Pharmacokinetic Profile of Twice- and Once-daily Tacrolimus in Pediatric Kidney Transplant Recipients

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ABSTRACT

Background. The aim of this study was to assess the differences in pharmacokinetic (PK) profiles after the 1:1 ratio-based conversion from a twice-daily to a once-daily tacrolimus formulation (TD-TAC and OD-TAC, respectively) in pediatric recipients of kidney transplants.

Methods. TD-TAC was initially administered to 29 pediatric patients who underwent kidney transplantations between April 2010 and September 2015 and were then subsequently switched to OD-TAC. The switch dose ratio was 1:1, and the 24-hour complete PK parameter assessment was performed before and after the regimen was changed from TD-TAC to OD-TAC.

Results. The mean total daily dose at baseline was 5.5 ± 2.9 mg (0.18 ± 0.10 mg/kg body weight). Consecutive PK studies revealed no significant difference in the mean time to achieve maximum concentrations and the area under the concentration–time curve from 0 to 24 hours (AUC_{0-24}) of both drug formulations. However, the mean trough concentration (C_{min}) and the maximum concentration of OD-TAC were 22% and 6% lower and higher, respectively, than those of TD-TAC. Therefore, a better correlation was observed between the AUC_{0-24} and C_{min} of OD-TAC than between those of TD-TAC.

Conclusions. After the change from TD-TAC to OD-TAC, the AUC_{0-24} values were equivalent despite a 22% reduction in C_{min}. C_{min} may therefore be an excellent predictor in the therapeutic drug monitoring of OD-TAC because of its superior correlation with AUC_{0-24}.

THE MODIFIED-RELEASE, ONCE-DAILY tacrolimus (OD-TAC) extended-release formulation of TAC was approved as Advagraf in the European Union in 2007, Graceptor in Japan in 2008, and Astagraf in the United States in 2013. Several adult studies have shown a significant improvement in the intrapatient variability of systemic TAC exposure after converting from twice-daily tacrolimus (TD-TAC) to the OD-TAC formulation [1–5]. Moreover, there was no marked difference in the efficacy and safety profiles of OD-TAC and TD-TAC. The immunosuppressive efficacy of TAC has been shown to be similar in pediatric and adult patients. However, because of potential age-related pharmacologic differences, it is important to determine the distinctive pharmacokinetic (PK) profiles of both TAC formulations and the doses required to produce similar effects in children. Furthermore, a simpler dosing regimen is expected to improve medication adherence.

Nonadherence to immunosuppressive medication is a leading cause of preventable graft loss in pediatric recipients of kidney transplants [6]. In addition, an increased incidence of nonadherence was shown in adolescent (30%–53%) compared with prepubertal (3%–19%) recipients [7].

A prospective study was therefore conducted in pediatric recipients of kidney transplants to compare the 24-hour

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complete PK profiles before and after switching from TD-TAC to OD-TAC. We also examined the correlation of TAC concentrations at each time point with the area under the concentration–time curve from 0 to 24 hours ($AUC_{0–24}$) to find a superior therapeutic drug monitoring parameter for OD-TAC in the pediatric population.

PATIENTS AND METHODS

Twenty-nine children and young adults aged <20 years who had undergone kidney transplantations between April 2010 and September 2015 were enrolled in the study. According to the protocol, TD-TAC was initially administered and then switched to OD-TAC in patients with stable allograft function and a glomerular filtration rate >50 mL/min/1.73 m^2 calculated by using the Schwartz formula 2 to 4 weeks after the transplantation. The TD-TAC to OD-TAC switch dose ratio was 1:1; the 24-hour complete PK study was assessed before and after the switch under hospitalized conditions to ensure that both the morning and evening doses were administered on time according to our protocol. In addition, mealtimes, which may affect the PK profile, were fixed at 8:00 AM and 6:00 PM.

Each profile consisted of data from the analysis of 13 blood samples collected at 0, 1, 2, 3, 4, 6, 8, 12, 13, 14, 15, 16, and 24 hours after the morning dosing. The trough concentration (C_{min}) and maximum concentration (C_{max}) were obtained from the results of the profiles, and the AUC was derived from the concentration–time curve. TAC concentrations were determined by using chemiluminescent immunoassay methods.

The study protocol was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patients and their parents as well as the control subjects before commencement of the study. Statistical analyses were performed by using the Wilcoxon signed-rank test, and P values <.05 were considered significant.

