Optimal initial dose of orally administered once-daily extended-release tacrolimus following intravenous tacrolimus therapy after liver transplantation

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Abstract

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Introduction. Once-daily extended-release tacrolimus (Tac-OD) is expected to reduce nonadherence in recipients after liver transplantation. The aim of this study was to determine the optimal initial dose of orally administered Tac-OD following intravenous tacrolimus (Tac-IV) therapy after liver transplantation.

Patients and Methods. This prospective study included 10 adult recipients who had undergone liver transplantation at our institute. The recipients were prescribed tacrolimus by continuous intravenous administration with a steroid as initial immunosuppression therapy. Tacrolimus was converted from intravenous administration to once-daily oral intake when gastrointestinal function returned. We evaluated tacrolimus concentrations in blood 9 times a day and area under the blood concentration-time curve (AUC) during conversion. The optimal initial dose of Tac-OD was determined based on simple regression analysis between the oral dose of Tac-OD and the total dose of Tac-IV during a 24-hour period.

Results. The AUC before and after conversion showed no differences. We found that the optimal initial dose of Tac-OD was 8 times the dose of Tac-IV. There was a relationship between the AUC

and the trough level. No recipients experienced acute rejection or adverse effects such as renal failure, neurotoxicity, or cardiac failure during conversion.

Conclusions. We successfully converted continuous Tac-IV to oral intake of Tac-OD by adjusting the dose using trough levels without acute rejection or adverse effects. The AUC of Tac-OD correlated with the trough level. The optimal initial dose ratio of Tac-OD following Tac-IV was 8:1.

Introduction

Once-daily extended-release tacrolimus (Tac-OD, Graseptor® or Advagraf®, Astellas Pharmaceutical Corporation, Tokyo, Japan) has been developed to provide once-daily dosing with similar efficacy and safety to twice-a-day tacrolimus (Prograf®, Astellas Pharmaceutical Corporation) to reduce patient nonadherence after liver transplantation. However, Tac-OD might be unstably absorbed when gastrointestinal function is decreased, such as perioperatively. A *de novo* study of liver transplantation patients revealed that systemic exposure on day 1 was approximately 42% lower for Tac-OD than for twice-a-day tacrolimus[1]. We initially administered tacrolimus with continuous intravenous injection after liver transplantation and subsequently converted to oral intake of twice-a-day tacrolimus when gastrointestinal function returned[2, 3]. The optimal initial dose of twice-a-day tacrolimus was determined to be 4 times that of intravenous tacrolimus (Tac-IV) based on our experienced, but that of Tac-OD is still unknown. The aim of this study was to determine the optimal initial dose of orally administered Tac-OD following Tac-IV after liver transplantation.

Patients and Methods

This prospective study included 10 adult recipients (4 men and 6 women) who had undergone liver transplantation at our institute between June 2009 and April 2013. They obtained their liver graft from

a deceased donor in 3 cases or a living donor in 7 (children in 4, brother in 2, and nephew in 1). Primary diseases requiring liver transplantation included liver cirrhosis related to hepatitis C in 4 cases (with hepatocellular carcinoma in 2), familial amyloid polyneuropathy in 3, citrullinemia in 2, and Wilson disease in 1. Mean recipient age was 44.9 ± 16.0 years at the time of liver transplantation. Recipients were prescribed tacrolimus by continuous intravenous administration with a steroid as initial immunosuppression therapy. The blood level of tacrolimus was targeted to 15–20 ng/mL at the first and second week after liver transplantation. Tacrolimus was converted from intravenous administration to once-daily oral intake, targeting a trough level of 15 ng/mL, when recipient gastrointestinal function returned. First, one-fourth of the whole Tac-IV dose was replaced by Tac-OD. On the second day, one-half of the whole tacrolimus dose was replaced by Tac-OD after referring to the tacrolimus trough level. Replacement from intravenous to oral tacrolimus was sometimes suspended when the tacrolimus trough level was unstable. Finally, when the whole dose of tacrolimus was orally administered, intravenous administration was discontinued. We prospectively monitored tacrolimus concentrations in whole blood using chemiluminescent microparticle immunoassay (CMIA) with ARCHITECT *i*1000 System (Abbott Japan Co., Matsudo, Japan) at 0 (C_0), 1 (C_1), 2 (C_2), 3 (C_3), 4 (C_4), 6 (C_6), 8 (C_8), 12 (C_{12}), and 24 (C_{24}) hours after the initial administration of Tac-OD on days 1, 3, and 5 during conversion. The area under the blood concentration-time curve (AUC)

was calculated by the trapezoid rule, and the oral bioavailability (F) was calculated using the following formula:

$$F = \{Dose_{Tac\text{-}IV}\ (mg) \times AUC_{Tac\text{-}OD}\ (ng \times h/mL\} / \{Dose_{Tac\text{-}OD}\ (mg) \times AUC_{Tac\text{-}IV}\ (ng \times h/mL\}$$

