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Research Paper

A retrospective analysis of the safety and efficacy of low dose tacrolimus (FK506) for living donor liver transplant recipients

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Abstract

We sought to evaluate the efficacy and effects of low-dose tacrolimus (FK506) to recipients with living donor liver transplantation (LDLT). A total of 66 patients who underwent LDLT between 2001 and 2007 were enrolled in this study. According to different doses of tacrolimus, the recipients were randomly divided into two groups: the low-dose tacrolimus group (group A) and the normal-dose tacrolimus group (group B). The blood concentration of tacrolimus and its side effects including infection, hyperglycemia, hypertension, high blood creatinine and jaundice were monitored once a week at the perioperative period, and once a month thereafter. Besides, the survival rates of the recipients were analyzed at the 1- and 3-year time point after operation. Among these patients, no significant acute rejection was detected after LDLT. The incidences of infection, hyperglycemia, liver dysfunction and renal impairment in group A were markedly lower than those in group B. However, no significant differences were detected in the incidence of hypertension between the two groups. Moreover, the recipients in each group had a similar survival rate according to the results of 1- and 3-year follow-up. The incidence of side effects that associated with tacrolimus positively correlated with tacrolimus blood concentration. In conclusion, long-term and low-dose administration of tacrolimus is a safe and effective treatment for LDLT recipients.

Keywords: living donor liver transplantation, tacrolimus, low dose, side effect, survival rate

INTRODUCTION

Living donor liver transplantation (LDLT) is developed as a technique aimed at reducing the number of recipients waiting for liver transplantations. Since Strong et al. performed the first successful LDLT in 1989[1], there has been a significant increase in the number of LDLTs. Cyclosporine A (CsA) and tacrolimus form the basis of immunosuppressive regimens and are used at most liver transplantation centers. However, CsA therapy is associated with severe adverse effects, such as nephrotoxicity, dyslipidemia and hypertension. Recent studies showed that tacrolimus is preferred over CsA as an immunosuppressive agent[2,3]. In addition, another study suggested that although liver grafts from living donors showed immune compatibility to some extent, compatibility could be improved by lowering the concentration of

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immunosuppressive agents in blood[4]. Approximately 10% of LDLT recipients could survive without intake of any immunosuppressive agents. Low dose administration of immunosuppressive agents, such as tacrolimus, might reduce the risk of graft rejection, as well as cut down the cost of immunosuppressive therapy[5]. However, correlation between the dosage of tacrolimus and the associated side effects and survival rates in LDLT patients is largely unknown. In this study, we performed 66 cases of LDLT and carried out long-term follow up in these recipients. The blood concentration of tacrolimus and the incidences of infection, hyperglycemia, hypertension, high blood creatinine, jaundice and survival rate were monitored periodically.

SUBJECTS AND METHODS

Patients and clinical information

A total of 66 patients who underwent LDLT at the authors´ affiliated hospital between January 2001 and June 2007 were enrolled in this study. Among these patients, there were 45 males and 21 females, aged from 4 to 43 years (average 22.4±2.6 years). The primary diagnoses included Wilson´s disease (38 cases), post-hepatic cirrhosis (22 cases) and primary hepatic carcinoma (6 cases). The liver grafts were donated from the patients´ mothers (47 cases), fathers (16 cases), or wives (3 cases). The grafts were obtained from the following locations: the left lateral lobe (29 cases), the right lobe (28 cases), the left lobe (8 cases), and the extended right lobe (1 case). All the 66 recipients have undergone long-term follow-up. This study protocol was approved by the institutional review board of the authors´ affiliated institution.

Immunosuppressive regimens

Of the 66 cases, we administered the standard immunosuppressive regimen of tacrolimus (FK506, Fujisawa, Osaka, Japan), methylpred nisolone (Pfizer, Dalian, Liaoning, China) and mycophenolate mofetil (MMF, Shanghai Roche, Shanghai, China). The recipients were randomly divided into the low-dose tacrolimus group (group A, n = 33) and the normal dose tacrolimus group (group B, n = 33). In the two groups, an identical immunosuppressive regimen was given, except the dose of tacrolimus administration. In group A, tacrolimus was given at a mean dose of 0.05 mg/kg·day during the first year and at 0.03 mg/kg·day thereafter. In group B, FK506 was given at a mean dose of 0.1 mg/kg·day initially and at 0.05 mg/kg·day thereafter. The dose of tacrolimus was modestly adjusted according to blood concentration. Methylprednisolone and mycophenolate mofetil (MMF) were administered at conventional doses.

