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Impact of pre-transplant Anti-nuclear antibody (ANA) and Anti-smooth muscle antibody (SMA) titers on disease recurrence and graft survival following liver transplantation in autoimmune hepatitis (AIH) patients

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Abstract

Background and Aims—Disease recurrence following transplant occurs in 20-45% of patients with autoimmune hepatitis. Factors associated with an increased risk of recurrence include HLA DR3 and HLA DR4 positivity, inadequate immunosuppression and severity of inflammation in the native liver. Titers of several auto antibodies can be elevated in patients with autoimmune hepatitis including ANA and SMA however it is unclear whether or not the degree of elevation influences the risk of disease recurrence following transplant.

Methods—We conducted a retrospective study to evaluate the potential impact of pre transplant titers on post transplant outcomes for patients with autoimmune hepatitis. Sixty three patients with autoimmune hepatitis who underwent 72 liver transplants between January 1, 1989 and January 1, 2009 were included with a median follow up of 104 months. Patients were divided into group A (ANA or SMA 1:160) and group B (titers 1:160).

Results—There was no significant difference in recurrence rates or death between patients in group A and B respectively. Only race appeared to impact outcomes with African American patients having a higher incidence of death and recurrent disease post transplant compared to other ethnicities.

Conclusions—Based on our findings, pre transplant ANA and ASMA levels do not appear to impact recurrence rates or outcomes following liver transplantation for autoimmune hepatitis.

Keywords

Autoimmune hepatitis; Anti-nuclear antibody (ANA); Anti-smooth muscle antibody (SMA); liver transplantation

Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory disease of unknown etiology that may progress to liver failure. Up to 10% of patients with AIH will ultimately require

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orthotopic liver transplantation (OLT), and autoimmune hepatitis is currently the 7th leading indication for liver transplantation, accounting for approximately 6% of all liver transplant cases in the United States [1-5]. Data on long term outcomes following liver transplantation amongst AIH patients are conflicting. Some studies have shown similar rates of graft survival at 1, 3 and 5 years following transplant, whereas others have shown higher rates of chronic rejection and graft loss [6-10]. Unfortunately, all of these studies are limited by small sample sizes and relatively short duration of follow up.

Disease recurrence occurs in up to 20-45% of patients at 5 years following transplantation with histological recurrence often preceding clinical and biochemical recurrence [11]. Recurrent disease increases the risk of graft failure, progression to cirrhosis and need for re-transplantation, and presents a major challenge in the post transplant care of these patients [11-16]. Factors associated with an increased risk of recurrence include HLA DR3 and HLA DR4 positivity, inadequate immunosuppression, severity of inflammation in the native liver, and possibly anti-SLA (anti soluble liver antigen) positivity [17].

Furthermore, patients with AIH often require higher doses and more prolonged courses of corticosteroids following OLT and this may predispose to various well known side effects of steroids, including osteoporosis, risk for infection and post transplant diabetes. On the other hand, early withdrawal of steroids may increase the risk of recurrence as well as the risk for acute rejection amongst this patient population [11, 18-21].

Given the significant impact of disease recurrence on post-transplant outcomes as well as the known toxicities of chronic steroid use, it would be very beneficial to identify patients who are at a higher risk for AIH recurrence, as these patients may require closer monitoring and specially tailored immunosuppressant regimens. Patients who are at low risk of recurrence on the other hand may benefit from early withdrawal of steroids and steroid free maintenance regimens.

Titers of several autoantibodies are usually elevated in patients with AIH, including ANA (antinuclear antibody), SMA (smooth muscle antibody) and anti-SLA in type 1 AIH, and LKM1 (liver/kidney microsome type 1 antibody) and anti-LC1 (anti-liver cytosol type 1 antibody) in type 2 AIH. It is unclear whether there is a relationship between pre transplant titers of these autoantibodies and outcomes following OLT, particularly whether the degree of elevation influences the risk of disease recurrence following transplant. Measurement of autoimmune antibody titers is routinely performed during the evaluation of AIH patients and identifying a correlation with post transplant outcomes would be a valuable marker for risk stratifying these patients. Therefore, we designed a study to determine whether or not the degree of elevation of autoantibody titers prior to OLT is associated with an increased risk for AIH recurrence following transplant, and to compare outcomes including acute rejection, AIH recurrence, chronic rejection, graft failure, need for re- transplant and all cause mortality between patients with elevated autoantibody titers prior to OLT and those with lower titers.

