, PSC (5.21 ± 2.72; median, 4.58; range, 0.22-9.43), PBC (6.03 ± 2.55; median, 6.28; range, 1.28-9.74), and AIH (5.40 ± 2.65; median, 5.63; range, 0.07-9.14). Median follow-up of the cohort was 5.5 years (range, 0.07-9.74 years) with overall survival at 1, 3, 5, 7 years being 95.9%, 90.4%, 82.2%, 74.9%, and regraft-free survival was 93.2%, 86.3%, 79.9%, 72.8%, respectively. In the first 90 days after transplantation, 1 patient needed re-LT due to chronic rejection along with concomitant hepatic venous outflow obstruction leading to graft failure. Two patients died during the first 90 days of posttransplant follow-up period, one due to ischemic hepatic necrosis and PNF of the liver, and another one due to early development of NK/T-cell leukemia lymphoma. Both also had sepsis-related complications. Another LT recipient suffered from cerebrovascular accident in the early post-LT period, and after rehabilitation, he was relocated to an outside facility and lost to follow-up. There were 21 graft losses (death/re-LT; PSC, 5; PBC, 6; AIH, 10). The etiologies of the graft losses are summarized in Table 2. Patient survival at 1, 3, 5, and 7 years of follow-up was 90%, 90%, 90%, 90% in PSC, 100%, 91.3%, 80.6%, 74.4% in PBC, and 96.8%, 90.1%, 78.8%, 67.4% in AIH group, respectively (Figure 1). Regraft-free survival at 1, 3, 5, and 7 years follow-up was 85%, 80%, 80%, 80% in PSC, 100%, 91.3%, 80.6%, 74.4% in PBC, 93.4%, 86.8%, 79.4%, 67.9% in AIH group,

TABLE 1.

Baseline clinical and demographic characteristics

Variables	All patients (N = 74)	PSC group (n = 20)	PBC group (n = 23)	AIH group (n = 31)
Recipients factors				
Age at transplant (± SD), y	48.96 ± 14.19	41 ± 13.75	58.78 ± 8.73	46.81 ± 13.90
Sex				
Male	29 (39.19)	11 (55)	6 (26.09)	12 (38.71)
Female	45 (60.81)	9 (45)	17 (73.91)	19 (61.29)
Race				
White	48 (64.86)	10 (50)	20 (86.96)	18 (58.06)
African American	22 (29.73)	10 (50)	2 (8.70)	10 (32.26)
Hispanic	4 (5.41)	0 (0)	1 (4.35)	3 (9.68)
BMI	26.52 ± 4.87	25.09 ± 5.04	25.79 ± 4.41	28.00 ± 4.83
Hypertension	22 (29.73)	3 (15)	6 (26.09)	13 (41.94)
Diabetes	9 (12.16)	3 (15)	3 (13.04)	3 (9.68)
Known coronary artery disease	4 (5.41)	0 (0)	3 (13.04)	1 (3.23)
MELD score at LT	21.59 ± 6.70	21.10 ± 6.23	20.13 ± 5.29	23.00 ± 7.77
Donor factors				
Donor age	40.76 ± 16.72	42.70 ± 14.39	44.35 ± 17.40	36.84 ± 17.29
Donor sex				
Male	32 (43.24)	6 (30)	10 (43.48)	16 (51.61)
Female	42 (43.24)	14 (70)	13 (56.52)	15 (48.39)
Donor BMI	26.39 ± 6.42	27.70 ± 8.42	25.13 ± 5.10	26.48 ± 5.83
Donor type				
DBD	72 (97.30)	19 (95)	22 (96.65)	31 (100)
DCD	2 (2.70)	1 (5)	1 (4.35)	0 (0)
Intraoperative factors				
Cold ischemia time, min	269.68 ± 100.24	245.63 ± 68.12	292.30 ± 112.82	267.65 ± 106.77
Warm ischemia time, min	33.14 ± 7.74	34.16 ± 10.38	34.22 ± 8.30	31.71 ± 5.01

MELD, Model for End-Stage Liver Disease.

TABLE 2.

Etiologies of graft loss

Etiology of graft loss	N = 21
Cholangitis	1
Complication of stem cell transplant	1
Graft cirrhosis	2
Leukemia	1
PNF of the liver	1
Lung cancer	1
Infectious complications	5
Retransplant	4
Unknown	5

respectively (Figure 2). Eight patients underwent retransplant (PSC, 3; PBC, 1; and AIH, 4) for hepatic artery thrombosis (3), chronic ductopenic rejection (3), PNF (1), and de novo AIH (1). Of these 8 retransplanted recipients, 4 have expired (sepsis, 2; PNF, 1; unknown etiology, 1).

