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Original Article/Transplantation

Lower tacrolimus trough levels in the late period after living donor liver transplantation contribute to improvements in long-term clinical outcomes

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ABSTRACT

Background: Previous studies have emphasized the need to reduce tacrolimus (TAC) trough levels in the early post-liver transplantation (LT) period. However, whether late-period TAC trough levels influence the long-term outcomes of liver recipients is not clear.

Methods: We enrolled 155 adult liver recipients survived more than 3 years after living donor liver transplantation because of non-malignant liver diseases. The maintenance immunosuppressive regimens were TAC monotherapy and combined therapy with mycophenolate mofetil. Patients were divided into three groups according to their late-period TAC trough levels: < 3 ng/mL group, 3–5 ng/mL group, and <5 ng/mL group. The complications and adverse effects of TAC were analyzed.

Results: Each group showed similar rejection, graft loss and mortality. Patients achieved the <5 ng/mL state in less than 4 years had fewer new-onset diabetes, hyperlipidemia, *de novo* malignancies, and hepatitis B virus recurrence; the complications of renal dysfunction and hypertension rates were the same among these 3 groups.

Conclusions: Collectively, our findings indicated that lower TAC trough levels in the late period of liver transplantation are safe, improve the long-term outcomes.

Introduction

Graft rejection rates have decreased and recipient survival after liver transplantation (LT) has improved significantly during recent decades due to the availability of more efficient immunosuppressive drugs. However, most transplant patients will likely remain on chronic immunosuppression therapy for their entire lives. The current standard life-long treatment for such patients is tacrolimus (TAC), a potent and effective immunosuppressive agent [1,2]. However, adverse effects associated with TAC, such as renal dysfunction, arterial hypertension, diabetes and hyperlipidemia, have now become primary concerns for long-term surviving recipients [3–5]. At the same time, the high prevalence of TAC-related toxicity and lower incidence and impact of liver allograft rejection suggest that most liver recipients are likely over-immunosuppressed [2]. Thus, a TAC dose-minimization strategy designed to improve clinical outcomes has been developed in recent years.

The phases of immunosuppression are classified as induction and maintenance according to the time post-LT. The induction immunosuppression phase is often defined as the initial immunosuppressive regimen used in the first 30 days after LT. The maintenance immunosuppressive phase refers to the immunosuppressive regimen after 30 days and continued indefinitely thereafter [2]. Lower TAC trough levels during the early post-transplant period are reported to be associated with fewer adverse effects and longer graft survival [6,7]. However, very few studies have evaluated the relationship between late maintenance TAC trough levels and long-term clinical outcomes, and the true impact of lower TAC trough levels at late time points on the occurrence of TAC-related adverse

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effects, acute cellular rejection (ACR), chronic rejection, graft loss, mortality, and other complications, is unknown.

To evaluate the optimal ranges for maintenance TAC trough levels after LT, we performed a retrospective analysis of the safety and efficacy of various TAC trough levels in long-term surviving adult living donor liver transplantation (LDLT) patients and provided evidence related to optimal late-period TAC trough levels.

Methods

Patient selection and data collection

A total of 155 adult patients who received blood-group-compatible LDLT between February 1, 2001 and December 30, 2011 at the First Affiliated Hospital of Zhejiang University School of Medicine (Hangzhou, China) were retrospectively analyzed. The majority of them have hepatitis B virus (HBV)-related cirrhosis or liver failure as a primary disease. The follow-up time after LDLT was at least 3 years. Patients with autoimmune liver diseases were excluded from this study.

Liver grafts were obtained from living donors. Data collection was based on medical records, both written and digital, containing the pre- and post-operative medical history and conditions of the patients. All patients received TAC administration for more than 3 years, and their TAC trough levels were monitored monthly. Baseline liver function, renal function tests, and other related laboratory examinations were also performed routinely. Patients received nucleoside analog plus hepatitis B immunoglobulin for the prevention of HBV recurrence. The study was approved by the Ethics Committee of the Affiliated Hospital of Zhejiang University School of Medicine, and informed consent was obtained from the patients.