Patients and Methods

This was a retrospectively designed study to evaluate whether or not the level of autoantibodies in patients with AIH and end stage liver disease undergoing liver transplantation is associated with an increased risk of recurrent AIH following OLT, and to compare long term outcomes following transplantation between patients with low autoantibody titers pre transplant and those with higher titers. Data was collected via chart review, using the Emory transplant computer database, on all patients with AIH who underwent OLT between January 1, 1989 and January 1, 2009.

Inclusion and Exclusion criteria

Patients were included if they had end stage liver disease due to biopsy proven autoimmune hepatitis, documented autoimmune serologies, had received a liver transplant and had follow up data for at least one year post transplantation. Patients were excluded from the study if they had other documented causes of end stage liver disease, if they did not have biopsy proven AIH as an underlying etiology for liver disease or if they lacked data on pre transplant autoimmune titers. Patients without adequate follow up data were also excluded. Eligible patients were divided according to their pre transplant autoantibody titers into 2 groups. Group A included patients with low titers defined as less than 1:160 (including patients who tested negative for ANA and SMA), while group B included patients with titers greater than or equal to 1:160. Most studies use titers of > 1:40 to define a positive ANA and SMA; therefore we decided to use a value of at least 4 times the upper limit of normal (1:160) to define a high titer.

Autoantibody detection

ANA, SMA and LKM-1 were detected in serum using an indirect immunofluorescence (IIF) method on unfixed cryostat sections of rat liver, kidney and stomach. ANA was also screened by IIF on Hep-2 cell monolayers. Positivity cutoffs for ANA, SMA and LKM-1 were a titer > 1:40. Gamma globulin levels were determined by serum electrophoresis. Gamma globulin values of 1700 mg/dL or more were considered significant. All autoantibody measurements were obtained within 12 months of transplantation.

Post transplantation immunosuppression protocol

All patients were discharged on oral Tacrolimus with almost half receiving concurrent Mycophenolate mofetil. Tacrolimus dosing was adjusted to maintain trough levels of 8-12 ng/ml initially then tapered within 6 months to maintain trough levels of around 5 ng/ml. Patients were also started on oral prednisone at a dose of 20 mg daily and tapered down to 5 mg daily within 3 months. Patients were then maintained on 5 mg/d of prednisone indefinitely.

Follow up protocol

Following discharge, all patients were followed up at the Emory Transplant Center at 3 month intervals for the first year then at 6-12 month intervals if they had stable graft function. Immunosuppressant trough levels, complete blood counts, platelet counts, complete metabolic panels including liver enzymes, serum albumin and prothrombin times were checked at each visit. Patients with elevated liver enzymes were evaluated immediately with imaging including abdominal Ultrasound with Dopplers, abdominal MRI with MRCP (magnetic resonance cholangiopancreatography), viral hepatitis serologies, and CMV titers. An ultrasound guided liver biopsy was performed if the initial work up including imaging did not reveal an etiology for the abnormal liver enzymes. Protocol biopsies were not routinely performed in this patient population and autoantibody titers were not routinely measured in the post transplant setting.

Definition and management of recurrent disease

Recurrent disease post transplant was diagnosed based on several criteria: a sustained increase in serum aminotransferase levels, elevated serum immunoglobulins, compatible liver histology (portal lymphoplasmacytic infiltration, lobular activity and interface hepatitis) and exclusion of other causes of elevated liver enzymes or graft failure such as acute and chronic rejection, drug induced hepatotoxicity, biliary disease (anastomotic or

ischemic strictures, choledocholithiasis, and biliary casts), hepatic artery thrombosis or underlying infection. Patients with recurrent disease received an initial dose of 40-60 mg daily oral prednisone and this was tapered down as tolerated based on response. Ten patients with recurrence received a combination of prednisone and Azathioprine (dose range: 50-100 mg).