On univariate Cox regression analysis, the need for IV methylprednisolone use for ACR (P = 0.007; hazard ratio [HR], 3.34; 95% confidence interval [CI], 1.40-7.97), hospital admission for sepsis (yes vs no) during post-LT period (P = 0.03; HR, 2.57; 95% CI, 1.09-6.08), and younger age (<40 years) at LT (P = 0.04; HR, 2.47; 95% CI, 1.05-5.84) predicted poor graft survival, whereas need for IV steroid use for ACR (P = 0.002, HR 4.37: 95% CI 1.76-11.32) and younger age (<40 years) at LT (P = 0.04; HR, 2.65; 95% CI, 1.05-6.87) were predictors for mortality of the patients with autoimmune liver diseases (Table 3). In a multivariate Cox regression model using variables with P less than 0.05, steroid use for ACR (P = 0.037; HR, 2.60; 95% CI, 1.06-6.34), sepsis during post-LT period (P = 0.040; HR, 2.52; 95% CI, 1.04-6.11), and younger age (<40 years) at LT (P = 0.038; HR, 2.53; 95% CI, 1.05-6.10) predicted graft survival, whereas steroid use for ACR was the only variable that was predictive of overall patient survival (P = 0.004; HR, 4.10; 95% CI, 1.59-10.52) (Table 4).

ACRs

Thirty-four biopsy-proven ACR were noted in 22 (29.7%) LT recipients with an indication of autoimmune liver disease:

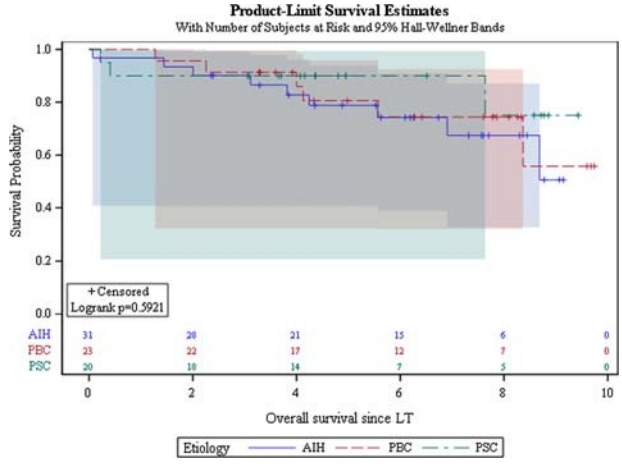

FIGURE 1. Overall survival in the PSC, PBC, and AIH groups.

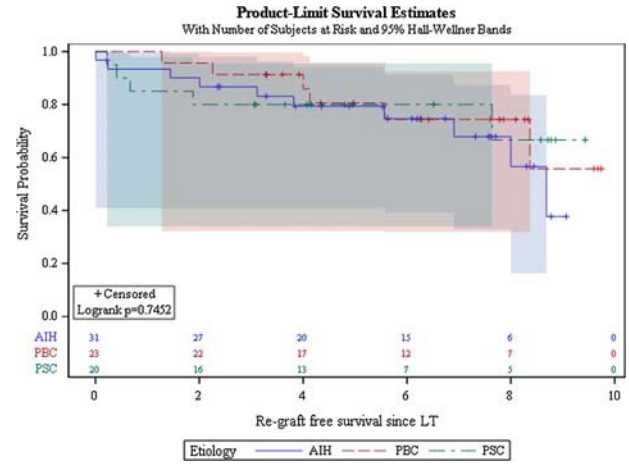

FIGURE 2. Regraft-free survival in the PSC, PBC, and AIH groups.

9 ACR in 6 PSC recipients, 5 ACR in 5 PBC recipients, and 20 ACR in 11 AIH recipients (Table 5). On histopathological examination, 12 of the 34 episodes were mild, 19 were moderate, and 3 were severe. Recipients with ACR mostly had a single episode (15 [68.2%] of 22), but 4 (18.2%) had 2 episodes, 2 (9.1%) had 3 episodes, and 1 patient had 5 episodes. In the 22 recipients who had ACR, 15 episodes (occurred in the first year), 7 episodes (within 1 and 3 years), and 6 episodes (beyond 3 years) after LT. Seventeen of the 34 episodes required IV methylprednisolone for the management of the ACR, and 3 patients required IV antithymocyte globulin due to refractory severe ACR. Optimization of maintenance immunosuppression was used for management in the rest of the cases. Chronic rejection occurred in 6 (8.1%) of the recipients using the current immunosuppression protocol: 3 of them had PSC, 2 with PBC, and 1 with AIH. Five patients died on follow-up: 2 of them secondary to sepsis and unknown etiology in 3 patients, and 1 patient was salvaged with retransplant.

Recurrent Disease Posttransplantation

Recurrence of liver disease was noted in 13 (17.5%) of the LT recipients; 3 (15%) of 20 had recurrent PSC, 5 (21.7%) of 23 recurrent PBC, and 5 (16.13%) of 31 with recurrent AIH (Table 6). Three patients (AIH, 1; PBC, 2) had recurrent disease in their allograft within 1 year of their LT, 7 patients (PSC, 2; PBC, 2; AIH, 3) between 1 and 3 years, and the rest 3 (AIH = 1, PBC = 1, PSC = 1) following 3 years. Overall, there was no difference in time-to-recurrence among these 3 groups (P = 0.924, Log Rank, Figure 3). One hundred four liver biopsies were performed with the majority performed for abnormal liver function tests (LFTs). Twenty-eight biopsies at 1 year, 5 biopsies at 3 years, and 0 biopsies at 5 years were performed per protocol since LT in this cohort. Of the 13 patients with recurrent disease, 3 (23%) of 13 had the recurrent disease diagnosed on protocol liver biopsies, and 10 (77%) of 13 were diagnosed on liver biopsies that were performed for abnormal LFTs. Off note, the single patient who received DCD donor did not have disease recurrence.