Immunosuppression regimen

TAC was administered at the recommended dose of 0.075 mg/kg as the initial immunosuppressant following LDLT, together with corticosteroids and mycophenolate mofetil (MMF). The dose was then adapted to maintain trough levels > 10 ng/mL for the first 6 weeks, 8–10 ng/mL from week 7 to 12, and < 8 ng/mL from month 4 to 12. Then patients were recommended to gradually reduce the dose and trough levels of TAC to a stable state (with concurrent liver function monitoring) until 2 years post-LDLT, after which time stable TAC trough levels were maintained for at least 1 year.

Methylprednisolone was used at a dose of 1000 mg during the operative period and was then tapered slowly and withdrawn within the first month after LDLT. The maintenance immunosuppressive regimen after LDLT included TAC monotherapy and combination therapy with MMF, administered at a dose of 500 mg MMF twice daily. For the treatment of ACR, either a bolus dose of methylprednisolone or a reinforcement dose of TAC was administered.

Definition of rejection and HBV recurrence

ACR and chronic rejection were diagnosed based on the combination of allograft dysfunction and characteristic liver biopsy findings according to Banff criteria. Worsening or persistence of allograft dysfunction constituted an indication for liver biopsy, whereas a liver biopsy was not required in cases where the patient showed improvement. HBV recurrence was defined as the reappearance of circulating levels of HBV surface antigen (HBsAg) after LDLT, with or without HBV DNA positivity or histological evidence of disease.

Definition of TAC-related adverse events

Chronic renal dysfunction (RDF) was defined as a repeated increase in the serum creatinine level above 130 μmol/L one year or later after LDLT and lasted for at least 1 month [6]. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg [8]. Diabetes was based on American Diabetes Association guidelines for the diagnosis of diabetes. According to these guidelines, patients with a fasting plasma glucose level ≥ 6.99 mmol/L or a random plasma glucose level ≥ 11.1 mmol/L were considered diabetic [9]. Hyperlipidemia was defined as a repeated increase in the serum total-cholesterol > 200 mg/dL or additional abnormal exceptions [10].

Three groups of stable TAC trough levels and three stages of stable trough levels

Patients were divided into three groups based on late stable TAC trough levels, defined as a steadily maintained trough level of TAC for at least 1 year after having taken TAC for more than 3 years: group 1, > 5 ng/mL; group 2, 3–5 ng/mL; and group 3, < 3 ng/mL.

We also divided the TAC trough level tapering process into three stages according to the two stable trough level states as follows: stage 1, from the highest level to 5 ng/mL; stage 2, from 5 ng/mL to 3 ng/mL; and stage 3: < 3 ng/mL.

Statistical analysis

The main clinical parameters were expressed as frequencies and percentages or means and standard deviations. The impact of different TAC trough levels on the several clinical outcomes between groups using Student's *t* test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables. Furthermore, the multivariable statistical test using logistic regression was performed to explore the factors influencing on renal function. The Chi-square test for frequencies and log-rank test for Kaplan-Meier curves were used to detect the influence of late TAC exposure on rejection and long-term survival outcomes, respectively. Statistical analyses were performed using SPSS 16.0 (Chicago, IL, USA). All tests were two-tailed, and a P value < 0.05 was considered statistically significant.

Results

Baseline patient characteristics

A total of 155 consecutive LDLT patients were screened for study eligibility, and their characteristics are summarized in Table 1. There were 134 males (86.5%) and 21 females (13.5%) with a mean age of 44.2 ± 9.5 years at LDLT. Major etiologies for LT were fulminant hepatitis (n = 51; 32.9%) and virus hepatitis related liver cirrhosis (n = 87; 56.1%), most of the enrolled patients (69.7%) were graded C on the Child-Pugh scale, and their mean model for end-stage liver disease (MELD) score was 23.0 ± 8.9.

Three groups of stable TAC trough levels and three stages of stable trough level achievement

Patients were divided into three groups based on late stable TAC trough levels as mentioned above: group 1, > 5 ng/mL (n = 22); group 2, 3–5 ng/mL (n = 45); and group 3, < 3 ng/mL (n = 88). The mean time to reach 5 ng/mL in groups 2 and 3 were 4.2 ± 2.0 and 2.9 ± 1.7 years, respectively, which represents a significant difference (P = 0.0002) indicating that reaching a stable state in a

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