The steady-state concentration (C_{ss}) was estimated for Tac-IV. The optimal initial dose of Tac-OD was determined based on simple regression analysis between the oral dose of Tac-OD and the total dose of Tac-IV during a 24-hour period. The relationship between the AUC and the trough level of Tac-OD was also evaluated.

This study was approved by the institutional review board of Shinshu University School of Medicine, and written informed consent was obtained from the patients and their families.

Data are expressed as average ± standard deviation. Statistical analysis was performed using StatView (Version 5.0, SAS institute Inc., Cary, NC), and a *p* value of less than 0.05 was considered statistically significant for the *t* test and Pearson correlation coefficient by rank.

Results

In all 10 patients, continuous Tac-IV was successfully converted to Tac-OD by a mean of 15.4 ± 6.8 days after liver transplantation. Liver function remained stable during conversion. Serum creatinine level, blood sugar, and blood pressure also remained stable without any additional medications. No

recipients experienced acute rejection or adverse effects such as renal failure, neurotoxicity, or cardiac failure during conversion. Conversion duration was 4.6 ± 1.5 days. There were no differences between the mean AUC 1, 2, and 3 days before conversion (399.0 ± 53.5 ng × h/mL) and that on day 1 (374.8 ± 65.0 ng × h/mL, $p = 0.070$), day 3 (369.0 ± 47.4 ng × h/mL, $p = 0.115$), and day 5 (413.4 ± 132.1 ng × h/mL, $p = 0.781$) during conversion (Fig. 1A). The AUC correlated with the trough level (C_{24}) during conversion ($R = 0.769$, $p < 0.0001$, Fig. 1B). The C_{ss} for Tac-IV was 16.6 ± 2.6 ng /mL at the day before conversion. The dose of Tac-IV before conversion was 1.1 ± 0.6 mg/day, and that of Tac-OD after conversion was 8.3 ± 6.7 mg/day. The oral bioavailability was 0.13 ± 0.09 and the optimal initial dose ratio of Tac-OD to Tac-IV was 8:1 (Fig. 2).

Discussion

We successfully converted Tac-IV to Tac-OD without any adverse effects in all 10 recipients. We had considered that conversion from Tac-IV to Tac-OD was more difficult than that to twice-a-day tacrolimus because interpatient variation of absorption might have greater effect on Tac-OD. Therefore, we adapted a systematic protocol in which each one-fourth dose of Tac-IV was replaced by Tac-OD. The trough level (C_{24}) of tacrolimus correlated with the AUC during conversion. We accordingly were able to avoid fluctuation of the AUC by adjusting trough level during conversion.

The optimal dose of Tac-OD was determined to be 8 times that of Tac-IV in this study, and we expect to shorten the duration of conversion in the future.

We monitored tacrolimus concentrations using an immunoassay that might cross-react with tacrolimus metabolites. We should have confirmed the concentrations using liquid chromatography-tandem mass spectrometry (LC-MS/MS) that is considered the reference method for tacrolimus testing. The CMIA method has been published that the results correlated well to those measured by LC-MS/MS in liver, kidney, bone marrow and lung transplantation recipients[4].

In conclusion, we successfully converted continuous Tac-IV to oral intake of Tac-OD by adjusting the dose using the trough level without acute rejection or adverse effects. The AUC of Tac-OD correlated with the trough level. The optimal initial dose ratio of Tac-OD following Tac-IV was 8:1.