Five patients who were originally diagnosed with AIH (+/– overlap) had recurrent autoimmune liver disease, 3 had recurrent AIH, 1 had recurrent AIH/PBC, and 1 had

TABLE 3.

Predictors of graft and patient survival based on Univariate Cox-regression analysis V

	Graft survival			Patient survival		
Variables	***R***	***P***	**HR (95% CI)**	***R***	***P***	**HR (95% CI)**
Patient age, y	–0.02	0.20	0.98 (0.95-1.01)	–0.015	0.37	0.98 (0.96-1.02)
Age, < 40 vs ≥ 40 y	0.91	0.04	2.47 (1.05-5.84)	0.97	0.04	2.65 (1.05-6.87)
Gender (male vs others)	–0.015	0.97	0.99 (0.41-2.25)	–0.45	0.37	0.64 (0.24-1.71)
Race (white vs others)	0.21	0.66	1.24 (0.48-3.20)	0.30	0.56	1.36 (0.48-3.81)
BMI	0.016	0.74	1.02 (0.92-1.12)	–0.009	0.86	0.99 (0.89-1.10)
Donor age	0.01	0.45	1.01 (0.98-1.04)	0.006	0.60	1.01 (0.98-1.03)
Donor sex (male vs others)	–0.71	0.13	0.49 (0.20-1.22)	–1.014	0.06	0.36 (0.13-1.03)
Donor-recipient sex mismatch	–0.32	0.48	0.73 (0.30-1.77)	–0.25	0.61	0.78 (0.30-2.02)
Donor BMI	0.008	0.81	1.01 (0.94-1.08)	–0.001	0.97	1.00 (0.93-1.08)
Donor type: DBD vs DCD	–14.07	0.99	0.00 (0.00-0.00)	–14.07	0.99	0.00 (0.00-0.00)
Cold ischemia time	–0.003	0.20	1.00 (0.99-1.00)	–0.003	0.23	0.98 (0.99-1.00)
Warm ischemia time	–0.005	0.87	0.99 (0.94-1.06)	–0.001	0.75	0.99 (0.92-1.06)
MELD score		0.40	1.03 (0.96-1.10)	0.008	0.83	1.01 (0.94-1.08)
Hypertension	–0.26	0.61	0. 77 (0.28-2.12)	–0.76	0.23	0.47 (0.14-1.62)
Diabetes	–0.56	0.45	0.57 (0.13-2.47)	–0.34	0.65	0.71 (0.16-3.13)
Coronary artery disease	0.23	0.83	1.25 (0.17-9.51)	0.44	0.67	1.56 (0.20-1.97)
ACR (yes vs no)	0.67	0.12	1.96 (0.83-4.64)	0.75	0.11	2.12 (0.84-5.38)
IV steroid for ACR	1.21	0.007	3.34 (1.40-7.97)	1.50	0.002	4.47 (1.76-1.32)
Sepsis (yes vs no)	0.94	0.03	2.57 (1.09-6.08)	0.72	0.13	2.05 (0.81-5.23)
Recurrent disease	0.07	0.89	1.07 (0.39-2.95)	–0.018	0.98	0.98 (0.32-3.02)

AIH/PSC. Recurrent disease was diagnosed in these 5 patients on liver biopsy. Among the 3 with recurrent AIH, serology for ANA was positive in one, smooth muscle antibody in the second case, and no serological data were available in the third patient. One of these 3 had graft failure secondary graft cirrhosis and needed a retransplant, and another patient developed graft cirrhosis and expired while waiting for re-LT. One of the patients with overlap syndrome with AIH/PSC had recurrent PSC that was diagnosed on routine protocol liver biopsy at 1 year since LT, continues to do well with excellent allograft function, and has no imaging abnormalities to suggest PSC recurrence. One of the 5 patients with recurrent disease was found to be noncompliant to medication.

All patients with PSC had hepaticojejunostomy per our center's approach. Associated inflammatory bowel disease (IBD) was noted in 12 (63.2%) PSC patients before their LT. Of the 19 patients with PSC, 3 had recurrent PSC. Two of the 3 patients had a medical history of ulcerative colitis, and one had a history of total colectomy with ileoanal anastomosis before LT. No recurrent or de novo inflammatory bowel disease was noted on follow-up. In 5 patients who had recurrent PBC, the diagnosis was established on histology. Liver biopsy was performed for evaluation of elevated LFTs in 4 patients, and 1 patient who had protocol liver biopsy after 1 year of LT. Three have excellent allograft function with ursodiol. The fourth patient, who was transplanted for overlap syndrome with AIH/PBC, had recurrent PBC, developed chronic rejection that ultimately progressed to graft cirrhosis with graft failure, and expired.

