Experience of a liver transplant center in Medellín, Colombia with liver transplantation for autoimmune hepatitis and characteristics associated with post-transplant recurrence

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Abstract

Introduction: The recurrence of post-transplant autoimmune hepatitis implies risk of cirrhosis and graft loss. Risk factors have been proposed for recurrence, of which few data are known in Latin American patients. **Objectives:** To describe the characteristics of patients with liver transplantation for autoimmune hepatitis and to evaluate those associated with their recurrence during post-transplant. **Methods:** Historical cohort included patients with autoimmune hepatitis diagnosed after the age of 16 years and who were taken to liver transplant in a university hospital in Medellin, Colombia between January 2010 and September 2017. Collection of information from the registers of clinical history. **Results:** 25 patients were included. Recurrence was diagnosed in 24%. Median follow-up was 59.5 months and recurrence 32.5 months (range 11-123 months). 100% of the recurrence group were women and none of these were transplanted due to acute liver failure. There were no differences in the pre-transplant and treatment characteristics, although a higher biochemical and histological inflammatory activity was found pre-transplant in the recurrence group. Of the group with recurrence, 100% received long-term glucocorticoids and 33.3% had graft loss related to recurrence requiring retransplantation (p = 0.008). **Conclusion:** The recurrence of autoimmune hepatitis after liver transplantation in our patients is similar to that reported worldwide, is a cause of graft dysfunction to be taken into account especially after the first year post-transplant, it predominates in women. 33.3% of patients require hepatic retransplantation due to graft dysfunction.

Keywords

Autoimmune hepatitis, liver transplant, Latin America, Colombia.

INTRODUCTION

Since autoimmune hepatitis (AIH) was first described in 1950, it has been understood as a chronic inflammatory liver disease of unknown etiology that causes acute liver failure and liver cirrhosis. It can be an indication for liver transplantation. (1, 2)

AIH has been described as an indication for liver transplantation in up to 5% of the series published internationally. (3) In Colombia, autoimmune liver diseases are the reasons for 12% of liver transplants in adults. (4) Post-transplant liver survival of patients treated for AIH is good, reaching 90% at one year and 80% at 5 years. (5) Nevertheless, recurrences of AIH occur in 12% to 46% of these patients and lead to cirrhosis and graft loss in up to 50% of the cases. (3, 6-9) When this happens, retransplantation is required, and there is a risk of death.

Exactly which factors are associated with risks of AIH recurrence have not yet been clearly elucidated, but studies have described associations with early suspension of glucocorticoids in the post-transplant period, incompatibility of the donor's human leukocyte antigen (HLA) system with that of the recipient, post-transplant immunosuppression schemes, and the amounts of biochemical and histological inflammatory activity at the time of transplant. (8, 10)

The objective of this study is to describe characteristics of patients who underwent liver transplantation to treat AIH at a referral hospital Colombia, evaluate factors associated

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with recurrences of AIH in the post-transplant period, and describe the post-transplant evolution of these patients.

MATERIALS AND METHODS

Population

This is an observational study of a historical cohort that included patients aged 16 and up who had undergone liver transplantation at the Hospital Pablo Tobón Uribe in Medellín, Colombia, between January 1, 2010 and September 30, 2017, to treat AIH. Diagnoses were made according to the simplified criteria for AIH diagnosis of the International Autoimmune Hepatitis Group (GIHA). (11)

Patients without complete clinical, biochemical and histological data, and those who underwent liver transplantation because of overlap syndromes including autoimmune hepatitis and primary biliary cholangitis (AIH-PBC) or autoimmune hepatitis and primary sclerosing cholangitis (AIH-PSC), or other chronic liver diseases were excluded.

Variables

Data was collected through a review of the hospital's electronic clinical records using a form designed for this purpose.

Demographic, clinical, surgical, serological, radiological, histological and treatment variables were collected for pre-transplant and post-transplant periods.

Recurrence of AIH

Recurrence of AIH was defined by hepatic histology (portal and periportal lymphoplasmacytic infiltrates), biochemistry (elevation of transaminases at least twice the upper limit of normal), and the absence of other causes of liver graft dysfunction.

