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ORIGINAL ARTICLE

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# Outcome of orthotopic liver transplantation in autoimmune hepatitis according to subtypes

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**Abstract** The relevance of autoimmune hepatitis (AIH) classification for clinical purposes is controversial. We analyzed the outcome after orthotopic liver transplantation (OLT) of nine type I and seven type II AIH patients. Type II patients had a significantly higher incidence of cirrhosis at the time of diagnosis, more resistance to steroid therapy, and a higher Child-Pugh score at the time of OLT. OLT was performed in emergency in three type II patients and electively in all type I patients. Four type II and one type I patients died in the postoperative period. There was no difference regarding the incidence of post-OLT infection and rejection between the two types. No recurrence of AIH was observed. The 6-year actuarial survival rates for type I and type II patients were 76% and 43%, respectively. Type II AIH patients who have a poor response to medical therapy should be considered for OLT with a shortened delay.

**Keywords** Autoimmune hepatitis · Subtypes · Liver transplantation

## Introduction

Autoimmune hepatitis (AIH) is a chronic necrotizing hepatitis associated with autoimmune features, including the presence of autoantibodies, high level of immunoglobulins, and good response to steroid or immunosuppressive therapy. Depending on the type of circulating autoantibodies, two main types of AIH have been described [12]. Type I AIH is associated with a high prevalence of anti-nuclear antibodies and antiactine components of smooth muscle antibodies (SMA), while type II AIH is characterized by the presence of antibodies to liver/kidney microsome type 1 (ALKM1), directed against cytochrome mono-oxidase P450 IID6, and frequently associated with antibodies to liver cytosol type 1. A third type of AIH, characterized by antibodies to soluble liver antigen without SMA and ALKM1, has been proposed but is not as well established [14]. The relevance of this classification for clinical purposes is controversial. An international panel of hepatologists has concluded that this classification is not relevant to the clinical setting because of the absence of therapeutic consequences [12].

Prednisone alone or in combination with azathioprine induces prolonged remission in more than 70% of patients and extends survival in those patients [17]. However, deterioration despite medical therapy may require liver transplantation. In this study we report a poorer outcome of type II AIH patients early after transplantation, suggesting that the AIH subtype should be taken into account while planning liver transplantation.

## Patients and methods

### Patients

Between March 1987 and May 1998, 534 patients underwent orthotopic liver transplantation (OLT) in our institution. Sixteen of them were transplanted for type I ($n=9$) or type II ($n=7$) AIH. All patients were white women, with a median age of 23.9 years (17.5–41) for type I and 18.5 years (6.5–32) for type II AIH. HLA typing was essentially similar in the two groups and revealed a A1, B8, phenotype in 3 type I and 1 type II patients, a DR3 phenotype in 4 type I and 2 type II AIH patients, and a DR4 phenotype in 2 type I and 1 type II patients.

All patients fulfilled the criteria for a definite diagnosis of AIH, as established by the International Autoimmune Hepatitis Group in Brighton in 1992 [1, 12]. Identification of serum autoantibodies was performed on rat organ sections by immunofluorescence as described by Roitt and Doniach [23]. All sera reacted with SMA or LKM 1 at a dilution of 1:100 or greater. SMA-positive sera were tested on a human epithelioma cell line (Hep-2) and stained actin filaments at 1:40 serum dilution. Positivity for anti-LKM 1 was confirmed by obtaining a line of identity with a reference antiserum by the Ouchterlony immunodiffusion method. HBs antigen was negative in all patients. Hepatitis C virus antibodies, detected by a second-generation enzyme-linked immunosorbent assay (Ortho HCV ELISA; Ortho Diagnostic Systems, Raritan, N.J., USA) were negative in all patients but one. In this case RIBA test (Chiron RIBA HCV, Chiron, Emeryville, Calif., USA) and polymerase chain reaction were negative. Histological analysis performed on specimens obtained by percutaneous needle biopsy or on explanted livers showed lesions suggesting a diagnosis of AIH in all cases, including periportal or periseptal piecemeal necrosis with or without lobular hepatitis or central-portal bridging necrosis, lymphoplasmocytic infiltration, and fibrosis. No other change suggestive of a different cause was observed.

### Course of disease before liver transplantation

The median duration of disease before OLT was 8 years (range 4–20) in type I and 6 years (0.1–14) in type II AIH patients. Apparent onset of the disease was insidious in seven patients and acute in nine. Two patients, both with type II AIH, presented with acute liver failure and encephalopathy. One of them recovered after plasma exchange, while the other required emergency OLT. According to the criteria of the International Autoimmune Hepatitis Group [12], seven of the nine type I patients had a complete response to initial steroid therapy, while five type II patients had a poor response, including two cases of steroid resistance ($P=0.05$). At the time of first liver biopsy cirrhosis was present in five of the nine patients with type I and in all seven patients with type II AIH ($P=0.02$).