On logistic regression, ACR was found to be the sole predictor for disease recurrence (P = 0.04; OR, 3.58; 95% CI, 1.04-12.32; Table 7), and analysis for predictors of disease recurrence based on disease etiology revealed the strongest association of disease recurrence with ACR in patients with AIH (P = 0.047; OR, 10.86; 95% CI, 1.03-114.58). Cumulative hazards of disease recurrence are shown in Figure 4. As noted majority of the patients have disease recurrence in the first 5 years since LT. Cirrhosis developed in 2 of the 13 patients with recurrent disease. Four patients died at a mean follow-up interval of 2 ± 1.45 years. One patient had a retransplant after 8 years due to graft cirrhosis and allograft failure. All patients were maintained on the dual immunosuppression regimen as described in Table 6: 9 with tacrolimus/mycophenolate, 3 with sirolimus/mycophenolate, and 1 with tacrolimus/sirolimus at the time of disease recurrence. A Cox regression analysis with time-dependent covariant analysis revealed no impact of disease recurrence on patient survival even on subanalysis of the individual groups.

Posttransplant Infectious Complications and Malignancy Risk

Thirty-four episodes of sepsis occurred in 19 (25.7%) patients (Table 8). Sepsis occurred in 10 (50%) PSC patients,

TABLE 4.

Predictors of graft and patient survival on Multivariate Cox-regression analyses

Parameter	***R***	***P***	**HR (95% CI)**
Graft survival			
Sepsis (yes vs no)	0.93	0.040	2.52 (1.04-6.11)
IV steroid for ACR (yes vs no)	0.96	0.037	2.60 (1.06-6.34)
Age, < 40 vs ≥ 40 y	0.93	0.038	2.53 (1.05-6.10)
Patient survival			
IV steroid for ACR (yes vs no)	1.41	0.004	4.10 (1.59-10.52)
Age < 40 vs ≥ 40 y	0.82	0.08	2.28 (0.90-5.79)

TABLE 5.

Patterns and characteristics of ACR

	All (N = 74)	PSC (n = 20)	PBC (n = 23)	AIH (n = 31)
ACR—yes, n (%)	22 (29.7%)	6 (30%)	5 (21.7%)	11 (35.5%)
Cumulative number of ACR (n)	34	9	5	20
Cumulative episodes of ACR by severity, n (%)[a]				
Mild	12 (35.3%)	2 (22.2%)	2 (40%)	8 (42.11%)
Moderate	19 (55.9%)	6 (66.7%)	3 (60%)	10 (52.6%)
Severe	3 (8.8%)	1 (11.1%)	0 (0%)	2 (10%)
No. patients with ACR (n, %)[b]				
Within 1 y	15 (20.3%)	5 (25%)	4 (17.4%)	6 (19.4%)
1 to 3 y	7 (9.5%)	2 (10%)	0 (0%)	5 (16.1%)
Beyond 3 y	6 (8.1%)	0 (0)	1 (4.3%)	5 (16.1%)
IV methylpredisolone—yes (based on cumulative number of ACR)	17 of 34	6 of 9	3 of 5	8 of 20
Thymoglobulin use—yes	3 of 33	1 of 9	1 of 5	1 of 19

[a] Proportion of patients with ACR was calculated based on cumulative number of ACR episodes.

[b] Proportion of patients with ACR was calculated based on overall subjects at risk divided by number of patients with ACR within the specified interval.

4 (17.4%) PBC recipients, 5 (16.1%) AIH recipients. Twelve patients (16.2%) had 1 episode of sepsis, whereas the remaining 7 had 2 or more episodes of sepsis. Pneumonia was the most common cause of hospitalization with sepsis, accounting for 7 of the 32 episodes. Death could be directly attributable to sepsis in 8 (25.6%) of the 34 episodes: 2 (10%) in PSC, 3 (13%) in PBC, and 3 (9.7 %) in AIH. No cases of *Pneumocystis jirovecii* were noted. Etiology of sepsis is summarized in Table 5. We noted a low incidence of de novo bone marrow or solid organ malignancy 6 (8.1%) with dual immunosuppression regimen (metastatic small cell lung cancer at 15 months, 1; breast cancer at 44 months, 1; prostate cancer at 31 months, 1; myelodysplastic syndrome at 90 months, 1; acute myeolplastic leukemia at 60 months, 1; NK/T-cell leukemia lymphoma at 90 days, 1; and nonmelanoma skin cancer, 3).

DISCUSSION

In the current study, we report the results of disease recurrence and long-term survival in the first and largest cohort of autoimmune liver disease recipients for LT using a steroid-free dual immunosuppression. We noted an overall similar

TABLE 6.