Primary and secondary outcomes

Primary outcomes of interest were disease recurrence and graft survival amongst group A and B patients. Other outcomes of interest were compared between patients in both groups including acute and chronic rejection, the need for re-transplantation and mortality from all causes, the overall incidence of AIH recurrence, as well as graft and patient survival for all AIH patients receiving OLT. Variables including liver enzymes, bilirubin, prothrombin time, platelet counts and immunoglobulin levels were collected immediately before transplant (baseline) then at 1, 3, 5 and 10 years post transplantation. Autoantibody titers, and HLA DR3 and DR4 status was also documented when available. Immunosuppressant regimens at discharge following transplantation were also documented.

Statistical Analysis

Statistical analysis was performed using the Fisher exact test to compare dichotomous variables. The unpaired t-test was used to evaluate the significance of differences in means for continuous variables and the Mann Whitney test was used to compare non parametric data. Allograft survival was calculated from the time of transplant to the time of first graft loss or day of last follow up. Patient survival was calculated from the time of transplant to the last day of follow up. Kaplan-Meier plots were used to compare survival between the two patient groups. A proportional hazards regression model was used to evaluate possible predictors of recurrent disease. We also used logistic regression models to develop a predictive model for recurrence or death at 1 and 5 years post transplant. A p value < 0.05 was used to determine statistical significance. The study protocol was approved by the IRB at Emory University School of Medicine.

Results

Over a period of 20 years, a total of 1,787 OLTs were performed in 1,437 patients, of whom 63 patients with AIH received a total of 72 allografts and fulfilled the inclusion criteria. Forty eight (76%) were female. Thirty three (52%) patients were Caucasian, 26 (41%) were African American and 4 (7%) were Hispanic. Patients were followed up for a mean of 101 ± 60 months post transplant (median: 104 months; range 1-229). Mean age at transplant was 38.5±16 years; 4 (7%) had diabetes (type 1), 7 (11%) were hypertensive, and 5 (8%) had chronic kidney disease (not requiring hemodialysis) at the time of transplant.. Explant histology was available in 30 cases (42%); 23 patients had no or mild inflammation and 7 had moderate to severe inflammation. HLA DR3 and HLA DR4 status was available for only 27 patients (43%).

Recurrence occurred in 26/63 patients (42%) and 30/72 (42%) of the liver grafts. Mean time to recurrence was 57.5±46 months (median: 54.5 months) and mean graft survival was 92.5± 63 months (median: 92 months). Acute rejection occurred in 13 (18%) of grafts, chronic rejection in 19 (27%) and 7 patients (9%) required repeat liver transplantation. Most re-transplants occurred within the first 12 months post transplantation (8/12; 67%); and the main indications for re-transplantation were hepatic artery thrombosis (4/12; 33%), graft failure (6/12; 50%) and primary graft non function (1/12). A total of 7 malignancies developed in 6 patients (2 colon cancers, 4 skin cancers [squamous and basal cell carcinoma] and 1 lung cancer). Thirteen patients (21%) died during follow up; the main

causes of death were sepsis (5 patients) and liver failure (4). Other causes of death were cancer (1), acute pancreatitis (1), cardiovascular disease (1) and intracranial bleeding (1). Post transplant diabetes developed in 19 (30%) patients and 2 serious cardiovascular events (1 stroke and 1 myocardial infarction) occurred, both in the same patient. Six patients with recurrent disease post transplant died; the causes of death were liver failure (2 patients), sepsis (1), intracranial hemorrhage (1), colon cancer (1) and pancreatitis (1). Four patients (including one patient who received 3 allografts) with recurrent disease required re-transplantation. The cause of graft failure was hepatic artery thrombosis in 1 patient and recurrent autoimmune hepatitis in the remaining patients. The majority of patients with recurrence (18/26; 70%) responded to treatment with Prednisone and Azathioprine and did not have an adverse outcome.

