Acute Liver Allograft Rejection After Living Donor Liver Transplantation: Risk Factors and Patient Survival

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ABSTRACT

Background: Acute rejection (AR) is an important problem after liver transplantation. We aim to evaluate the incidence and risk factors of AR and to identify significant prognostic factors that can influence posttransplant survival in living donor liver transplantation.

Methods: A retrospective database of 169 consecutive adult patients who underwent living donor liver transplantation from June 2001 to August 2015 was reviewed. The patients were divided into an AR group and nonAR group. The clinical data of the 2 groups were compared.

Results: The median follow-up time for this study was 90.7 months (range: 0.03-124.9 months). Twenty five (14.8%) patients developed AR with a median period of 158 days (3-1,975 days) after transplantation. A multivariate analysis revealed that high posttransplant model for predicting mortality score (hazard ratio, [HR] = 3.462; $P = 0.023$) was an independent risk factor for AR. Multivariate analysis was used to evaluate factors that influenced the overall survival and revealed that ABO-incompatibility (HR = 2.702; $P = 0.01$) and patient age ≥50 years (HR = 1.733; $P = 0.045$) were independent prognostic factors for overall survival after living donor liver transplantation.

Conclusions: Higher posttransplant model for predicting mortality score was associated with AR after living donor liver transplantation. ABO-incompatibility and patient age ≥50 years were independent prognostic factors for overall survival.

Key Indexing Terms: Acute rejection; Living donor; Liver transplantation. **[Am J Med Sci 2018;356(1):23–29.]**

INTRODUCTION

Due to donor organ shortage in China, living donor liver transplantation (LDLT) is an option to expand the donor organ pool for patients with life-threatening disease who cannot be supplied with a cadaver organ in time. Although LDLT may have an immunologic advantage over deceased donor transplantation, acute rejection (AR) is a common morbidity and sometimes leads to complications even after LDLT.[1] With the improvements in immunosuppression regimens and the introduction of agents such as tacrolimus and mycophenolate mofetil, the incidence of AR after liver transplantation has steadily decreased over the decades,[2-4] but it is still a common complication in around 20%-80% of liver transplants.[5-8]

Several factors associated with an increased risk of AR have been reported.[9,10] A younger patient age, absence of edema, longer cold ischemic time and surgical time, blood type-incompatibility, sex match and graft-to-patient weight ratio had been reported to increase the prevalence of AR.[11,12] But, some other studies have shown that donor and recipient's age, ascites and donor-patient blood type are not associated with the incidence of AR.[13]

The identification of clinical risk factors for AR and the effect of AR on subsequent patient outcome remain poorly defined. This study sought to evaluate the incidence and potential clinical risk factors of AR, as well as identify significant prognostic factors that can influence posttransplant survival in LDLT.

METHODS

Patient Characteristics

A total of 170 adult patients underwent LDLT at our institution between June 2001 and August 2015. One patient who died due to disseminated intravascular coagulation during the operation was excluded. Living donors were selected after considering their age, blood type, graft size, liver function and confirming their desire to volunteer. All the 169 patients enrolled were divided into an AR group and a nonacute rejection group (NAR group).

Each organ donation and transplantation strictly followed the guidelines of the Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine, the current regulation of the Chinese Government and the Declaration of Helsinki. Every precaution has been taken to protect the privacy of research subjects and the confidentiality of their personal information. Informed consent was obtained from all patients.

Diagnosis of AR

AR was suspected based on biochemical evidence of deteriorating liver function. After excluding vascular or biliary complications, a liver biopsy was performed to obtain histopathologic evidence of AR. The diagnosis of AR was based on internationally accepted histologic criteria and AR was defined as a biopsy-confirmed episode of cellular rejection after LDLT.[14,15]

Immunosuppression Protocol

The primary immunosuppressive regimen was triple therapy incorporating tacrolimus (target levels 10-15 ng/mL during the first month and 5-10 ng/mL from the second month), mycophenolate and steroid (methylprednisolone, 1,000 mg on the first day, 240 mg on the second day, 200 mg on the third day, 160 mg on the fourth day, 120 mg on the fifth day, 80 mg on the sixth day, 40 mg on the seventh day and then followed by an oral recycle of prednisone tapered to zero within the first 1 month). AR episodes were generally treated with the administration of 500 mg of methylprednisolone daily for 3 consecutive days and 240 mg tapered to zero within the first 1 month.