References

1. Undre NA: Use of a once daily modified release tacrolimus regimen in de novo liver transplant recipients. Am J Transplant. 5: 374, 2005

2. Hashikura Y, Kawasaki S, Matsunami H, Terada M, Ikegami T, Nakazawa Y, et al: Immunosuppressant switching between cyclosporine and tacrolimus after liver transplantation. Transplant Proc. 28: 1034, 1996

3. Ohno Y, Mita A, Ikegami T, Masuda Y, Urata K, Nakazawa Y, et al: Temporary auxiliary partial orthotopic liver transplantation using a small graft for familial amyloid polyneuropathy. Am J

Transplant. 12: 2211, 2012
4. Moscato D, Nonnato A, Adamo R, Vancheri M, Caropreso A : Therapeutic monitoring of Tacrolimus: Aberrant results by an immunoassay with automated pretreatment. Clin Chim Acta. 411: 77, 2010

Figure legends

Fig. 1: A: The area under the blood concentration-time curve (AUC) of tacrolimus before and during conversion from continuous intravenous to orally once-daily extended-release tacrolimus (Tac-OD). The AUC showed no differences at days 1 (D1), 3 (D3), and 5 (D5) after starting conversion, compared with the mean AUC of tacrolimus intravenously administered 1 to 3 days before conversion (Pre). **B**: Relationship between AUC and the trough level (C_{24}). The AUC correlated with the trough level (C_{24}) for Tac-OD (R = 0.769). Correlation was expressed as AUC = 22.663 × C_{24} + 79.604 (R^2 = 0.591, $p < 0.0001$).

Fig. 2: Simple regression between doses of once-daily extended-release tacrolimus (Tac-OD) and intravenous tacrolimus (Tac-IV). Simple regression was expressed as $Dose_{Tac\text{-}OD} = 7.827 \times Dose_{Tac\text{-}IV}$ ($R^2 = 0.6789$, $p < 0.0001$). Thus, optimal initial dose of Tac-OD was determined to be 8 times that of Tac-IV.

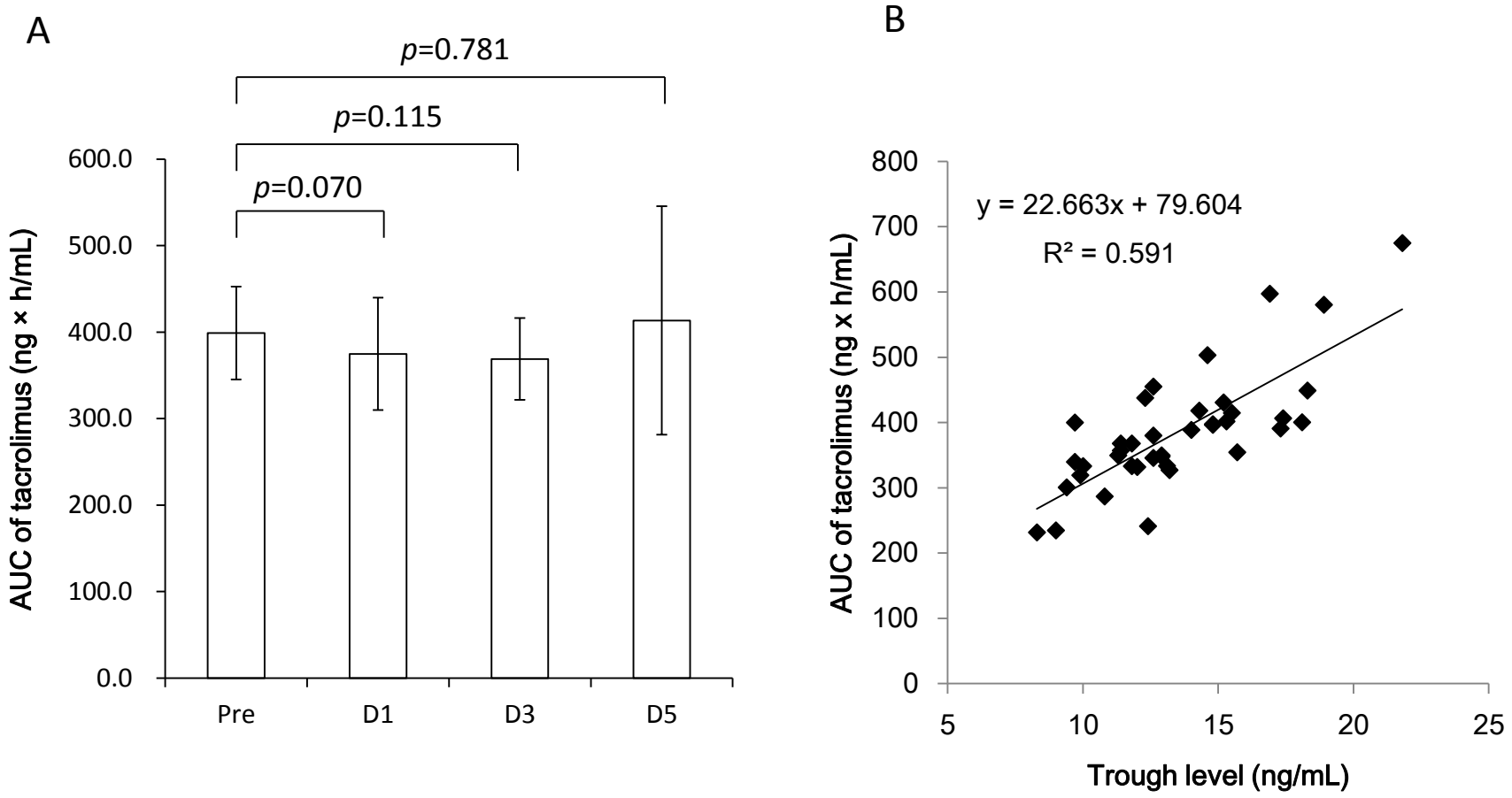
A
p=0.781
p=0.115
p=0.070
AUC of tacrolimus (ng × h/mL)
600.0
500.0
400.0
300.0
200.0
100.0
0.0
Pre
D1
D3
D5
B
y = 22.663x + 79.604
R² = 0.591
AUC of tacrolimus (ng x h/mL)
800
700
600
500
400
300
200
100
0
5
10
15
20
25
Trough level (ng/mL)