Baseline pre transplant serologies and titers were available for 52 patients (83%); 28 of these (54%) had ANA and/or SMA titers 1:160 (group A) and the remaining 24 had positive ANA and SMA serologies but with low titers (< 1:160) and these constituted group B. Only 8 patients had documented anti-LKM status (1 low positive and 7 negative), and none had anti-SLA or anti-LC1 serologies available. Baseline characteristics were similar between patients in both groups except for race distribution (53% African American patients in group A compared to 29% in group B) and HLA DR3 positivity (19% in group A compared to 58% in group B) (table 1). Initial Immunosuppressant regimens were similar for both groups.

There was no significant difference in long term outcomes between patients in both groups (table 2). Recurrent disease occurred in 11 (39%) of group A and 11 (46%) of group B patients with a mean time to recurrence of 54.8 ± 41.8 months (median: 54 months) and 37.7 ± 37 months (median: 18 months), respectively. Mean graft survival was also not significantly different; 90.1 ± 54.4 months (group A; median 93 months) and 76.5 ± 60.1 months (group B; median 89.5 months). Five patients in group A (18%) and 6 (25%) in group B developed acute rejection; chronic rejection developed in 9 (32%) and 6 (25%) of patients in group A and B, respectively. Cancer developed in 2 (7%) of group A patients and 4 (17%) of group B patients but this was not statistically significant; post transplant diabetes developed in 6 (21%) and 8 (33%) patients in group A and B, respectively. Five patients died in each group (group A: 18% vs. group B: 21%) and the difference was not significant. Kaplan-Meier survival curves summarizing time to recurrence or death for Groups A and B did not show any significant difference in disease-free survival times (log-rank test, $P=0.99$) (figure 1).

In a multivariate analysis, we fitted a proportional hazards regression model to assess prognostic factors for disease recurrence or death. Age, gender, race and autoantibody titer status were entered into the model. We were unable to include additional factors such as explant histology, HLA DR3 and DR4 status, in the regression analysis due to the substantial number of missing data. We found that African American patients had a higher risk of recurrence or death compared to other ethnicities (table 3).

We also developed predictive models of recurrence or death within 1 year and 5 years after transplant. This was accomplished by entering age, gender, race, and titer status into logistic regression models. None of these factors was predictive of recurrence or death within 1 year after transplant. African-Americans had a 56% chance, and other races had a 26% chance, of recurrence or death within 5 years after transplant ($P = 0.05$; Table 4).

Discussion

Autoimmune hepatitis recurs in up to 45% of patients post transplantation with a median time to recurrence of approximately 2 years [11, 22-24]. The wide range in recurrence rates reported by various studies is likely a reflection of the difference in follow up duration post transplant, variation in immunosuppressant regimens and surveillance protocols, as well as the lack of standardized criteria to diagnose recurrent AIH. Most available data on long term outcomes following liver transplantation for autoimmune hepatitis come from relatively small studies (less than 40 patients) with short duration of follow up (5 years or less). Our study included 63 patients with AIH who received a total of 72 allografts, and who were followed up for a median of 104 months post transplant. Patient survival was approximately 80% which is similar to that seen in patients transplanted for other etiologies of liver disease. Recurrence rate among our patients was 42% with a median time to recurrence of 54.5 months. The relatively higher recurrence rate noted amongst our patients is likely due to longer follow up as well as the predominance of AIH type 1 patients. Patients with recurrent AIH had similar survival rates and graft survival compared to patients without recurrent disease; a finding that is in agreement with other studies.

Risk factors for recurrent AIH have not been clearly elucidated. HLA DR3 positive recipients were noted to have worse graft survival in some studies but not in others. Ayata et al, found that high grade inflammation in the native liver, predisposed recipients to recurrent AIH post transplantation [12]. Montano-Loza et al also showed that patients with moderate to severe inflammation in their explants were at a higher risk for recurrence; other risk factors for recurrence in their study included elevated pre-transplant aminotransferase and immunoglobulin levels, as well as the presence of concomitant autoimmune diseases [25]. Unfortunately we were unable to assess the impact of HLA DR3 and DR4 status or explant inflammation severity on recurrence rates due to the significant number of missing data. We evaluated the impact of age, race, gender and autoimmune titer levels on recurrence rates or death and found that African Americans were at a higher risk for recurrence and death compared to other ethnic groups. We also attempted to develop a predictive model for recurrence or death post transplant for AIH using age, race, gender and autoimmune titers. None of these factors were predictive of death or recurrence at 1 year post transplant and only race was predictive of outcomes at 5 years whereby African Americans had a 56% chance of recurrent disease or death compared to 26% for the other ethnic groups.