Patterns of recurrence of the disease and their clinical characteristics

	All (N = 74)	PSC (n = 20)	PBC (n = 23)	AIH (n = 31)
Recurrence, n (%)	13 (17.5%)	3 (15%)	5 (21.7%)[a]	5 (16.1%)[b]
Sex				
Male	7 (53.85%)	1 (33.3)	3 (60%)	3 (60%)
Female	6 (46.15%)	2 (66.7%)	2 (40%)	2 (40%)
Recurrence since LT, n (%)[c]				
Within 1 y, n	3 (4.1%)	0 (0%)	2 (8.7%)	1 (3.2%)
Within 1-3 y, n	7 (9.5%)	2 (10%)	2 (8.7%)	3 (9.7%)
Beyond 3 y, n	3 (4.1%)	1 (5%)	1 (4.3%)	1 (3.2%)
Fibrosis progression rate (METAVIR units/y)				
Without recurrence	0.60 ± 1.38	0.52 ± 0.82	0.57 ± 0.85	0.69 ± 1.95
With recurrence	0.30 ± 0.36	0.14 ± 0.15	0.28 ± 0.40	0.41 ± 0.44
Immunosuppression regimen at recurrence				
Prograf/MMF	9 (69.2%)	1 (33.3%)	4 (80%)	4 (80%)
Rapamycine/MMF	3 (23.1%)	2 (66.7%)	0 (0%)	1 (20%)
Prograf/rapamycine	1 (7.7%)	0 (0%)	1 (20%)	0 (0%)
Prednisone	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Long-term outcome with recurrence				
Cirrhosis	2 (15.4%)	0 (0%)	1 (20%)	1 (20%)
Death	4 (30.8%)	1 (33.3%)	1 (20%)	2 (40%)
Retransplant	1 (7.7%)	0 (0%)	0 (0%)	1 (20%)

[a] Three patients with AIH had features suggestive of overlap syndrome, 2 with PSC, and 1 with PBC. One with AIH/PBC overlap had recurrent PBC. Of the 2 patients with PSC overlap, 1 had PSC recurrence. Both these AIH/PSC and AIH/PBC patients with recurrent PSC, and PBC on follow up had predominant AIH features on explant histology, hence they were grouped under the AIH category.

[b] One patient with predominant PBC with overlap feature with AIH on explant was grouped under the PBC group had recurrent PBC.

[c] Calculation is based on number of patients at risk of developing ACR.

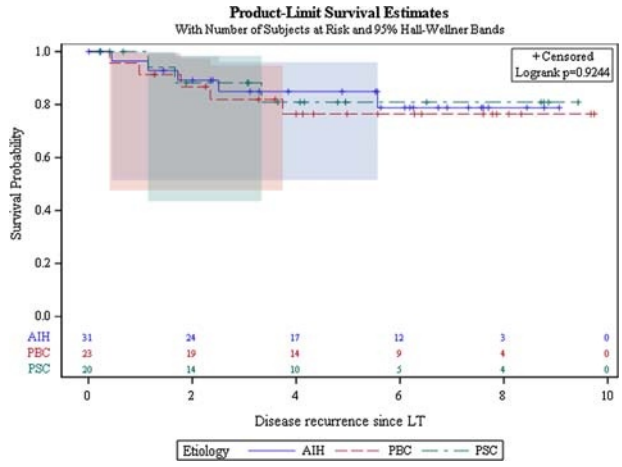

FIGURE 3. Time to posttransplant recurrence of autoimmune liver disease in the PSC, PBC, and AIH groups.

incidence of recurrence for autoimmune liver disease using this approach, 15% in PSC, 21.7% in PBC, and 16.1% in AIH, with an overall recurrence of 17.5%. Reported incidence of recurrent PSC, PBC, and AIH varies widely in the literature. In particular, PSC recurrence varies from 5% to 50%,[12-15] PBC recurrence rates range from 10% to 50%,[12,16-18] and AIH recurrence varies between 12% and 42%.[3,12,19-22]

We explored predictors of recurrence for the autoimmune liver disease as a group and noted the development of ACR was the single important predictor for autoimmune disease recurrence after LT. Strongest association of disease recurrence with ACR was noted in patients with AIH. Numerous risk factors for recurrence of the autoimmune disease have been described in the literature. Factors predisposing to recurrent PSC includes certain HLA associations with recipient or donor (HLA-DRB1*08, HLA DR52)[23,24]; male recipient,[25] recipient-donor sex mismatch[26]; recipient age[24]; an intact colon in the recipient before transplantation,[25] and the presence of ulcerative colitis (UC) after LT[27]; use of extended donor criteria grafts[14]; ACR,[24] steroid-resistant ACR[24,28] or use of OKT3,[29] and cytomegalovirus infection in the recipient.[24,30] Standard immunosuppressive agents using either cyclosporine or tacrolimus did not seem to affect PSC recurrence or did pre or posttransplant dose and duration of corticosteroid treatment or posttransplant (prophylactic) use of ursodeoxycholic acid (UDCA).[9,14,29] Rapid weaning of steroids post-LT has been suggested to be associated with higher recurrence rates.[31-33] Several, but not all studies reported that, when compared with cyclosporine, tacrolimus-based immunosuppression is associated with a higher frequency and shorter time to PBC recurrence post-LT.[34-36] However, the large meta-analysis by Gautam et al,[12] evaluating 16 studies summarizing a total of 1241 patients, failed to confirm that tacrolimus- and cyclosporine-based immunosuppression regimens are differentially associated with PBC recurrence.