Monitoring blood concentration of FK506 and the incidence of infection, blood glucose, blood pressure, blood creatinine and jaundice

In the two groups, the blood concentration of FK506 was monitored once a week during the perioperative period, and once a month thereafter (TDx/FLx, Abbott,

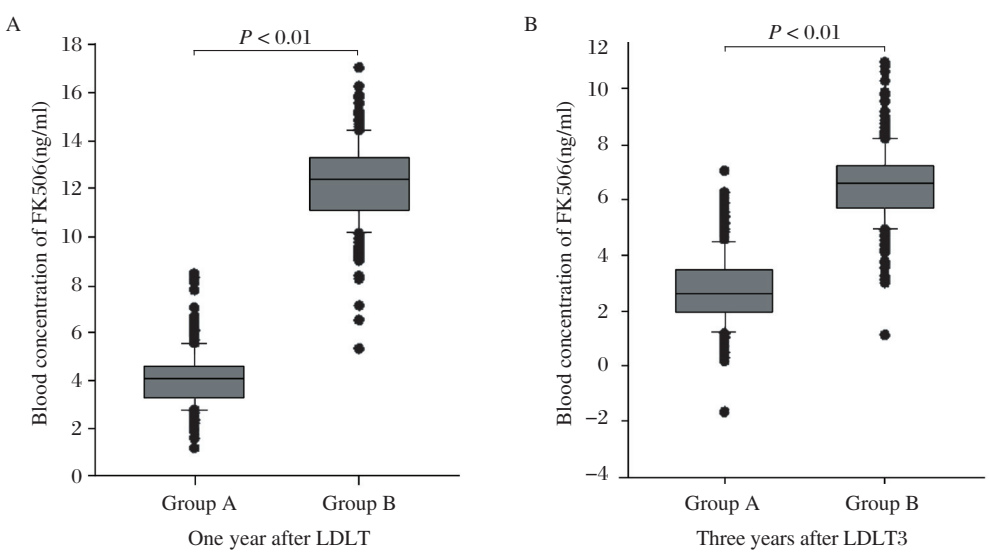

***Fig. 1* Tacrolimus blood concentration in the LDLT recipients.** The 1-year follow-up (A) and 2-3 year follow-up (B) data show that blood concentration of tacrolimus in group B was significantly higher than that in group A. Patients in group A were given a low dose of FK506 at 0.05 mg/(kg·day) during the first year and at 0.03 mg/(kg·day) thereafter and patients in group B were given a regular dose of FK506 initially at 0.1 mg/(kg·day) and 0.05 mg/(kg·day) thereafter.

Table 1 **Incidence of immunosuppressive regimen-associated intraoperative side effects**

Group	Acute rejection	Infection	Hyperglycemia	Hypertension	High blood creatinine	Jaundice	Graft survival rate
A (n = 33)	0	7 (21.21%)	8 (24.24%)	3 (9.09%)	11 (33.33%)	6 (18.18%)	32 (96.96%)
B (n = 33)	0	6 (18.12%)	11 (33.33%)	5 (15.15%)	7 (21.21%)	9 (27.27%)	32 (96.96%)
(χ^2, P)	-	(0, $P > 0.05$)	(0.30, $P > 0.05$)	(0.14, $P > 0.05$)	(0.69, $P > 0.05$)	(0.43, $P > 0.05$)	(0.52, $P > 0.05$)

IL, USA). At the same time point, the blood samples were examined to detect the amount of leukocytes, C-reactive protein (CRP), blood glucose, blood creatinine and serum bilirubin (Automated Biochemical Ana–lyzer, AU2700, Toshiba, Tokyo, Japan). In addition, blood pressure was monitored regularly.

Statistical analysis

Data were analyzed by using Student´s t test unless otherwise specified Chi-square test and Mantel-Cox test were used to compare differences between the two groups. Survival rate of each group was analyzed at 1 and 3 years after transplantation. A P value of less than 0.05 was considered statistically significant.

RESULTS

Tacrolimus contents in the blood

As tacrolimus was administered to these recipients at different doses, we monitored the blood concentra–tion regularly. As expected, low dose of tacrolimus led to a low level of blood concentration in group A, and normal dose of tacrolimus resulted in a higher level of blood concentration in group B (***Fig. 1A*** and ***1B***, $P <$ 0.001).