The aim of our study was to evaluate whether or not pre transplant ANA and ASMA levels had any impact on long term outcomes following transplantation in AIH patients. We did not find any significant difference in recurrence rates, graft and patient survival between patients with elevated titers ($\geq 1:160$) and those with low titers ($< 1:160$).

We recognize several limitations in our study. This was a retrospective study spanning a period of 20 years. During this time period standards of care in the management of transplant patients have evolved and this may have affected the outcomes amongst our patients who were transplanted at different time points. We attempted to stratify data by date and by pre and post MELD era however we were unable to do so due to the relatively small sample size. We were also unable to analyze the effects of HLA DR3 and DR4 status or explant histology on recurrence rates and death post transplant because of the significant amount of missing data. Another limitation was the lack of data on presenting symptoms for many of our patients. We were thus unable to determine if any of our patients presented with fulminant liver failure and this again may have impacted our outcomes since these patients have more severe inflammation and are likely at a higher risk of recurrence. We did not perform protocol biopsies for surveillance, but rather patients were biopsied if they had elevations in their liver enzymes. Even though the majority of our patients had at least one

liver biopsy over the course of follow up, it is possible that the recurrence rate in our cohort was underestimated, since patients with silent disease could have been missed. We used strict criteria to identify recurrence post transplantation including elevations in aminotransferase and globulin levels, in addition to histological findings consistent with AIH on liver biopsy in the absence of other causes of graft dysfunction. Standardized diagnostic criteria to define recurrent AIH post transplantation are certainly needed. The majority of our patients had type 1 AIH, which would be expected as type 1 is more common amongst adult patients in the US. That being said, data on anti-LKM titers and anti-LC1 was missing for the majority of our patients, and we therefore could not accurately identify patients with type 2 AIH.

In summary we presented data on long term outcomes for 63 patients with AIH who received a liver transplant at our institution. Patients were followed for a median of approximately 8.5 years post transplant, and patient survival was excellent, approaching 80%. We found a recurrence rate of 42% which is within the range noted in previous studies. Recurrent AIH was successfully managed with steroids and modifications in the immunosuppressant regimen in the majority of patients, however 4 patients had progressive graft failure and required re-transplantation. African American patients had a higher incidence of recurrent disease or death (HR: 4.11), compared to patients from other ethnicities. Gender, Age and Autoantibody titers (ANA, SMA) did not appear to impact long term outcomes. Unfortunately we were unable to evaluate the impact of HLA DR3 and DR4 status or explant histology on post transplant outcomes due to the significant number of missing data.

Recurrent disease is certainly a common problem complicating the post transplant course of many patients with AIH. Available data suggests that recurrent AIH can be successfully managed in the majority of patients; however, the disease can be silent and therefore a high index of suspicion is necessary. Larger prospective studies are needed to identify predictors for recurrent AIH post transplantation. Identifying patients at a higher risk for recurrence is important, as these patients may benefit from more intensive surveillance and modifications in their immunosuppressant regimens.

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Abbreviations

ANA	anti-nuclear antibody
SMA	anti-smooth muscle antibody
AIH	autoimmune hepatitis
OLT	orthotopic liver transplantation
anti SLA	anti soluble liver antigen
anti-LKM1	anti-liver/kidney microsome type 1 antibody
anti-LC1	anti-liver cytosol type 1 antibody

References

1. Vogel A, Heinrich E, Bahr MJ, Rifai K, Flemming P, Melter M, et al. Long term outcome of liver transplantation for autoimmune hepatitis. Clin Transplant. 2004; 18:62–69. [PubMed: 15108772]