RESULTS

Patients

Table 1 displays the characteristics of the 29 study patients (17 boys and 12 girls). Their mean age was 12.3 ± 3.4 years, and they underwent a mean follow-up of 532.5 ± 970.9 days. Mycophenolate mofetil and methylprednisolone were administered to all patients in combination with TAC. Before the conversion to OD-TAC, the mean total daily dose of TD-TAC was 5.5 ± 2.9 mg/d, and the mean glomerular filtration rate was 96.3 ± 35.7 mL/min/1.73 m^2.

Table 1. Patient Characteristics

Characteristic	No. (%) or Mean ± SD
Male sex	17 (58.6)
Height, cm	136.7 ± 16.3
Weight, kg	32.2 ± 9.8
Age at conversion, y	12.3 ± 3.4
Time from transplantation to conversion, mo	414.7 ± 829.9
Total daily dose per body weight, mg/kg	0.18 ± 0.1
GFR (Schwartz formula), mL/min/1.73 m^2	96.3 ± 35.7

Abbreviations: GFR, glomerular filtration rate; SD, standard deviation.

Oral Dosage and C_{min}

The analysis of the oral dosage based on weight and the C_{min} of both groups (Fig 1) revealed no significant correlations (TD-TAC and OD-TAC, r^2 = 0.015 and 0.012, respectively).

Comparison of the PK Profile

The comparison of the PK profile of TD-TAC and OD-TAC is summarized in Table 2. Mean $AUC_{0–24}$ was 214.8 ± 78.3 ng·h/mL for TD-TAC (range, 80.9–335.1 ng·h/mL) and 205.3 ± 72.3 ng·h/mL (range, 100.6–346.7 ng·h/mL) for OD-TAC. There was no significant difference between formulations (P = .1169).

The mean C_{max} of OD-TAC was 17.0 ± 6.6 ng/mL (range, 6.7–30.6 ng/mL), which was significantly higher (6%) than that of TD-TAC at 14.7 ± 6.7 ng/mL (range, 4.4–34.6 ng/mL) ng/mL (P < .05). The mean time to achieve C_{max} for TD-TAC and OD-TAC did not differ (4.2 ± 3.7 and 3.0 ± 1.7 hours for TD-TAC and OD-TAC, respectively; P = .0845). The mean C_{min} values were 7.2 ± 2.5 and 5.4 ± 1.8 ng/mL (range, 3.2–13.4 and 3.1–8.4 ng/mL) for TD-TAC and OD-TAC; thus, the C_{min} of OD-TAC was 22% significantly lower than that of TD-TAC (P < .01).

Correlation Between C_{min} and $AUC_{0–24}$

The analysis of C_{min} and $AUC_{0–24}$ of TD-TAC and OD-TAC (Fig 2) revealed a good correlation between them for both formulations. TD-TAC exhibited a slightly lower correlation coefficient than OD-TAC (r^2 = 0.623 and 0.834, respectively).

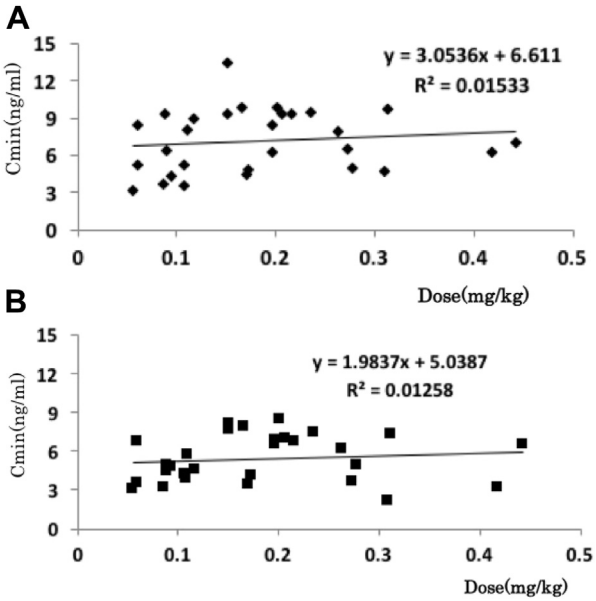

Fig 1. Oral doses versus whole blood trough concentration (C_{min}) of (**A**) twice-daily tacrolimus and (**B**) once-daily tacrolimus.