Fourteen patients had portal hypertension, with previous episodes of bleeding in 6 cases and ascites in 11 cases. One type I AIH patient had undergone a portocaval shunt 7 years earlier, and one type II AIH patient with acute liver failure had no sign of portal hypertension. Severity of cirrhosis according to the Child-Pugh classification [20] was significantly higher in type II AIH patients ($P=0.01$; Table 1), reflecting a higher operative risk. Three patients with type II AIH had acute liver failure with stage 3 encephalopathy at the time of OLT. These three patients required emergency OLT. Two other type II patients had intrapulmonary shunts with severe hypoxia ($PaO_2 < 60$ mmHg). OLT was performed electively in all type I AH patients.

### Surgical techniques and postoperative management

All donors and recipients were AB0-compatible. Standard OLT was performed in eight patients [26]. Reduced size grafts [9] or split grafts [10] were used in three type I and five type II AIH patients (Table 1). All explanted livers were cirrhotic. Two type I and one type II AIH patients had portal vein thrombosis. One of them required placement of an interposition Gore-Tex prosthesis between the recipient superior mesenteric vein and the portal vein of the graft, and the two others underwent thrombectomy. Mean cold ischemia times were 11 h (range 5–15) for type I and 8 h (4–14) for type II AIH patients, respectively. Mean volume of packed red blood cells transfused during OLT was 4,620 ml (0–1,1250) in type I and 5,440 ml (2,400–10,850 ml) in type II AIH patients. All patients were put on a cyclosporine-based triple immunosuppressive regimen.

### Graft rejection

Acute and chronic rejection were defined according to the criteria of Snover et al. [25]. Acute rejection was considered steroid-resistant when the decrease in serum liver function parameters was less than 50% after three steroids boluses. Steroids-resistant acute rejection episodes were treated with OKT3 monoclonal antibody (Ortho Pharmaceutical, Raritan, N.J., USA). Infections were defined using criteria proposed by the Center for Disease Control [7]. CMV disease was diagnosed according to established criteria [15].

### Follow-up

After discharge all patients were seen at the outpatient clinic on a weekly basis during the first month, then twice monthly for 2 months, and monthly thereafter during the first year. A complete protocol workup including liver biopsy was performed yearly in all recipients.

### Statistical analysis

Statistical analysis was performed using the Statistica software (Statsoft, Tulsa, Okla., USA). Actuarial survival was calculated by Kaplan-Meier analysis. Comparison of differences for statistical significance used the log rank test. The $\chi^2$ or Fisher's exact test were used wherever appropriate with categorical variables, and Student's $t$ test was used with continuous variables. Differences of $P<0.05$ were considered significant.

## Results

### Early mortality

Five patients died in the postoperative period (median 14 days, range 3–87): one of nine type I and four of seven type II AIH patients ($P=0.08$). One type I patient

**Table 1** Patient characteristics, orthotopic liver transplantation (*OLT*) feature and outcome

| Patient no. | AIH subtype | Age at OLT (years) | Child-Pugh score[a] | OLT feature | Early reoperations | Outcome |
|---|---|---|---|---|---|---|
| 1 | I | 20 | B8 | – | – | Alive at 8 years |
| 2 | I | 15 | C11 | Left liver | Intra-abdominal abscess | Death at 6 years, chronic rejection |
| 3 | I | 41 | B9 | Right liver | – | Death at 4 years, secondary biliary cirrhosis |
| 4 | I | 18 | C10 | – | – | Death at 8 days, primary nonfunction |
| 5 | I | 28 | C11 | – | Biliary fistula | Alive at 6 years |
| 6 | I | 19 | C10 | – | – | Alive at 11 years |
| 7 | I | 18 | B9 | Left liver | Hemoperitoneum, biliary fistula | Alive at 7 years |
| 8 | I | 28 | C10 | – | – | Alive at 5 years |
| 9 | I | 22 | B8 | – | – | Alive at 3 years |
| 10 | II | 15 | C11 | Left liver | Intestinal obstruction | Alive at 6 years |
| 11 | II | 19 | B9 | – | Hemoperitoneum, hepatic artery thrombosis | Retransplantation (twice) for chronic rejection and ischemic cholangitis, alive at 6 years |
| 12 | II | 20 | C13 | Emergency Left liver | Venous splenic infarction, hemoperitoneum, intra-abdominal abscess | Death at 3 months, multisystem organ failure |
| 13 | II | 32 | C10 | – | Biliary fistula | Alive at 10 years |
| 14 | II | 6 | C14 | Emergency Left liver | Hemoperitoneum | Death at 15 days, cerebral damage |
| 15 | II | 22 | C15 | Emergency Left liver | Hemoperitoneum, intra-abdominal sepsis | Death at 30 days, cerebral hemorrhage, multisystem organ failure |
| 16 | II | 17 | C12 | Left liver | – | Death at 9 days, severe acute rejection |

