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Brief Communication

Conversion of Twice-Daily Tacrolimus to Once-Daily Tacrolimus Formulation in Stable Pediatric Kidney Transplant Recipients: Pharmacokinetics and Efficacy

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The pharmacokinetics, efficacy and safety of once-daily tacrolimus formulation (Tac-OD) were assessed in 34 stable pediatric kidney transplant recipients. Enrolled patients received their dose of twice-daily tacrolimus formulation (Tac-BID) on study Days 0 through 7. On the morning of study Day 8, the total daily doses for patients were converted to Tac-OD on a 1:1 basis and maintained on a once-daily morning dosing regimen. Tacrolimus pharmacokinetic profiles were obtained on study Days 7, 14 and 28 (after dose adjustment). Although the mean C_0 concentrations (4.10 ± 1.16–3.53 ± 1.10 ng/mL, $p = 0.004$), and AUC_{0-24} (151.8 ± 41.6–129.8 ± 39.3 ng h/mL, $p < 0.001$) were decreased significantly after a 1:1 based conversion, there was high interindividual variability. The dose of Tac-OD was decreased in 26.5% and increased in 44.1% of patients. The resultant tacrolimus dose and pharmacokinetic profiles on study Day 28 were comparable to those on Day 7. There were no serious adverse events. In conclusion, Tac-BID can be safely converted to Tac-OD in stable pediatric kidney transplant patients with the heightened therapeutic drug monitoring. Effects of drug conversion on the cardiovascular risk factors, neurological side effects and adherence should be further evaluated.

Key words: Conversion, pediatric kidney transplantation, pharmacokinetics, tacrolimus

Abbreviations: AE, adverse event; AUC_{0-24}, 24-h area under the curve; CI, confidence interval; CV, coefficient of variation; GFR, glomerular filtration rate; IIV, intra-individual variability; ITBS, immunosuppressant therapy barrier scale; Tac-BID, twice-daily tacrolimus formulation; Tac-OD, once-daily tacrolimus formulation.

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Introduction

Nonadherence to prescribed immunosuppressive medication regimens is recognized as a leading cause of preventable graft loss for both adult and pediatric kidney transplant recipients (1,2). In the literature, up to 55% of renal transplant recipients have been reported to be nonadherent to immunosuppressive regimens, with adolescent and pediatric patients being more at risk (3,4). Therefore, effective interventions that improve patient adherence to immunosuppressive medications could be a core strategy to improve graft outcome after kidney transplantation in pediatric as well as adult patients (5,6).

Because a significant relationship of higher dosing frequencies to decreased adherence has been demonstrated (3), once daily morning administration of twice-daily tacrolimus formulation (Prograf®; Astellas Pharma, Tokyo, Japan; hereafter referred as Tac-BID) has been tried (7). Recently, a modified-release once-daily tacrolimus formulation (Advagraf®; Astellas Pharma, Tokyo, Japan; hereafter referred as Tac-OD) has been developed to provide more convenient once daily dosing that may contribute to improve patient adherence to immunosuppressive medication and by inference, graft survival, compared with twice-daily tacrolimus formulation. Robust data have been obtained on the pharmacokinetics of Tac-OD in adult transplant recipients. Most studies have shown consistent results of reductions in C_{min} in stable and *de novo* patients with Tac-OD (8–12). Although an issue of adherence is most important in pediatric or adolescent transplant recipients, only few researches have been published on Tac-OD use in these age groups (13–15). In contrast to adult recipients, the difference in tacrolimus exposure following conversion from Tac-BID to Tac-OD was not apparent in industry-designed phase II pharmacokinetic trial in pediatric liver transplant patients (13).

As more data are required for the routine use of Tac-OD in pediatric transplant recipients, this present study was performed to clarify: (i) changes in pharmacokinetic parameters following conversion from Tac-BID to Tac-OD, (ii) requirement of tacrolimus dose change after conversion and (iii) clinical efficacy and safety of Tac-OD in stable pediatric kidney transplant recipients.