Statistical analysis

The descriptive analysis of variables uses absolute and relative frequencies. Continuous variables are analyzed through means and standard deviations if they follow a normal or median distribution, and through interquartile ranges (ICR) if they do not follow normal distributions according to the Kolmogorov-Smirnov test. Qualitative variables were compared with Fisher's exact test and continuous variables were compared with Student's t test or the Mann-Whitney U test depending on their distributions. Patients were followed up until September 30, 2017 or until the last date that was documented in the clinical history in which case data were considered censored data if any of the measured outcomes were missing. The registered SPSS version 20 of the University of Antioquia was used.

The final manuscript adhered to the STROBE recommendations for reporting observational studies.

Ethical issues

The study adhered to the guidelines of the 2013 version of the Helsinki declaration for research on human beings and resolution 008430 of 1993 on clinical research in Colombia and was approved by the hospital ethics committee.

RESULTS

A total of 25 patients with AIH had liver transplants between January 1, 2010 and September 30, 2017. Of these, post-transplant AIH recurrences were diagnosed in six (24%) during this period. The incidence of recurrence was 0.59 cases per 100 people/year. The median follow-up time was 59.5 months (IQR: 19.2-94). The most frequent comorbidity was hypothyroidism (7 patients, 22.5%). Patients' characteristics at the time of diagnosis of AIH and prior to liver transplantation are described in Table 1.

Liver cirrhosis and its complications were the principal indication for transplantation in both groups. Sixteen percent of all transplant patients had experienced subacute liver failure. None of them developed post-transplant recurrences of AIH ($p = 0.218$).

Sixty-eight percent of all patients tested positive for antinuclear antibodies (ANA) while 32% tested positive for anti-smooth muscle antibodies (ASMA). There were no differences in the autoantibody profiles of two groups. Higher levels of pretransplant serum IgG in the AIH recurrence group were not statistically significant ($p = 0.840$).

The majority of patients in both groups received pharmacological treatment for AIH in the pre-transplant period, most frequently a combination of glucocorticoids and an immunomodulator (azathioprine [AZA] or mycophenolate mofetil [MMF]). In the group without recurrences, six patients (31.6%) did not receive pre-transplant pharmacological treatment. Of these, the indication for transplant was acute liver failure in four patients (66.6%) while the other two patients had cirrhosis without inflammatory activity reflected in liver biochemistry.

Frequency of AIH relapses was higher in the post-transplant recurrence group (33.3% versus 15.8%, $p = 0.347$). The most important cause of relapses was irregular adherence to pharmacological treatment.

Table 2 describes patients' characteristics at the time of liver transplantation and in the post-transplant period. The

median age at the time of liver transplantation and the time between the diagnosis of AIH and transplantation were lower in the post-transplant recurrence group.

The median post-transplant AIH recurrence time was 32.5 months (IQR: 17.7-72) (Figure 1).

No significant difference between groups was found regarding alloantibodies (specific donor antibodies).

Comparison of the histological findings from the explanted livers from the two groups showed greater inflammatory activity in the patients who had post-transplant recurrences ($p = 0.114$).

More than 90% of patients received long-term prednisolone treatment during the post-transplant period. At the time of diagnosis of AIH recurrence, 100% of patients were receiving prednisolone.

The most frequently used post-transplant immunosuppression scheme was a combination of an antimetabolite (MMF or AZA) and a calcineurin inhibitor (tacrolimus or CIC). In both groups, the most frequently prescribed antimetabolite was MMF. The post-transplant recurrence group had a greater use of CIC calcineurin inhibitor while non-recurrence

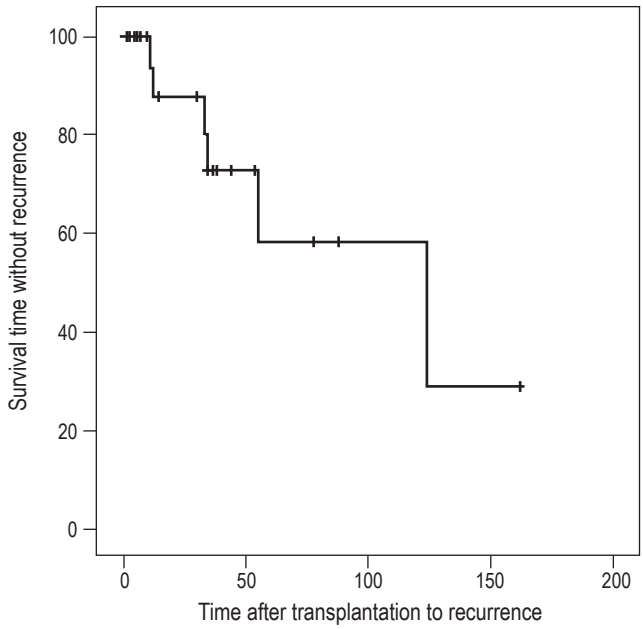

Figure 1. Posttransplant survival time in months without recurrence of autoimmune hepatitis.