[a] Child-Pugh score [6] was significantly higher in type II AIH patients ($P=0.01$; Student's $t$ test)

died immediately after retransplantation due to primary nonfunction. All three type II patients transplanted in emergency died in the perioperative period. One experienced delayed graft function and persisting portal hypertension with gastrointestinal bleeding. She underwent a secondary splenectomy for hypersplenism and venous splenic infarction and died of bacterial sepsis and diffuse hemorrhage 3 months after OLT. Another type II patient never recovered from coma despite a functioning graft, suggesting irreversible neurological damage. The third patient had diffuse bleeding with cerebral hemorrhage and died of multisystem organ failure in a context of *Aspergillus* sepsis. Lastly, one type II patient experienced severe acute rejection and did not survive despite retransplantation.

## Complications after OLT

Three of nine type I patients and six of seven type II patients had to undergo a second operation as the result of postoperative complications ($P=0.05$). The proportion of patients who experienced at least one episode of acute graft rejection was similar in the two types (5/9 type I patients vs. 5/7 type II patients). Similarly, the occurrence of steroid resistant rejection did not differ between the two groups (4/9 type I patients and 3/7 type II patients). One patient of each type developed chronic graft rejection. There was no significant difference in the incidence of postoperative bacterial, viral and fungal infections between the two types.

## Patient survival

The median duration of follow-up for all patients, including nonsurvivors, was 6 years (range 1 week–11 years). Two type I AIH patients died 4 and 7 years after OLT, of chronic rejection and secondary biliary cirrhosis, respectively, while awaiting retransplantation. The 6-year actuarial survival rates of type I and type II AIH patients were 76% and 43%, respectively ($P=0.33$). One type II AIH patient underwent two retransplantations for chronic rejection and ischemic cholangitis. At the time of last follow-up, six type I and three type II AIH patients were doing well. Their liver function was normal. No recurrence of AIH was observed on the basis of serological screening and graft biopsy in either type I or type II AIH patients. Results are summarized in Table 1.

## Discussion

Evidence for two distinct subtypes of AIH defined by immunological markers, genetic predispositions, and clinical features progressively emerge [2, 8]. However, typing of AIH is not endorsed by most international associations working in this field [5, 11, 12] because of uncertainties about its validity and use since the recognition of these subtypes did not already result in different therapeutic strategies.

Several reports of OLT for AIH have recently been published [16, 21, 24, 27]. Results were usually excellent with 5-year survival rates over 90%. No difference in outcome after OLT according to AIH subtypes has been reported so far, although the small number of type II AIH patients warrants caution in the analysis of results. In a series of 68 patients Milkiewicz et al. [16] found similar 5-year survival rates for type I and type II AIH patients after OLT but reported a significantly faster progression of disease for type II AIH.

The high early mortality observed in our series is justifiably of concern. Most patients, especially those with type II AIH, had a high operative risk and Child-Pugh score, and three had to undergo emergency OLT. This appears to be the major determinant of the poor overall outcome we report. The better results reported by others in type II AIH patients is likely to reflect a better selection of patients at the time of OLT in terms of physical condition and operative risk. Two other early deaths occurred despite early retransplantation and were related to unpredictable events, mainly severe acute rejection and primary nonfunction.

Early mortality concerned essentially type II AIH patients. This was not related to a higher incidence of post-OLT rejection or post-OLT infection but rather to a significantly more severe condition at the time of OLT. Three of these patients underwent emergency transplantation for acute liver failure with encephalopathy unresponsive to steroid therapy. Such a course was not observed in type I AIH patients. It has been previously reported that type II AIH often has an acute, or even fulminant presentation [8, 13, 19]. However, this type of onset has not been shown to be associated with a decreased response to steroid therapy [18], which is the only criterion that clearly affects survival in AIH patients [3]. Another specific feature of type II AIH is a marked propensity to progress rapidly toward cirrhosis [8]. However, development of cirrhosis does not affect survival in patients with AIH [4, 22]. Lastly, HLA A1/B8/DR3 typing is known to be associated with a more aggressive disease [6, 24]. We did not observe any significant differences in the distribution of this haplotype between the two types.

The rapid progression toward steroid-resistant liver dysfunction, leading in turn to acute liver failure requiring emergency OLT seems to be a distinctive feature of type II AIH.

Criteria predicting short-term survival in AIH patients are lacking. No parameter at the time of presentation has been identified as a predictor of poor outcome [3, 24]. Poor outcome can be identified only by evidence of deterioration during treatment [24]. Considering the specific features of type II AIH, we propose that in the absence of reliable predictive criteria for short-term progression an aggressive therapeutic approach must be adopted in the management of these patients. Liver transplantation should be considered without delay when signs of failure of medical therapy become apparent.

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