Materials and Methods

Patients

Pediatric ABO-compatible kidney transplant recipients (5–15 years) were eligible for enrollment if they had received kidney transplantation at least 1 year prior to enrollment and were receiving Tac-BID-based treatment. Recipients were required to have a stable renal function within at least 2 weeks prior to enrollment with a calculated glomerular filtration rate (GFR) > 40 mL/min/m^2 using the Schwartz formula (16) on a screening visit and to show tacrolimus whole blood trough levels between 3 and 20 ng/mL measured on at least two separate occasions and at least 1 week apart within 30 days prior to enrollment. Exclusion criteria included the following: experience of acute rejection episode within 90 days before the study entry, experience of acute rejection episode requiring antilymphocyte antibody therapy in the last 6 months, more than two rejection episodes within 12 months prior to study enrollment, aspartate aminotransferase or alanine aminotransferase higher than two times the upper limit of normal range, gastrointestinal disorder at the time of the pharmacokinetic study, a recipient of ABO-incompatible or cross match positive kidney transplantation, a recipient of multiorgan transplantation and current use of sirolimus.

The study (ClinicalTrials.gov NCT01476488) was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice and the International Conference on Harmonisation guidelines and Declaration of Istanbul. The protocol was approved by the Seoul National University Hospital Institutional Review Board (H-1010-056-336). Patients gave written informed consent before study enrollment.

Study design

This phase III, open label, single-center, prospective study was conducted at the Seoul National University Hospital. All enrolled patients received their current dosage of tacrolimus from study Day 1 and the evening of Day 7. After completion of the first 24 h pharmacokinetic study on Day 7, patients were converted to Tac-OD on a mg:mg basis for their total daily dose on the morning of Day 8. The second pharmacokinetic study for Tac-OD was carried out on Day 14. On Days 15 and 21, the doses of Tac-OD were adjusted to achieve pre–switching tacrolimus C_0 levels measured on Day 7. The third pharmacokinetic study was conducted on Day 28. The entire study has 6-month extension period for evaluation of safety and effectiveness (Figure 1).

Pharmacokinetic analysis

For pharmacokinetic study, enrolled patients were admitted to Clinical Trials Center on the morning of Days 7, 14 and 28. Serial blood samples were collected for pharmacokinetic profiles at 0 (predose), 0.5, 1, 2, 4, 6, 8, 12, 12.5, 13, 14, 16, 18, 20 and 24 h. The trough level as the lowest concentration just before tacrolimus administration (C_0), the peak tacrolimus concentration (C_{max}) and the time required to reach C_{max} (T_{max}) for each subject were obtained directly from the raw data. The AUC_{0-24} was calculated using linear trapezoidal rules from 0 to 24 h.

Enrolled patients were asked to fast for at least 2 h before and 1 h after receiving tacrolimus and also to take tacrolimus at a fixed time. On the day of the pharmacokinetic study, patients took tacrolimus 1 h before or 2 h after meals and the same food was served for lunch and dinner. Enrolled patients were instructed to avoid grapefruit and grapefruit juice during the study period.

Tacrolimus concentrations were determined, using high-performance liquid chromatography tandem mass spectroscopy using a Waters 2795 Alliance HT system (Micromass, Manchester, UK). The intraday coefficient of variation (CV) ranged from 5.2% to 9.3% and the accuracy was 96.0–104.0%. The interday CV varied from 3.6% to 9.6%. The lower limit of quantitation for tacrolimus was 0.8 ng/mL.