Table 1. Characteristics of AIH patients prior to transplantation

Characteristics	All patients (n = 25)	No post-transplant recurrence (n = 19)	Post-transplant recurrence (n = 6)	p
Female	19 (76)	13 (68.4)	6 (100)	0.114
Median age in years at diagnosis of AIH (IQR)	43 (24.2-72.2)	43 (28.5-57)	41 (18-61)	0.875
History of autoimmune disease	1 (4)	0 (0)	1 (16.7)	0.06
Reason for liver transplantation				
Acute liver failure	4 (16)	4 (21)	0 (0)	0.218
Liver cirrhosis	21 (84)	15 (79)	6 (100)	0.218
Child-Pugh pre-transplant-median (IQR)	10 (8-12)	10 (8-12)	9 (7-12)	0.740
Pretransplant-median MELD (IQR)	16 (12-22)	15.5 (11-25)	17.5 (14-20)	0.925
Complications of cirrhosis				
Ascites	17 (68)	13 (68.4)	4 (66.6)	0.936
Encephalopathy	9 (36)	7 (36.8)	2 (33.3)	0.872
Esophageal varices	8 (32)	6 (31.5)	2 (33.3)	0.936
Hepatocellular carcinoma	1 (4)	0 (0)	1 (16.6)	0.068
Antinuclear antibodies ≥1	17 (68)	13 (68.4)	4 (66)	0.936
Smooth antimuscle antibodies	8 (32)	6 (31.5)	3 (50)	0.412
Serum IgG mg/dL median (IQR)	2224 (1621-2641)	2174 (1592-2919)	2349 (1600-2350)	0.840
Treatment before transplant				
None (%)	7 (28)	6 (31.6)	1 (16.7)	0.477
Steroids (%)	2 (8)	1 (5.2)	1 (16.7)	0.368
Steroids + immunomodulator	13 (52)	9 (47.4)	4 (66.6)	0.412
Relapse (%)	5 (20)	3 (15.8)	2 (33.3)	0.347
Median follow-up time in months (IQR)	59.5 (19.2-94)	43 (17-74.5)	97 (40-152)	0.170

IgG: immunoglobulin G; MELD: model for end-stage liver disease.

Table 2. Characteristics of AIH patients during and after liver transplantation

Characteristics	All patients (n = 25)	No post-transplant recurrence (n = 19)	Post-transplant recurrence (n = 6)	p
Age in years at the time of transplantation-median (IQR)	42.5 (28-58.7)	43 (30-59.5)	38 (21-60)	0.664
Weeks between diagnosis of AIH and transplantation-median (IQR)	24.4 (9-172.3)	28.3 (2.3-179.9)	18.5 (15.8-129.6)	0.869
AST U/L pretransplant-median (IQR)	103 (70.5-178)	103 (70-323)	118.5 (82.7-178)	0.815
ALT U/L pretransplant-median (IQR)	101 (61-149.5)	101 (53-177)	95.5 (61.2-141.2)	0.969
Alkaline phosphatase U/L pretransplant-median (IQR)	198 (130-311.5)	167 (125-313)	237.5 (169.2-346.2)	0.586
Bilirubin mg/dL pretransplant-median (IQR)	6.1 (3.7-21)	7.4 (5.2-30)	4.2 (1.6-6.25)	0.056
Positivity of alloantibodies (%)	2 (8)	2 (10.5)	0 (0)	0.406
Moderate to severe inflammatory activity in the explant (%)	19 (76)	13 (68.4)	6 (100)	0.114
CIT in minutes-median (IQR)	380 (280-400)	380 (317.5-420)	300 (265-385)	0.228
WIT in minutes-median (IQR)	29 (25-32)	30.5 (25.7-36.2)	26 (24.5-29)	0.151
Basiliximab (%)	1 (4)	1 (5.3)	0 (0)	0.568
Post-transplant immunosuppression				
PRED (%)	24 (96)	18 (94.4)	6 (100)	0.568
PRED up to diagnosis of recurrence (%)	23 (92)	17 (89.4)	6 (100)	0.406
Calcineurin inhibitor				
CYC (%)	10 (40)	6 (31.6)	4 (66.7)	0.126
Tacrolimus (%)	15 (60)	13 (68.4)	2 (33.3)	0.126
Antimetabolite				
AZA (%)	8 (32)	6 (31.6)	2 (33.3)	0.936
MMF (%)	17 (68)	13 (68.4)	4 (66.7)	0.936
Posttransplant complications				
Acute moderate to severe cell rejection	11 (44)	8 (42.1)	3 (50)	0.727
CMV infection	2 (8)	2 (10.6)	0 (0)	0.406
Months between transplantation and recurrence			32.5 (17.7-72)	
AIH-median (IQR)	2 (8)	0 (0)	2 (33.3)	0.008
Liver transplantation (%)	3 (12)	3 (15.8)	0 (0)	0.298