2. Krawitt EL. Autoimmune Hepatitis. *N Engl J Med*. 2006; 354:54–66. [PubMed: 16394302]
3. Mottershead M, Neuberger J. Transplantation in autoimmune liver diseases. *World J Gastroenterol*. 2008; 14:3388–3395. [PubMed: 18528936]
4. Futagawa Y, Terasaki PI. An analysis of the OPTN/UNOS Liver Transplant Registry. *Clin Transpl*. 2004;315–329. [PubMed: 16704160]
5. Czaja AJ, Freese DK. Diagnosis and treatment of autoimmune hepatitis. *Hepatology*. 2002; 36:479–497. [PubMed: 12143059]
6. Campsen J, Zimmerman MA, Trotter JF, Wachs M, Bak T, Steinberg T, et al. Liver Transplantation for Autoimmune Hepatitis and the Success of Aggressive Corticosteroid Withdrawal. *Liver Transplantation*. 2008; 14:1281–1286. [PubMed: 18756454]
7. Neuberger J. Transplantation for Autoimmune Hepatitis. *Seminars in Liver disease*. 2002; 22:379–385. [PubMed: 12447709]
8. Khalaf H, Mourad W, El-Sheikh Y, Abdo A, Helmy A, Medhat Y, et al. Liver Transplantation for Autoimmune Hepatitis: A single center experience. *Transplantation Proceedings*. 2007; 39:1166–1170. [PubMed: 17524922]
9. Molmenti EP, Netto GJ, Murray NG, Smith DM, Molmenti H, Crippin JS, et al. Incidence and recurrence of autoimmune/alloimmune hepatitis in liver transplant recipients. *Liver Transpl*. 2002; 8:519–526. [PubMed: 12037782]
10. Gautam M, Cheruvattath R, Balan V. Recurrence of autoimmune liver disease after liver transplantation: a systematic review. *Liver Transpl*. 2006; 12:1813–1824. [PubMed: 17031826]
11. Duclos-Vallee JC, Sebah M, Rifai K, Johanet C, Ballot E, Guettier C, et al. A 10 year follow up study of patients transplanted for autoimmune hepatitis: histological recurrence precedes clinical and biochemical recurrence. *Gut*. 2003; 52:893–897. [PubMed: 12740348]
12. Ayata G, Gordon FD, Lewis WD, Pomfret E, Pomposell JJ, Jenkins RL, et al. Liver transplantation for Autoimmune Hepatitis: A long-term pathologic study. *Hepatology*. 2000; 32:185–192. [PubMed: 10915722]
13. Kotlyar DS, Campbell MS, Reddy KR. Recurrence of Diseases following Orthotopic Liver Transplantation. *Am J Gastroenterol*. 2006; 101:1370–1378. [PubMed: 16771963]
14. Hubscher SG. Recurrent autoimmune hepatitis after liver transplantation: diagnostic criteria, risk factors and outcome. *Liver Transpl*. 2001; 7:285–291. [PubMed: 11303286]
15. Schreuder TC, Hubscher SG, Neuberger J. Autoimmune liver disease and recurrence after orthotopic liver transplantation: what have we learned so far? *Transpl Int*. 2009; 22:144–152. [PubMed: 18662365]
16. Mendes F, Couto CA, Levy C. Recurrent and de novo autoimmune liver diseases. *Clin Liver Dis*. 2011; 15:859–878. [PubMed: 22032533]
17. Montana-Loza AJ, Carpenter HA, Czaja AJ. Clinical significance of HLA DRB1*03-DRB1*04 in type 1 autoimmune hepatitis. *Liver International*. 2006; 26:1201–1208. [PubMed: 17105585]
18. Czaja AJ. Autoimmune liver disease. *Current Opinion in Gastroenterology*. 2008; 24:298–305. [PubMed: 18408457]
19. Hayashi M, Keefe EB, Krams SM, Martinez OM, Ojogho ON, So SKS, et al. Allograft rejection after liver transplantation for autoimmune liver diseases. *Liver Transpl Surg*. 1998; 4:208–214. [PubMed: 9563959]
20. Narumi S, Hakamada K, Sasaki M, Friese CE, Stock PG, Roberts JP, et al. Liver transplantation for autoimmune hepatitis: Rejection and recurrence. *Transplant Proc*. 1999; 31:1955–6. [PubMed: 10455934]
21. Milkiewicz P, Hubscher SG, Skiba G, Hathaway M, Elias E. Recurrence of autoimmune hepatitis after liver transplantation. *Transplantation*. 1999; 68:253–256. [PubMed: 10440397]
22. Czaja AJ. Recurrent autoimmune hepatitis after liver transplantation: A disease continuum or a fresh start? *Liver Transplantation*. 2009; 15:1169–1171. [PubMed: 19790163]
23. Padilla M, Mayorga R, Carrasco F, Bedregal T, Bobadilla F, Rondon C, et al. Liver transplantation for autoimmune hepatitis in Peru: outcomes and recurrence. *Ann Hepatol*. 2012; 11:222–227. [PubMed: 22345339]