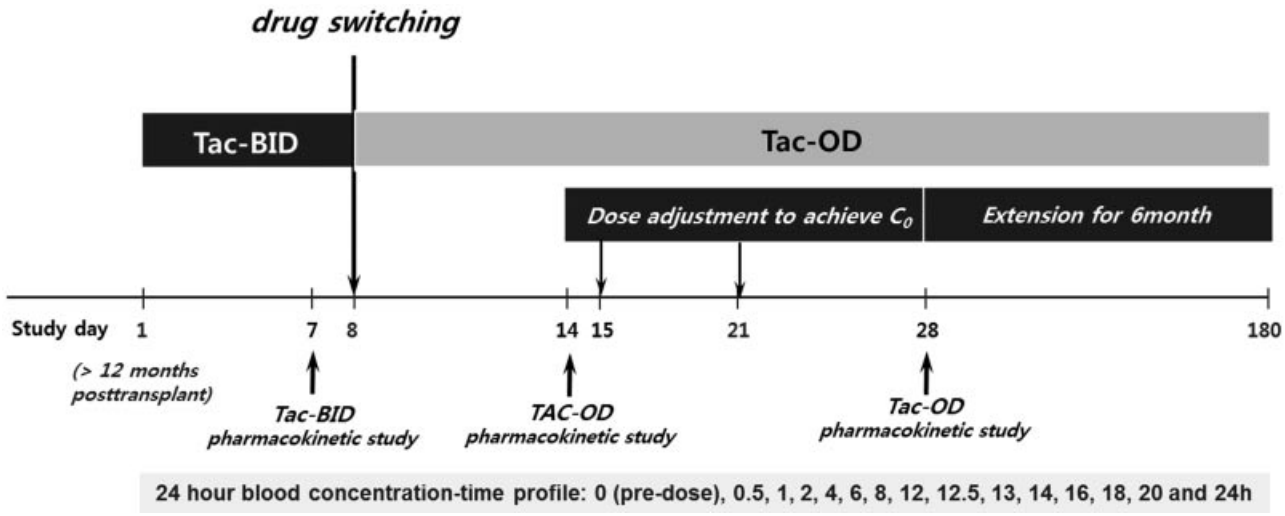


Figure 1: Study design and schedule of pharmacokinetic profiles (ClinicalTrials.gov NCT01476488). Tac-BID, twice-daily tacrolimus; Tac-OD, once-daily tacrolimus.

End points

The primary end point was comparability of AUC, which was within the bioequivalence range of 80–125% at equivalent daily doses in stable pediatric kidney transplant recipients.

The secondary end points included renal function as indicated by the calculated GFR with the use of Schwartz formulation during the course of the study, changes in blood pressure, fasting blood glucose and blood lipid profile, event rate of biopsy-proven acute rejection, incidence of patient-reporting adverse events (AEs), and all AEs including biochemical and hematological assessment. Intra-individual variability (IIV) of tacrolimus levels was also compared (17). For calculation and comparison of IIV between two formulations, the results of the tacrolimus-level measurement between 6 months prior to drug switching and 6 months after drug switching were included.

Genetic polymorphism

Data on the genetic polymorphisms of *CYP3A5* 6986A>G could be obtained from previous studies in 27 patients. Genotyping protocol was published in a previous study (18).

Survey

An immunosuppressant therapy barrier scale (ITBS) was used to measure the impact of drug conversion on the adherence to patients' immunosuppressive medication (19). The ITBS was a valid and reliable instrument to assess patients' adherence barriers and was administered on Day 7 (before conversion) and on Day 180 in all patients. For this study, the additional statement of ''The immunosuppressant medication(s) affects my daily life'', which has not been validated, was added in order to better understand effect of drug conversion on adherence, and the 13th statement related with drug cost was removed because 'National Health Insurance Cooperation' always covers the immunosuppressive drug cost in Korea. The survey was completed by the interview with the patients' parents.

Statistical analyses

Statistical comparisons of tacrolimus exposure ($AUC_{0–24}$) and C_{min} at steady state (Day 7 for Tac-BID, Day 14 and Day 28 for Tac-OD) were performed using a 90% confidence interval (CI) approach. The primary end point (comparability of $AUC_{0–24}$ between Days 7 and 14) comparison was performed by testing for noninferiority. A 90% CI was constructed for the difference in mean natural log-transformed data between Tac-BID and Tac-OD. The CI was transformed back to the original scale and compared to an 80–125% range to determine the equivalence of tacrolimus exposure. In addition, a statistical analysis of $AUC_{0–24}$ and C_{min} using total daily dose (dose-adjusted) was also performed. Previous studies indicate that $AUC_{0–24}$ can be estimated at 200 ± 80 ng h/mL (8,13,20). An estimated 34 patients would be required to reach a power of 80% to show noninferiority. To account for 10% of patients who will drop out of the study, 38 patients were enrolled.

Statistical analyses were conducted using SPSS software version 17.0 (SPSS, Inc., Chicago, IL). All tests were two tailed, and differences at p-values of <0.05 were considered significant.