CYC: cyclosporine; CMV: cytomegalovirus; PRED: prednisolone; WIT: warm ischemia time; CIT: cold ischemia time.

group was more likely to have received tacrolimus, but the difference was not statistically significant.

Two patients (33.3%) of the AIH recurrence group required retransplantation (p = 0.008) due to graft dysfunction. The retransplant incidence rate was 0.78 cases per 100 people/year. Both patients were female, had moderate inflammatory activity in the explant, and had histories of acute cellular rejection. The times between the recurrence of AIH and retransplant were 30 months and 113 months.

In total, 3 patients died (all from the group without AIH recurrence) due to infectious complications: two due to septic shock (at 7 and 17 months post-transplant), and one at 61 months due to pulmonary tuberculosis and a CMV infection.

Individual characteristics of patients with post-transplant recurrences of AIH are described in Table 3.

DISCUSSION

AIH is a major cause of liver transplantation in every part of the world, (2) but most data comes from studies of the Caucasian population, and little is known about the course of the disease in Latin American patients. (12) Studies that our group has recently published show that autoimmune liver diseases are the reason for 12% of liver transplants in Colombian adults, (4) and that 10.1% of patients with AIH (including AIH-PBC and AIH-PSC overlap syndromes) required liver transplantation with an incidence of 2.5

Table 3. Characteristics of patients whose AIH recurred after transplantation

Patient	Age in years at diagnosis of AIH	Indication for transplant	Pretransplant Child-Pugh score	Pretransplant MELD score	Pretransplant treatment	Weeks between diagnosis of AIH and transplantation	Age at the time of transplant	Post-transplant treatment	Months between transplantation and recurrence	Replantation
1	66	Liver cirrhosis	12	19	AZA, PRED	16	66	PRED, AZA, CYC	55	No
2	57	Liver cirrhosis	7	22	None	19	58	PRED, MMF, TAC	11	No
3	41	Liver cirrhosis	11	16	None	16	42	PRED, MMF, CYC	33	Yes
4	19	Liver cirrhosis	8	12	CYC, PRED	217	23	PRED, MMF, TAC	20	No
5	ND	Liver cirrhosis	8	15	CYC, PRED	SD	34	PRED, AZA, CYC	123	No
6	17	Liver cirrhosis	12	20	PRED, MMF	42	17	PRED, MMF, CYC	32	Yes

ND: no data.

transplants per 100 patients/year (95% confidence interval: 1.7-2.7). (12) AIH recurrences were found in 24% of the transplant patients with a recurrence incidence rate of 0.59 cases per 100 people/year. These are similar to the figures reported elsewhere in the world literature. (6, 7, 8) Although our sample size in this study is too small and limited to find statistically significant differences between groups, there are several issues that deserve to be highlighted.

The median time until recurrence was 32.5 months (range 11-123 months) while the median reported in the literature is 26.4. (13) This suggests that recurrence of AIH should be considered when graft dysfunction occurs, especially after the first year after transplantation.