For AIH, poor control before LT,[37] coexistent autoimmune diseases, and high transaminases and IgG before transplant have been reported to be associated with an increased AIH recurrence.[38] Molmenti et al[39] have reported no association between ACR and the recurrence of AIH. However, we did find a strong association for recurrence of autoimmune liver disease as a group with ACR and individually in AIH subgroup. Similarly, it has been reported that the incident rate of ACR after LT is higher in AIH patients than non-autoimmune diseases,[12,40,41] although the impact of ACR for recurrent AIH is uncertain.[42] The true incidence of ACR may be underestimated as it is still an unsolved question whether ACR in AIH recipients is a true autoimmune disease or a type of rejection. Studies containing data on the incidence of ACR after LT for PSC have recently been reviewed[43] with a wide variation from center to center based on the immunosuppression protocol, even up to 100% has been reported in earlier series.[44] Unfortunately, despite improved immunosuppression medications in the last decade, the rate of ACR has still been reported as high as 73%.[45] There is, however, a paucity of data with regard to the rate of ACR in recipients with LT for PBC. Using steroid-free dual immunosuppression, we have noted a lower rate of ACR compared with published series, 30% for PSC, 21.7% for PBC, and 35.5% for AIH. Additionally, using this approach, we have noted histologically severe ACR in less than 10% of the patients, mostly presenting within 1 year. AIH subjects continued to remain at risk for ACR even beyond 3 years since LT, but were less likely in the PSC and PBC patients. We also witnessed rare steroid-refractory ACR requiring IV antithymocyte globulin for management.

In both univariate and multivariate Cox Regression analyses, overall patient survival predictors included the need for steroids for control of ACR during post-LT period. The need for steroids leading to graft loss and death is probably linked to more aggressive rejection and to higher infection rate due to more immunosuppression contributing to patient deaths. Other predictors for graft loss on univariate analysis included sepsis during post-LT period, and younger age at LT.

Although hospitalizations secondary to sepsis were not uncommon (34 episodes in 19 patients), deaths clearly related to sepsis were rare (8 of 74, 10.8% of the patients). Pneumonia was the most common infection, followed by cholangitis and liver abscesses. Schram et al[46] found infectious complications occurring early after transplantation as the main cause leading to death after first LT (7.6% AIH and 4.3% PBC recipients). In another study, early deaths posttransplantation for AIH were mainly due to infection, which was unrelated to the duration of immunosuppressive treatment before transplantation.[47] These data are, however, inconsistent because even excellent survival rates without increased rates of infectious complications have also been reported elsewhere.[48] Several reasons can be attributed to these discrepancies including center level differences, nonstandardized second-line and third-line treatment protocols, different immunosuppressive regimens, use of protocol biopsies with early diagnosis of disease recurrence, and early modification of immunosuppression regimen. Our current data show that use of steroid-free dual immunosuppression is safe, effective, and has a low rate of infections and infection-related death.

We also noted no impact of disease recurrence on graft and patient survival. The clinical impact of disease recurrence on survival has been evaluated in several studies using either long-term immunosuppression with or without low-dose steroid. Although short and midterm patient and graft survivals do not appear to be impaired by PSC recurrence, PSC recurrence can affect graft outcome and may increase the need for

TABLE 7.

Predictors of recurrence of autoimmune liver disease on logistic regression analysis