Results

Patients

A total of 38 patients were enrolled in the study. Four patients were excluded from the pharmacokinetic evaluation because of protocol violation or incomplete pharmacokinetic profiles resulting from poor venous access. All 34 patients had evaluable pharmacokinetic profiles on all of the three time points as well as the safety data for the 6 months postconversion.

The mean age was 12.3 ± 2.8 years (range: 7.0–15.9 years) and the patients in this study received their grafts 40.3 ± 22.3 months before conversion to Tac-OD (Table 1). None of the patients had hyperlipidemia or diabetes mellitus, and 18 patients (52.9%) had received antihypertensive medications at baseline. No patients had neurological symptoms such as insomnia or tremor at study entry. None of the patients received non–immunosuppressive drugs that interact with tacrolimus.

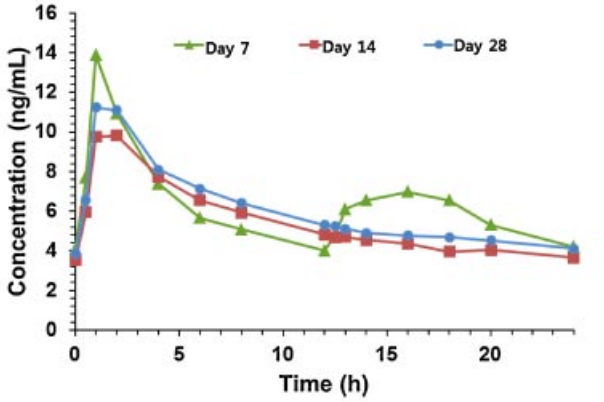
The total daily dose of Tac-BID was 3.69 ± 1.40 mg (0.10 ± 0.04 mg/kg) before drug conversion. Thirty-three (97.1%) patients received mycophenolate mofetil, one patient (2.9%) was administered azathioprine and seven patients (20.6%) received prednisone at the time of study entry. All of the patients receiving adjunctive immunosuppressive medications continued to receive the same doses of their medications throughout the study period.

Tacrolimus exposure

Figure 2 shows tacrolimus time-concentration curves and provides a summary of pharmacokinetic parameters on each time point. Taken as a whole, the mean blood trough concentration and $AUC_{0–24}$ were significantly decreased from 4.10 ± 1.16 to 3.53 ± 1.10 ng/mL ($p = 0.004$), and from 151.8 ± 41.6 to 129.8 ± 39.3 ng h/mL ($p < 0.001$),

Table 1: Summary of patient baseline characteristics

Patient characteristics	n = 34
Male, n (%)	20 (58.8)
Living donation, n (%)	18 (52.9)
Height (cm), mean (range)	143.7 (107.7–170.0)
Weight (kg), mean ± SD	40.7 ± 15.3
BMI, mean ± SD	19.0 ± 3.8
Age at conversion (years)	
Mean ± SD	12.3 ± 2.8
Median	12.5
Range	7.0–15.9
Time from transplantation to conversion (months)	
Mean ± SD	40.3 ± 22.3
Median	34.0
Range	14.0–106.0
Pre–existing conditions (%)	
Diabetes/hypertension/hyperlipidemia	0/52.9/0
Total daily dose of prograf at baseline (mg)	
Mean ± SD	3.69 ± 1.40
Median	4.0
Range	1.5–6.0
Adjunctive immunosuppressive regimen	
Mycophenolate mofetil, N (%)	33 (97.1)
Prednisolone, N (%)	7 (20.6)
Azathioprine, N (%)	1 (2.9)



	Day 7	Day 14	Day 28
C_0 (ng/mL)	4.10±1.16	**3.53±1.10	3.87±1.06
AUC_{0-24} (ng.h/mL)	151.8±41.6	**129.8±39.3	144.9±37.1
C_{max} (ng/mL)	14.4±5.1	**11.4±4.0	*12.5±4.4
T_{max} (hr)	1.3±0.6	**1.8±0.9	*1.8±1.2
Daily dose (mg)	3.69±1.40	3.69±1.40	3.66±1.32
Daily dose per weight (mg/Kg)	0.099±0.04	0.099±0.04	0.100±0.04