Pre-transplant characteristics associated with recurrence vary, as reported by Montano-Loza in Canadian patients. (8) In that study, none of the patients who underwent transplantation for acute liver failure had recurrences of AIH. Although no statistically significant association was found, this could be because of the limited number of patients included. In the same study, the pretransplant degree of liver inflammation (reflected by serological markers such as IgG or histology) was significantly associated with recurrence of AIH in the multivariate analysis. The histological hazard ratio (HR) was 6.9 and for moderate to severe inflammation, and the HR for serum IgG levels was 7.5. This suggests that reaching pre-transplant biochemical and histological remission could reduce the recurrence of AIH. In the AIH recurrence group, higher levels of serum IgG and higher inflammatory histological activity were found (100% vs. 68.4%). Both were without statistical significance, possibly due to the small number of patients.

Evaluation of post-transplant characteristics found no association between different regimens of post-transplant immunosuppressive treatment and recurrence of AIH, as described in systematic reviews throughout the world. (13, 14) This is in contrast to other pathologies such as primary biliary cholangitis (PBC) for post-transplant recurrences have occurred more frequently with the use of tacrolimus than when cyclosporine was used. (14) Previous studies have shown that indefinite use of low doses glucocorticoids in the post-transplant period reduce the recurrence of AIH by 0% and at one year, but by 11% at 10 years. (15) In our study, despite the fact that 92% of all patients who underwent transplantation because of AIH and 100% of the recurrence group received low doses of prednisolone over the long term, there was a 24% recurrence rate. No analysis of the relation between recurrence of AIH and long-term use prednisolone could be made because indefinite administration of glucocorticoids is a long-established practice in our group for treating these patients.

Recurrence of AIH is an important cause of graft dysfunction, cirrhosis, need for liver retransplantation and death. (9) For these reasons, it is important to identify patients at risk of recurrence and establish actions to reduce these risks during both the pre-transplant and post-transplant periods. (14) Prior to transplantation an effort should be made to achieve biochemical and histological remission, while after transplantation long-term administration of low-dose glucocorticoids should be used. Follow-up liver biopsies are important since histological recurrence has been shown to precede clinical and biochemical recurrence. (16) The difference between requirements for liver retransplantation in the recurrence group, 33.3% of the group, and those of the non-recurrence group, 0%, $p = 0.008$, was statistically significant. Liver retransplantation, the therapeutic option described in up to 50% of patients who suffer

recurrence, (9) is associated with higher costs and higher rates of morbidity. Moreover, it is not always available, especially in regions with low rates of organ donation.

This study suffers from the limitations of a retrospective study and from being done at a single center. The information bias resulting from collecting data from the hospital's medical records registry and the small sample size are worth noting. Inferences requiring statistical significance could not be made for this reason. another limitation was that HLA was not evaluated in patients even though it is associated with recurrence and worse outcomes in the post-transplant period, especially for patients with HLA-DR3. (17, 18) In addition, there are no validated criteria for diagnosis of AIH recurrence, and the simplified criteria used for pretransplant diagnosis are not recommended following transplantation. (11) Nevertheless, findings of portal and periportal lymphoplasmacytic infiltrates, elevation of transaminases and serum IgG combined with the absence of other etiologies help confirm a diagnosis of recurrence. (14, 15) Our patients met these criteria. Finally, follow-up biopsies were not performed per protocol in the absence of alteration of the hepatic biochemical profile, so the incidence of recurrence may have been underestimated since recurrence of AIH has been described on rare occasions in patients whose transaminase levels are not elevated. (19)

We would also like to highlight this study's strengths. It was conducted at a national referral center for liver diseases and transplantation that has the largest number of patients with AIH not only in Colombia, but in all of Latin America. (12) In addition, long follow-up times (median: 59.5 months) allowed us to document the behavior of the AIH in the adult population from pre-transplant through the post-transplant period.

CONCLUSIONS

AIH is an important indication for liver transplantation in Colombia worldwide and elsewhere. Post-transplant recurrence in our population is similar to that reported worldwide. It is a cause of graft dysfunction to be taken into account especially after the first year after transplantation, since 33.3% of patients with recurrence require retransplantation. A multicenter study of the transplant centers in Colombia with a larger number of patients would help determine factors associated with post-transplant AIH recurrence in the Colombian population.

Sources of financing

None.

Conflicts of Interest

The authors have no conflicts of interest.

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