Side effects associated with tacrolimus

At the perioperative period, none of the recipients had experienced severe acute rejection. However, a recipient in group A underwent re-transplantation as a result of acute hepatic artery thrombosis, and another recipient in group B died of respiratory failure on the 16th day after transplantation. No significant differ–ences in the incidences of immunosuppressive regi–men-associated adverse effects were detected between group A and B (***Table 1***).

The 1-year follow-up data showed that none of the survived recipients had experienced severe rejection. The incidence of infection, hyperglycemia, liver dys–function and renal impairment in group A was mark–edly lower than that in group B. However, the inci–dences of hypertension were comparable in the two groups (***Table 2***). The 3-year follow-up data displayed a similar result (***Table 3)***.

Survival

The recipients in the two groups had a comparable 1-year survival rate (90.9% vs 93.75%). In group A, 1 recipient died of pulmonary infection and 2 recipients died of small-for-size syndrome. In group B, 1 patient died of respiratory failure; 1 patient suffered from vi–ral meningitis, which led to death (***Fig. 2A***). The 3-year survival rates were 81.82% and 87.5% in group A and B, respectively. In group A, 6 recipients died in total. Among them, 1 died of recurrent hepatitis, 2 cases died of pulmonary infection, 2 cases died of small-for-size syndrome and 1 recipient died of recurrent hepat–ic carcinoma. Four recipients died in group B due to small-for-size syndrome, recurrent hepatic carcinoma associated with lung metastasis, pulmonary infection and viral meningitis, respectively.

DISCUSSION

Tacrolimus (FK506), a hydrophobic macrolide lactone, is a potent immuno- suppressive agent be–longing to the calcineurin inhibitor class of drugs. It is widely used to prevent allograft rejection in organ-transplant recipients. However, tacrolimus showed multiple side effects, such as infection, hyperglyc–emia, hypertension, renal injury and neurotoxicity, among which nephrotoxicity and neurotoxicity are the most serious side effects[6,7]. These side effects are closely related to the blood levels of immunosup–pressive agents[8,9]. Among these side effects, most of the infectious complications after liver transplantation occur during the first month after transplantation, and to a lower extent, between the second and the sixth month after transplantation. After the sixth month,

Table 2 **Patient outcome and safety profile at 1-year follow-up**

Group	Graft rejection	Infection	Hyperglycemia	Hypertension	High blood creatinine	Jaundice	1-year survival rate
A (n = 33)	0	2 (6.06%)	2 (6.06%)	2 (6.06%)	3 (9.09%)	4 (12.12%)	30 (90.9%)
B (n = 33)	0	9 (28.13%)	10 (31.25%)	2 (6.25%)	11 (34.38%)	6 (18.75%)	30 (93.75%)
(χ^2, P)	-	(4.17, $P < 0.05$)	(5.28, $v < 0.05$)	(0.24, $P > 0.05$)	(4.74, $P < 0.05$)	(0.18, $P > 0.05$)	(0.001, $P > 0.05$)

Table 3 **Patient outcome and safety profile at 3-year follow-up**

Group	Graft rejection	Infection	Hyperglycemia	Hypertension	High blood creatinine	Jaundice	3-year survival rate
A ($n = 33$)	0	3 (9.09%)	5 (15.15%)	2 (6.06%)	6 (9.37%)	5 (15.15%)	27 (81.82%)
B ($n = 33$)	0	11 (34.38%)	14 (43.75%)	3 (9.38%)	14 (43.75%)	13 (40.63%)	28 (87.5%)
(χ^2, P)	-	(4.74, $P < 0.05$)	(5.12, $P < 0.05$)	(0.001, $P < 0.05$)	(3.88, $P < 0.05$)	(4.07, $P < 0.05$)	(0.085, $P < 0.05$)