Figure 2: Summary of mean blood tacrolimus concentration-time profiles and tacrolimus pharmacokinetic parameters for Day 7 (Tac-BID), Day 14 (Tac-OD, 1 week after mg:mg conversion) and Day 28 (Tac-OD, after Tac-OD dose-adjustment) . Tac-BID, twice-daily tacrolimus; Tac-OD, once-daily tacrolimus. *$p < 0.05$, **$p < 0.01$; compared with Day 7.

respectively, after drug conversion on a 1:1 basis for total daily dose. The peak blood concentration of tacrolimus was also significantly decreased to 11.4 ± 4.0 ng/mL ($p = 0.001$), as expected. However, changes in pharmacokinetic parameters were highly variable in the individual cases (Figure S1). Tacrolimus trough concentration and even C_{max} was increased in nine patients. Therefore, in more than 70% of patients, the Tac-OD dose needed to be adjusted to achieve preconversion tacrolimus trough concentration and only 10 (29.4%) of the 34 pediatric patients did not require a dose adjustment; the dose was increased for 15 (44.1%) patients (3.3 ± 1.4–3.9 ± 1.4 mg/day, $p < 0.001$) and was decreased for 9 (26.5%) patients (4.7 ± 1.4–3.7 ± 1.5 mg/day, $p = 0.021$). After dose adjustment, C_0 (3.87 ± 1.06 ng/mL) and AUC_{0-24} (144.9 ± 37.1 ng h/mL) on Day 28 were comparable with those on Day 7. Interestingly, the dose of Tac-OD (3.66 ± 1.32 mg/day) was similar with that of preconversion Tac-BID (3.69 ± 1.40 mg/day, $p = 0.843$) despite dose adjustment in more than 70% of patients (Figure 2).

Patients with CYP3A5*3/*3 genotype (CYP3A5 nonexpressers) tended to experience significantly decreased dose-normalized C_0 and AUC_{0-24} after mg:mg-based drug conversion (Table 2). No other clinical characteristics including age, body weight and body mass index were associated with tacrolimus dose change.

Tacrolimus pharmacokinetics

There was a similar correlation between AUC_{0-24} and C_{min} for both tacrolimus formulations, with the correlation coefficient for Tac-BID (0.784) on study Day 7 being similar to Tac-OD (0.754) on Day 14 (Figure S2).

The equivalence of tacrolimus exposure was not demonstrated based on $lnAUC_{0-24}$ at steady state (Table 3); the ratio of $lnAUC_{0-24}$ for Tac-OD/Tac-BID was 84.7 with 90% CI of 79.1–90.8% after mg:mg conversion. In spite of dose adjustment, the ratio of $lnAUC_{0-24}$ was 87.8 (90% CI: 78.1–98.9%) on study Day 28. These ranges of CIs did not meet the accepted limits of 80–125% for equivalence. lnC_{min} and lnC_{max} were also not demonstrated to be equivalent; the 90% CIs were 78.7–93.0% and 70.7–89.1%, respectively, on Day 14.

The mean dose-normalized IIV of the Tac-OD oral clearance was 21.4 ± 7.6%, and this was significantly higher than that of the Tac-BID oral clearance (16.5 ± 10.2%, $p = 0.033$).

Clinical results

There were no cases of discontinuation of Tac-OD, acute rejection, clinically indicated allograft biopsy, graft loss or

Table 2: Effects of *CYP3A5* genetic polymorphism on the pharmacokinetic variability