Data Collection

The following variables were recorded for study population: age, sex, family history, primary liver diseases, body mass index, blood pressure, cold ischemia time and immunosuppressive therapy (agents and blood levels). Pretransplant data were collected within 24-hours before LDLT. The serum creatinine and total bilirubin were also collected at 24-hours after LDLT to calculate the posttransplant model for predicting mortality (PMPM) score, which was described by our previous study to predict short and medium-term mortality in liver transplant patients.[16] PMPM score $= -5.359 + 1.988$ * ln (serum creatinine [mg/dL]) $+ 1.089$ * ln (total bilirubin [mg/dL]). The posttransplant immunosuppressive agent levels were observed as close as possible to 3 months after liver transplant.

Statistical Analysis

The statistical analysis was performed using the statistical software IBM SPSS software (Ver. 19.0; SPSS Inc, Chicago, IL). Quantitative variables are expressed as mean ± standard deviation or median and range, depending on the distribution. Categorical variables are presented as values and percentages. Student's *t* test was used to compare quantitative variables. Chi-square test was used to compare categorical variables. To identify risk factors for AR, a multivariate analysis was performed using the Cox proportional hazard's model with backward elimination. Overall survival was defined as the time span from initial diagnosis until death from any cause or last known contact. Overall survival analysis was performed by Kaplan-Meier methodology with log rank testing. Cox proportional hazard models were used to estimate hazard ratios for overall survival, and to determine independent risk factors. All tests were 2-sided, and $P<0.05$ was considered statistically significant.

RESULTS

Overview

The median age of the 169 patients was 47.0 years (range: 17-68 years), and 138 patients (81.7%) were male. With a median follow-up period of 90.7 months (range: 0.03-124.9 months), all the patients received partial liver grafts from living donors within 6 degrees of kinship or from their spouses.

Compared with the NAR group, the AR group showed significantly higher serum alanine transaminase (ALT) in 30 days (173.3 ± 52.0 U/L versus 71.0 ± 8.2 U/L, $P = 0.001$) after LDLT and higher serum aspartate transaminase (AST) in 14 days (66.5 ± 9.9 U/L versus 44.7 ± 3.1 U/L, $P = 0.007$), 30 days (63.5 ± 12.3 U/L versus 35.7 ± 3.7 U/L, $P = 0.005$), 60 days (63.2 ± 11.5 U/L versus 32.1 ± 1.9 U/L, $P = 0.000$) and 90 days (54.6 ± 10.9 U/L versus 35.4 ± 2.8 U/L, $P = 0.015$) after LDLT (Figure 1). There was no significant differences of blood tacrolimus levels between the 2 groups after LDLT (Figure 2, $P > 0.05$)

Incidence of AR

A total of 25 patients (14.8%) developed histopathologically confirmed cellular allograft rejection. Of these patients, 10 patients (40.0%) developed cellular rejection within the first 2 months and 13 (52.0%) developed AR within the first 6 months after LDLT. The median time to AR was 158 days (range: 3-1,975 days) after transplantation. The number of rejection events was 1 event in 25 patients (100%).

Clinical Factors Related to AR

The univariate results shown in Table 1 corresponded to the incidence of AR. There are more patients in the AR group with PMPM score >-1.4 (24 hours post-LDLT) compared with the NAR group (16% versus. 3.5%, $P = 0.028$). No other variables were associated with the incidence of AR. All factors with $P < 0.1$ were entered into multivariate Cox proportional hazard's model (Table 2). Eventually, a higher PMPM score