patients can be divided into two different categories according to the degree of immunosuppression achieved[10]. In this study, the incidence of infection in group A was significantly lower than that in group B. Three patients had infections in group A (1 patient had urinary tract infection and 2 patients had upper respiratory tract infection). In contrast, 11 recipients in group B had infection after LDLT (7 recipients had upper respiratory tract infection, 3 recipients had gastrointestinal tract infection, and 1 recipient had an unknown infection). Tacrolimus is known to be more diabetogenic than cyclosporine, particularly during the first month, when a high dose of these drugs is administered. However, when the doses are reduced significantly during long-term administration, this difference is decreased[11]. In the current study, during the early stage after transplantation, the incidences of hyperglycemia were 24.24% and 36.36% in group A and B, respectively. Thereafter, the incidence markedly decreased in group A, but not in group B. Therefore, the reduction of hyperglycemia occurrence is mainly related to low dose of FK506. In addition, the occurrence of hyperglycemia had also been related to liver dysfunction. As the level of serum bilirubin is closely associated with liver function, low dose of tacrolimus contributed to a lower incidence of jaundice. Among all these side effects, the most severe one is renal injury, which is most frequently associated with the toxicity of calcineurin inhibitors[12,13]. These drugs may cause renal failure by the following pathogenic mechanisms, including functional change which occurs as a result of renal arteriolar vasoconstriction, leading to reduction of glomerular filtration rate and eventually the development of tubular necrosis, structural injuries, such as ischemic arteriolopathy, glomerular sclerosis, tubular atrophy and renal fibrosis[14]. In this study, the incidence of renal dysfunction in group A was significantly lower than that in group B. However, none of the patients suffered from apparent nervous system injury.

A previous study showed that immunosuppressive agents such as calcineurin inhibitors and corticosteroids induce arterial hypertension. In this study, all the patients were administered an identical dose of corticosteroids, except tacrolimus. The percentages of patients with high blood pressure (HBP) were 6.06% and 9.38% in group A and B, respectively. Therefore, there was no correlation between the incidence of HBP and the dose of tacrolimus. Moreover, despite that low dose of tacrolimus contributed to a lower incidence of adverse effect, no significant difference in survival rate was detected between the two groups ac-

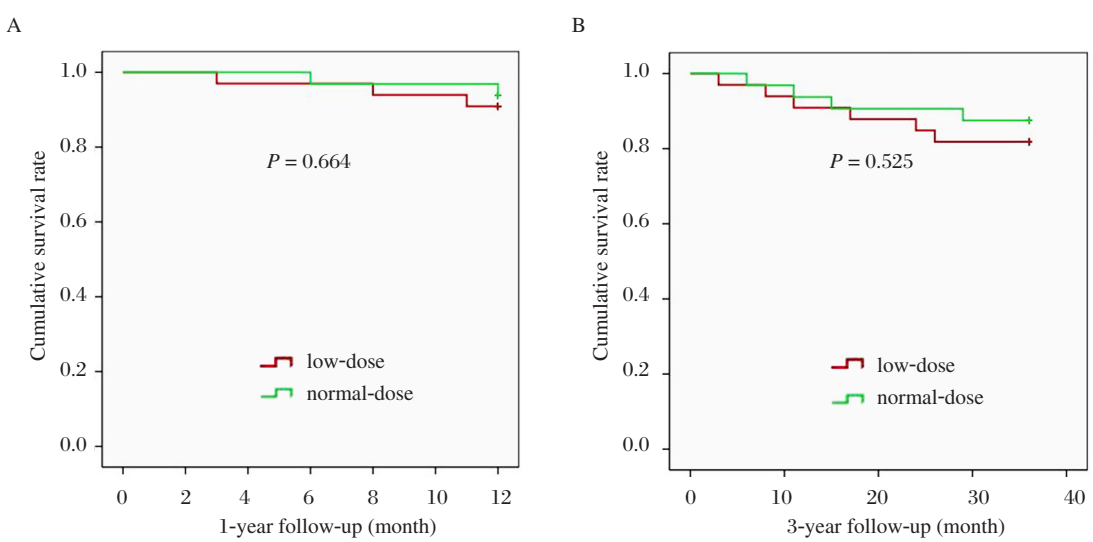

Fig. 2 **Survival analysis of the recipients in the two groups after LDLT.** 1-year follow-up (A) and 2-3 year follow-up (B) data show that no significant difference was detected in the 1-year survival rate and 3-year survival rate between the two groups ($P > 0.05$).

cording to the 3-year follow-up data.

Graft ischemia reperfusion injury, surgical trauma and other factors are also associated with liver dys−function, and reduced resistance to infection, all of which could overlap with the side effects of tac−rolimus. Therefore, we could not assess the side ef−fects precisely. In summary, the administration of low dose of tacrolimus lowers the incidences of side effects without decreasing the long term survival of LDLT recipients.

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