	CYP3A5 expresser (n = 10)			CYP3A5 nonexpresser (n = 17)		
	Day 7	Day 14	p-value	Day 7	Day 14	p-value
Dose/weight (mg/kg)	0.121 ± 0.045			0.075 ± 0.029		
C_0 (ng/mL)	3.87 ± 1.06	3.39 ± 0.91	0.266	4.07 ± 0.93	3.38 ± 1.12	0.019
C_{max} (ng/mL)	13.7 ± 5.4	12.3 ± 3.0	0.508	12.3 ± 5.4	8.2 ± 3.4	<0.001
T_{max} (h)	1.1 ± 0.3	1.4 ± 0.5	0.250	1.5 ± 0.8	2.3 ± 1.1	0.037
AUC_{0-24} (ng h/mL)	149.3 ± 36.6	125.8 ± 27.3	0.105	135.4 ± 49.1	110.4 ± 47.1	<0.001
Dose-normalized C_0 (ng/mL/mg/kg)	38.1 ± 19.9	32.5 ± 18.2	0.232	65.1 ± 38.3	52.3 ± 25.8	0.026
Dose-normalized C_{max} (ng/mL/mg/kg)	137.5 ± 88.5	116.7 ± 59.3	0.432	183.2 ± 99.2	128.1 ± 79.0	0.001
Dose-normalized AUC_{0-24} (ng h/mL/mg/kg)	1460.5 ± 769.6	1216.1 ± 630.4	0.002	2090.2 ± 1200.4	1705.2 ± 1029.5	<0.001

Table 3: Equivalence of tacrolimus exposure

	Tac-BID LS mean	Tac-OD LS mean	Ratio (Tac-OD/Tac-BID)	90% CI
Nondose-adjusted data				
Day 7 vs. Day 14 (after mg:mg conversion)				
ln(AUC_{0-24})	151.7	129.8	84.7	79.1–90.8
ln(C_{min})	4.19	3.65	85.5	78.7–93.0
ln(C_{max})	13.4	10.6	79.4	70.7–89.1
Day 7 vs. Day 28 (after dose adjustment)				
ln(AUC_{0-24})	151.7	144.9	87.8	78.1–98.9
ln(C_{min})	4.19	4.12	96.5	89.1–104.4
ln(C_{max})	13.4	11.8	88.4	78.7–99.3
Dose-adjusted data				
Day 7 vs. Day 14 (after mg:mg conversion)				
ln(AUC_{0-24})	42.7	36.2	84.7	79.1–90.8
ln(C_{min})	1.15	0.99	85.7	78.8–93.2
ln(C_{max})	3.92	3.11	79.4	70.7–89.2
Day 7 vs. Day 28 (after dose adjustment)				
ln(AUC_{0-24})	42.7	40.9	95.7	88.7–103.3
ln(C_{min})	1.15	1.08	94.1	84.2–105.1
ln(C_{max})	3.92	3.44	87.9	78.1–98.9

LS mean from ANOVA. Natural log (ln) parameter means, ratios and confidence intervals were calculated by transforming the natural log means back to the linear scales.
Tac-BID, twice-daily tacrolimus; Tac-OD, once-daily tacrolimus; CI, confidence interval.

patient death at any time during the 6-month post–conversion extension period.

Mean eGFR was 79.6 ± 27.0 mL/min at the end of the study and this was comparable to the baseline renal function (77.8 ± 27.9 mL/min, $p = 0.223$). Drug conversion to Tac-OD had a positive effect on hypertension. The amount of anti-hypertensive medication administered was significantly decreased from 0.65 ± 0.8 to 0.5 ± 0.7 ($p = 0.007$), with blood pressure remaining stable throughout the 6-month postconversion period. The fasting serum glucose level was slightly decreased from 93.6 ± 7.8 to 90.7 ± 7.9 mg/dL ($p = 0.061$) in spite of no cases of diabetes mellitus.

No AEs were reported and no patients needed to discontinue Tac-OD due to AEs during the 6-month post–conversion period. There were also no remarkable findings in clinical laboratory profiles including blood urea nitrogen, serum albumin, total bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, hemoglobin, hematocrit, total cholesterol and low-density lipoprotein cholesterol.

Adherence

All of 34 patients completed the modified ITBS. Drug conversion to Tac-OD had a beneficial effect on patients' barrier to immunosuppressants adherence (Table S1). More than 70% of patients 'strongly agree or agree' with the statement 'the immunosuppressant medication(s) affects my daily life' before drug conversion. However, this answer changed to 'disagree or strongly disagree' in 63.6% of patients after drug conversion ($p < 0.001$). Tac-OD had a positive effect on the perceptual complexity of dosing frequency ($p = 0.001$), and on the burden of capsules (or tablets) number ($p = 0.001$).