	All patients		PSC		PBC		AIH	
Variables	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**
Patient age	0.61	0.99 (0.95-1.03)	0.58	1.03 (0.93-1.13)	0.52	0.96 (0.86-1.08)	0.18	0.95 (0.89-1.02)
Sex (male vs others)	0.24	2.07 (0.62-6.93)	0.43	0.35 (0.03-4.65)	0.07	7.50 (0.85-66.12)	0.30	2.83 (0.40-20.18)
Race (white vs others)	0.78	0.84 (0.24-2.89)	0.54	0.44 (0.03-5.88)	0.97	>999.99 (<0.001 to > 999.99)[a]	0.38	0.42 (0.06-2.95)
BMI	0.67	1.03 (0.91-1.16)	0.41	1.09 (0.87-1.34)	0.36	0.88 (0.68-1.15)	0.39	1.10 (0.89-1.35)
Donor age	0.43	1.02 (0.98-1.05)	0.65	0.98 (0.90-1.07)	0.85	1.01 (0.95-1.07)	0.24	1.04 (0.98-1.11)
Donor gender (male vs others)	0.32	0.52 (0.15-1.89)	0.95	<0.001 (<0.001 to > 999.99)[a]	0.86	0.83 (0.11-6.26)	0.57	0.57 (0.08-4.01)
Donor BMI	0.45	1.03 (0.95-1.13)	0.94	1.01 (0.87-1.16)	0.87	0.98 (0.80-1.20)	0.13	1.14 (0.96-1.35)
CIT	0.25	1.00 (0.99-1.00)	0.85	0.78 (0.07-9.42)	0.28	0.99 (0.98-1.01)	0.52	1.00 (0.99-1.01)
WIT	0.98	1.00 (0.92-1.08)	0.83	0.99 (0.86-1.13)	0.54	0.95 (0.81-1.11)	0.27	1.11 (0.92-1.35)
MELD score	0.36	1.04 (0.95-1.14)	0.38	1.13 (0.86-1.48)	0.48	1.07 (0.89-1.28)	0.70	1.03 (0.90-1.16)
Donor-recipient sex mismatch	0.48	0.65 (0.19-2.20)	0.66	0.56 (0.04-7.44)	0.69	1.50 (0.20-11.24)	0.24	0.25 (0.03-2.55)
Diabetes	0.97	<0.001 (<0.001 to > 999.99)[a]	0.96	<0.001 (<0.001 to > 999.99)[a]	0.97	<0.001 (<0.001 to > 999.99)[a]	0.97	<0.001 (<0.001 to > 999.99)[a]
ACR (yes vs no)	0.04	3.58 (1.04-12.32)	0.89	1.20 (0.09-16.44)	0.28	3.33 (0.38-29.39)	0.05	10.86 (1.03-114.58)
IV Steroid use for ACR	0.31	2.02 (0.53-7.77)	0.54	2.25 (0.16-34.90)	0.97	<0.001 (<0.001 to > 999.99)[a]	0.08	6.30 (0.82-48.34)
Sepsis (yes vs no)	0.25	2.10 (0.59-7.45)	0.54	2.25 (0.17-29.77)	0.86	1.25 (0.10-15.50)	0.14	5.11 (0.59-44.15)

[a] Very few observations for the predicted outcome to calculate odds ratio and CI.

WIT, warm ischemia time; CIT, cold ischemia time.

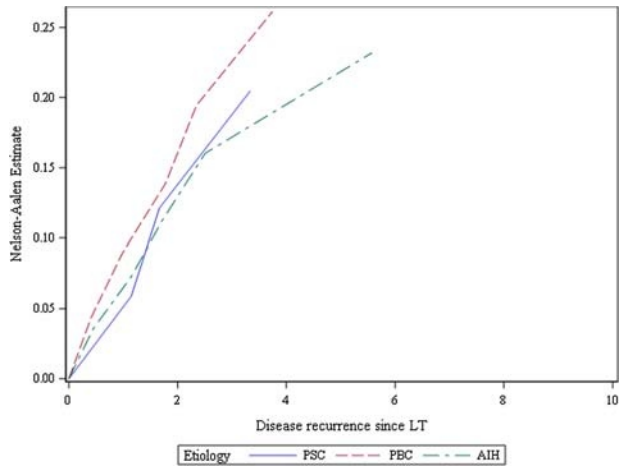

FIGURE 4. Cumulative hazards of disease recurrence in the PSC, PBC, and AIH groups.

retransplantation and affect patient survival with longer patient follow-up.[15,41,49] A study specifically comparing long-term outcomes in PSC and PBC noted that retransplantation for graft failure secondary to recurrent disease is relatively higher in PSC (12.4%) than in PBC (1%-5%).[50] Long-term graft and patient survival, in general, is not affected with recurrent PBC.[50-52] In fact, in the 2 largest reported experiences with LT for PBC, only 3 of 485 and 2 of 154 cases, respectively, required retransplantation.[53,54] Although recurrent PBC has also been described after a second and third LT, the proportion of graft failure due to disease recurrence seems again low after re-LT (7%-14%).[55] Long-term outcomes do not appear to be impaired in the vast majority of patients with recurrent AIH, fewer than 5% requiring re-LT for disease recurrence.[3,56-59] Our center does not use UDCA routinely for primary prevention of PBC recurrence. However, all patients transplanted for PBC who develops recurrence do receive UDCA. Hence, the disease recurrence is not modified with UDCA in our cohort of patients.

In the literature, there is wide variation in the rate of recurrence primarily because of inconsistency in diagnostic approach and criteria. Additionally, recurrent autoimmune liver diseases may remain asymptomatic early and can present in the absence of biochemical or clinical abnormalities leading to under-reporting. Centers that use protocol biopsies will report greater rates of recurrence. Further, AIH in the graft can occur de novo, that is, after LT for non-autoimmune liver disorders[2,60] confounding the true recurrence rate. Some have chosen to give other names like "graft dysfunction mimicking AIH" and "plasma cell hepatitis."[61] We have summarized reported long-term outcomes of LT recipients with autoimmune liver diseases from other studies in Table 9.

The limitations of the current study are those inherent to any retrospective, single-center study. The selection criteria are center specific and introduce a bias which may limit wider applicability to other centers. Additionally, the management approach to immunosuppression and complications can impact results at a single center, which may not be widely applicable. Also, we acknowledge that the small number of patients especially when analyzing predictors of recurrence may have introduced type II errors, and the data may need to be further validated in larger number of patients. In addition, few overlapping diagnoses have resulted in difficulty in accurately categorizing them into any particular entity. However, we have tried to address this issue by categorizing them based on their predominant findings on histology. However, single-center analysis does provide some clarity to certain variables that may not be captured in large registries. It is important to place data into the appropriate context to assure the best outcomes. However, retrospective review of medical records likely underestimates the true prevalence of recurrence due to limitations in recognition of the diagnosis. Multicenter, prospective studies with emphasis on clear assessment of risk factors already identified and validated response to immunosuppression approach as well as uniform criteria for defining recurrences might help strengthen the results.