Fig. 1

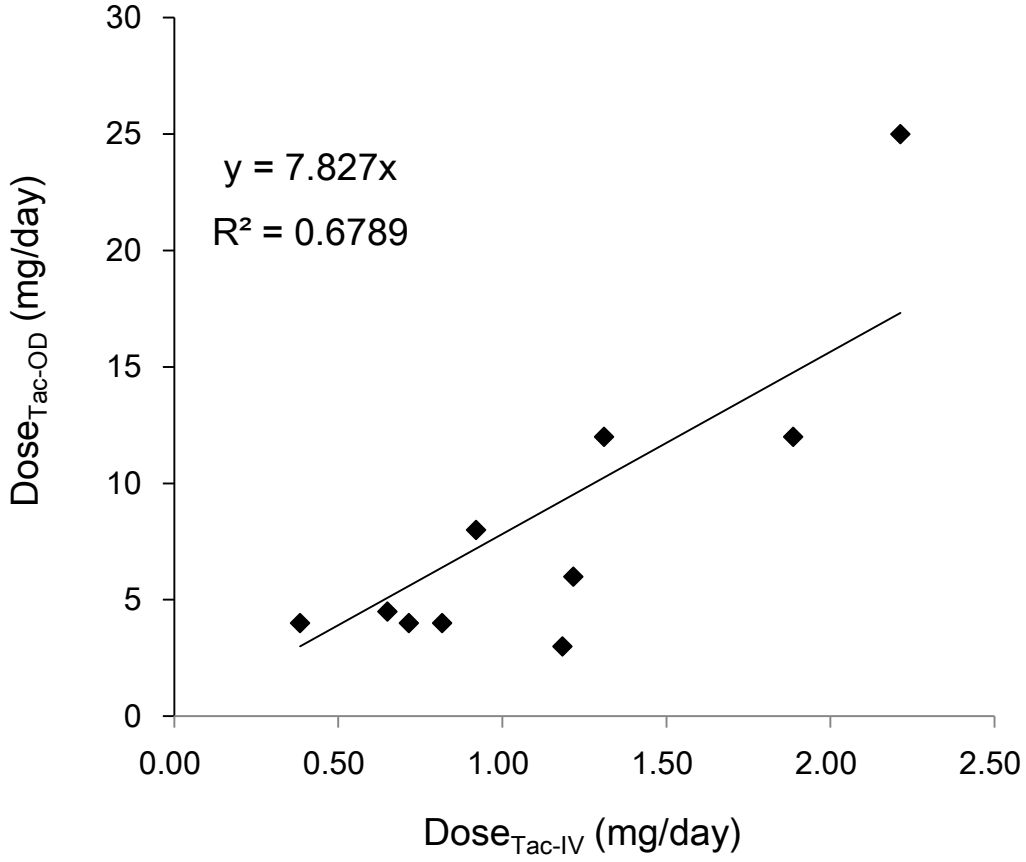
y = 7.827x
R² = 0.6789
Dose Tac-OD (mg/day)
Dose Tac-IV (mg/day)
0
5
10
15
20
25
30
0.00
0.50
1.00
1.50
2.00
2.50

Fig. 2