24. Mendes F, Couto CA, Levy C. Recurrent and de novo autoimmune liver diseases. Clin Liver Dis. 2011; 15:859–878. [PubMed: 22032533]
25. Montano-Loza AJ, Mason AL, Ma M, Bastiampillai RJ, Bain VG, Tandon P. Risk factors for recurrence of autoimmune hepatitis after liver transplantation. Liver Transplantation. 2009; 15:1254–1261. [PubMed: 19790153]

Figure 1.
Kaplan Meier curves summarizing time to recurrence or death for groups A and B

Table 1

Baseline characteristics for patients in group A and group B.

	Group A (n=28)	Group B (n=24)	p-value
Age at transplant (years)			
Mean (Median)	44.8±16.2 (46)	37.1±13.0 (38)	P=0.07
Gender			
M (%)	8 (29)	5 (21)	P=0.53
F (%)	20 (71)	19 (79)	
Race: n (%)			
Caucasian	10 (36)	16 (67)	P=0.03
African American	15 (53)	7 (29)	
Other	3 (11)	1 (4)	
HLA DR3 n (%)			
(+)	3 (19)	7 (58)	P=0.01
(-)	16 (81)	5 (42)	
HLA DR4 n (%)			
(+)	5 (26)	1 (8)	P=0.23
(-)	14 (74)	11 (92)	
ALT (IU/L) at baseline			
Mean	53.5±50.0	311.3±661.3	P=0.07
AST (IU/L) at baseline			
Mean	73.8±72.7	251.8±353.5	P=0.02
Explant histology n(%)			
Mild inflammation	11(79)	13(81)	P= 0.5
Moderate to Severe inflammation	3 (21)	3 (19)	
Diabetes Mellitus (pretransplant)	1 (4)	3 (12)	P=0.21
Hypertension pretransplant	5 (18)	1 (4)	P=0.14

Table 2

Comparison of long term outcomes between patients in Group A and B.

	Group A (n=28)	Group B (n=24)	P value
Recurrent disease post transplant; n (%)	11 (39)	11 (46)	0.63
Acute rejection; n (%)	5 (18)	6 (25)	0.53
Chronic rejection; n (%)	9 (32)	6 (25)	0.57
Re-transplantation; n (%)	4 (14)	3 (12)	0.54
Death; n (%)	5 (18)	5 (21)	0.79
Graft survival (months)			
Mean	90.1±54.4	76.5±60.1	0.39
Median	93	89.5	
Time to recurrence (months)			
Mean	54.8±41.8	37.7±37.0	0.31
Median	54	18	
New malignancy post transplant; n (%)	2 (7)	4 (17)	0.29
Post transplant Diabetes; n (%)	6 (21)	8 (33)	0.30

Table 3

Results of a proportional hazards regression model of the time to recurrence or death.

Prognostic Factor	P-Value	Hazard Ratio (95% CI)
Titer Status	P = 0.78	
Group A		0.88 (0.37, 2.09)
Group B		1.0
Gender	P = 0.59	
Female		1.37 (0.44, 4.20)
Male		1.0
Race	P = 0.005	
African-American		4.11 (1.53, 11.0)
Other		1.0
Age (per decade)	P = 0.75	0.95 (0.69, 1.31)

Table 4

Predictive model of the probability of recurrence or death within 5 years after transplant.

Prognostic Factor	P-Value	Probability of recurrence or death within 5 years after transplant (95% CI)
Race	P = 0.05	
African-American		0.56 (0.33, 0.76)
Other		0.26 (0.13, 0.45)