In conclusion, steroid-free dual agent immunosuppression with a combination of tacrolimus, sirolimus, and MMF can provide acceptable long-term outcomes for limiting disease

TABLE 8.

Posttransplant infectious complications

Parameters	Severe sepsis
No. patients with sepsis (all groups)	19
No. patients with sepsis categorized based on underlying disease	
PSC	10 (50.0%)
PBC	4 (17.4%)
AIH	5 (16.1%)
No. episodes of sepsis (all groups)	34
No. episodes of sepsis categorized based on underlying disease:	
PSC	19 (55.9%)
PBC	10 (29.4%)
AIH	5 (14.7%)
No. episodes of sepsis based on time since LT:	
Less than 1 y	17 (50.0%)
Within 1-3 y	5 (14.7%)
More than 3 y	12 (35.3%)
Death related to sepsis[a]	8 (23.5%) of 34
Attributable etiology of sepsis	
Pneumonia	7 (20.6%)
Cholangitis	4 (11.8%)
Liver abscess	4 (11.8%)
Sepsis of unclear source	3 (8.8%)
Histoplasmosis	3 (8.8%)
SBP	2 (5.9%)
Nocardia infection	1 (2.9%)
Herpes zoster	1 (2.9%)
Urinary tract infection	1 (2.9%)
Otitis media	1 (2.9%)
Abdominal abscess	1 (2.9%)
Intestinal perforation with sepsis	1 (2.9%)
Cellulitis	1 (2.9%)
Spider bite	1 (2.9%)
Severe sinusitis	1 (2.9%)
Clostridium difficile colitis	1 (2.9%)
Follow-up interval, y	5.6 ± 2.6

[a] Etiology of death was unknown in 3 patients.

TABLE 9.

Published studies with autoimmune liver diseases compared to our study with regard to long-term survival, incidence of ACR, and sepsis related deaths

		Survival outcome			Regraft-free survival				
Author et al (year)	N	1 y	5 y	10 y	1 y	5 y	10 y	ACR, n (%)	Sepsis-related death, n (%)
PSC									
Satapathy et al.[a] (2016)	20	90	90	—	85	80	—	6 (30%)	2 (10%)
Kashyap et al.[48] (2010)	972	95.4	93	87.5	87.1	87	79.2	—	—
Albraba et al.[10] (2009)	230	80	68	57	75	60	50	—	— (25%)
Carbone et al.[46] (2011)	1731	83	75	66	78	65	54	—	—
Moncrief et al.[44] (2000)	59	97	86	79	96.6	83.6	67.6	11 (73.3%)	3 (—)
Cholangitas et al.[23] (2008)	53	—	85	76	—	—	—	—	7 (—)
Oldakowska-Jedynak et al.[49] (2006)		88	65	—	80	60	—	11 (65%)	—
Brandsaeter et al.[24] (2005)	49	82	74	64	—	—	—	35 (—)	—
Kugelmas et al.[25] (2003)		—	—	—	90	—	—	—	—
Liden et al.[50] (2001)	61	82	73	64	—	—	—	—	—
Primary biliary cirrhosis									
Satapathy et al.[a] (2016)	23	100	91.3	—	100	91.3	—	5 (21.7%)	3 (13%)
Schramm et al.[51] (2010)	1524	—	83	—	—	71			59 (4.3%)
Kashyap et al.[48] (2010)	757	90.1	89.6	85.1	80.9	85.2	80.7	—	—
Carbone et al.[46] (2011)	2959	83	77	69	79	71	64	—	—
Montano-Loza et al.[52] (2010)		—	86	76	—	—	—	—	—
Charatcharoenwitthaya et al.[53] (2007)	154	93	90	79	856	82	72	—	—
AIH									
Satapathy et al.[a] (2016)	31	96.8	90.1	—	93.4	86.8	—	12 (35.5%)	3 (9.7%)
Schramm et al.[51] (2010)	827	—	73	—	—	66	—		52 (7.6%)
Kashyap et al.[48] (2010)	545	94.3	89.1	80.4	89	84.9	74.5	—	—
Montano-Loza et al.[14] (2009)		—	81	77	—	—	—	—	—
Campsen et al.[15] (2008)		—	91	—	88	59	—	—	—

[a] Current study, 7-year overall patient survival for PSC, PBC and AIH were 90%, 74.4%, and 67.4%, and graft survival was 80%, 74.4%, and 67.9%, respectively.

Studies included adult patients with DDLT with reported survival up to 5 years posttransplant. Only studies published after 2000 were included.

recurrence, patient morbidity, and mortality when transplantation is indicated for autoimmune liver diseases.

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