Discussion

In the previous pediatric liver study, Heffron et al. (13) showed the difference in exposure between Tac-BID and Tac-OD was not apparent while studies for adult transplant patients consistently showed that AUC_{0-24} and C_{min} were lower for Tac-OD compared with Tac-BID (9,10). Therefore, some authors have suggested a possible modifying influence of young age on between-formulation pharmacokinetic variability (11). In this study, however, we clearly show for the first time that exceedingly high percentages of stable pediatric transplant patients experience highly variable changes in pharmacokinetic parameters when their medications are converted from Tac-BID to Tac-OD. Therefore, in more than 70% of patients, the tacrolimus dose needed to be changed to adjust the baseline tacrolimus exposure. The equivalence of tacrolimus exposure was not demonstrated at Day 14 (1 week after mg:mg conversion) and even at Day 28 (after Tac-OD dose adjustment). These findings in pediatric transplant patients are similar to those recently published studies in adult transplant patients (9,10).

The oral clearance of Tac-OD has been reported to be lower in patients with CYP3A5*3/*3 (15). In this study, the *CYP3A5* genetic polymorphism is the only covariate that influences the pharmacokinetics of Tac-OD.

Conversion from Tac-BID to Tac-OD did not affect the mean C_0 and AUC_{0-24} in patients carrying *CYP3A5**1 allele but patients with *CYP3A5**3/*3 had a significantly lower C_0, C_{max} and AUC_{0-24} after conversion (Table 2). This result is compatible with the result from the previous study in adult patients (21) and is partly explained by the evidence that suggests that the CYP3A5 messenger RNA and protein levels may be higher in the proximal small intestine (22). However, two studies with small number of patients have showed the opposite impact of *CYP3A5* polymorphisms on the pharmacokinetics of Tac-OD, and tacrolimus exposure significantly decreased in CYP3A5 expressers in stable or *de novo* renal transplant patients (23,24). Further research into this controversial impact of *CYP3A5* polymorphisms during formulation switching is required.

A high intraindividual pharmacokinetic variability of tacrolimus has been associated with a poor long-term transplant outcome (17,25). This study shows that IIV of dose-normalized C_{min} in pediatric patients is significantly higher for Tac-OD compared with Tac-BID ($21.4 \pm 7.6\%$ vs. $16.5 \pm 10.2\%$, $p = 0.033$). Although this may be partially caused by the dose change in 70% of patients after drug conversion, transplant physicians need to pay particular attention to the within-subject variability of tacrolimus oral clearance during Tac-OD therapy in pediatric transplant patients.

Despite the variable changes in tacrolimus pharmacokinetic parameters and significant dose adjustment when converting to Tac-OD, no serious AEs were shown. In addition, some benefits were shown in cardiovascular risk factors. Impaired insulin secretion from pancreatic beta cells, changes in hemodynamics and intense renal vasoconstriction can be caused by tacrolimus. Given these effects are related to the tacrolimus dose and concentration, Tac-OD may have beneficial effects on glucose metabolism and blood pressure due to low peak concentration compared with Tac-BID (26–28). In the clinical perspectives, these positive effects are quite important because cardiovascular disease is a leading cause of death after kidney transplantation in pediatrics as well as adults (29,30). Considering that Tac-OD can improve patient adherence to immunosuppressants by reducing barriers to adherence (Table S1), the beneficial effects of Tac-OD in the long-term outcome is certainly worth investigating.

This study has several limitations such as the small study population, the single ethnic group and short follow-up period. Because no patient had neurological side effects at baseline, effect of drug conversion on those side effects of tacrolimus was not able to be investigated in this study and this should be evaluated in future studies. The survey data should be interpreted with caution because the modification is not validated and it is not clear how many patients take medication on their own. However, this study clearly shows that the conversion of Tac-BID to Tac-OD results in highly variable changes in pharmacokinetic parameters of tacrolimus in stable pediatric kidney transplant patients.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Figure S1. Changes of pharmacokinetic parameters after 1:1 based conversion in individual cases.

Figure S2. Correlation of $AUC_{0–24}$ and C_{min} for Days 7, 14 and 28.

Table S1. Results of modified immunosuppressant therapy barrier scale (ITBS) survey