# Effect on Dosage Change and Intrapatient Variability After Conversion From Twice-Daily to Once-Daily Tacrolimus Among Thai Kidney Transplant Patients With and Without CYP3A4/5 Inhibitors

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ABSTRACT

Background. Converting to once-daily tacrolimus (Advagraf [Adv]) among renal transplant patients results in better drug adherence. Data regarding dosage and intrapatient variability changes after conversion among patients with CYP3A4/5 inhibitors (CYPinh) is lacking.

Method. A retrospective chart review among all kidney transplant recipients at Siriraj Hospital was performed. Patients were enrolled who had been on standard release twice-daily tacrolimus and subsequently replaced it with Adv for at least 6 months with no change in CYPinh type or dosage.

Results. Fifty-three patients were eligible. Conversion occurred at a mean time after transplant of 51.25 (SD, 40.30) months. Ten patients (18.9%) did not receive CYPinh, while 19 (35.8%), 21 (39.6%), and 3 (5.7%) received diltiazem, ketoconazole or fluconazole, and both diltiazem and ketoconazole, respectively. After conversion, median increment of tacrolimus dosage was 14.29% (−50% to 167%), while no significant change in IPV was demonstrated (17.46% [SD, 11.25%] vs 14.83% [SD, 6.78]; $P = .11$). Patients receiving azole had less dosage increment than those not receiving CYPinh ($P = .02$). After conversion, 14 of 22 patients with IPV $> 17\%$ (63.6%) had reduced IPV to $\leq 17\%$, while 25.8% of patients with lower IPV had an increase in IPV $> 17\%$.

Conclusion. Conversion to Adv required a dosage increment of 30% to achieve the same trough level. Concomitant use of CYPinh significantly reduced tacrolimus dose increment. A trend was noted toward improved IPV after conversion. Conversion to Adv resulted in better IPV among patients with high IPV while receiving twice-daily tacrolimus.

CONVERTING from standard release twice-daily tacrolimus (Tac bid) to the once-daily formulation (Advagraf [Adv]) among kidney transplant (KT) patients has advantages in better drug adherence and reduced interaction with other drugs and meals [1,2]. A conversion ratio of drug dosage of 1:1 is suggested among stable renal recipients [3], but several publications demonstrated an increment of total daily dose by 10% to 30% to achieve the same target trough level [4,5].

Intrapatient variability (IPV) of tacrolimus represents the amount of fluctuation of trough level over a definite period of time. The pivotal factor affecting IPV is drug compliance. High IPV in tacrolimus exposure is associated with acute rejection and worse allograft outcome [6–8]. Conflicting evidence exists regarding improved IPV after conversion [9–11].

To minimize drug expenses, we have still prescribed cytochrome P450 (CYP) 3A4/5 inhibitors to increase the trough level of calcineurin inhibitors as recommended by Kidney Disease: Improving Global Outcomes guideline [12]. Data regarding alteration of drug dosage and IPV after conversion to Adv among patients receiving CYP3A4 inhibitors is still lacking. Thus, we conducted this study to determine change in

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IPV and total daily dosage of tacrolimus after converting from Tac bid to Adv.

## MATERIAL AND METHODS

We performed a retrospective chart review among all adult KT and simultaneous pancreas kidney transplant recipients followed up at Siriraj Hospital between January 1, 2014, and December 31, 2017. This study was approved by the ethics committee of the Faculty of Medicine Siriraj Hospital. Patients undergoing a conversion from Tac bid to Adv at more than 6 months after transplant were enrolled. All patients in our study had received both Tac bid and Adv for at least 6 months. Exclusion criteria comprised (1) receiving additional or adjusted drug dosages that inhibit or enhance CYP3A4/5 activity within 6 months pre- and postconversion, (2) switching mycophenolate to mammalian target of rapamycin inhibitors within 6 months before and after conversion or vice versa, (3) extreme noncompliance despite comprehensive education, and (4) estimated glomerular filtration rate $\geq$ 15.0 mL/min/1.73 $m^2$ at time of conversion.

Medical records were reviewed for baseline characteristics, immunosuppression, doses, and trough level of tacrolimus before and after conversion, dose and type of CYP3A4/5 inhibitors (CYPinh), and complications. Intrapatient variability was calculated using the coefficient of variation from at least 5 consecutive samples based on the dose-adjusted trough level of tacrolimus within 1 year before and after conversion. Because of altered tacrolimus level in the early phase of postconversion, all patients had at least 1 occasion of drug level monitoring within 1 month after switching. We calculated the change in drug dosage and IPV post conversion when achieving stable tacrolimus level but not beyond 3 months after switching.

Baseline characteristics and demographic data were summarized as percentage or mean (SD) for normally distributed data or median with interquartile ranges for others. Categorical variables were compared using the $\chi^2$ test. Continuous variables were compared using the *t* test or Mann-Whitney test. Continuous data between pre- and postconversion were compared by paired *t* test. All statistical analyses were executed using SPSS Version 17.0 (IBM, Armonk, NY, United States).

## RESULTS

Of 90 patients receiving Adv in our center, 53 were eligible for this study. All enrolled patients had been regularly followed up at our center with mean follow-up time of 82.1 (SD, 42.9) months. Conversion from Tac bid to Adv occurred 50.1 (41.0) months post KT. Baseline demographic data are shown in Table 1. Most patients received concomitant mycophenolate (94.3%) with mean daily dosage of **1250** (SD, 396) mg equivalent to mycophenolate mofetil. Two patients (3.8%) received tacrolimus along with everolimus. Prednisolone was prescribed for 49 patients (92.5%) with mean daily dosage **4.29** (1.29) mg. Ten patients (18.9%) did not receive any CYPinh, while 19 (35.8%), 11 (20.8%), and 10 (18.9%) received diltiazem, ketoconazole, and fluconazole, respectively. Three patients (5.7%) received both ketoconazole and diltiazem. Mean daily dosage of Tac bid among patients not receiving CYPinh did not differ from patients in the CYPinh group (0.055 [SD, 0.037] vs 0.051 [SD, 0.052] mg/kg; $P = .78$).

**Table 1. Baseline Characteristics for All Enrolled Patients**

| Characteristics | Value |
|---|---|
| Age at KT, mean (SD), y | 40.8 (11.0) |
| Follow-up time after KT, mean (SD), mo | 82.1 (42.9) |
| Conversion time after KT, mean (SD), mo | 50.1 (41.9) |
| Female sex, No. (%) | 24/53 (45.3) |
| Simultaneous pancreas KT, No. (%) | 3/53 (5.7) |
| Previous KT, No. (%) | 2/53 (3.8) |
| Living donor KT, No. (%) | 32/53 (60.4) |
| HLA mismatch, No. (range) | 3 (0–6) |
| History of chronic active ABMR, No. (%) | 12/53 (22.6) |
| History of nonadherence, No. (%) | 6/53 (11.3) |

Abbreviations: ABMR, antibody-mediated rejection; KT, kidney transplant.

After conversion for 3 months, mean daily tacrolimus dosage was increased from **0.053** (SD, 0.050) mg/kg to **0.061** (SD, 0.050) mg/kg ($P = .009$), which was 129.9% (SD, 53.4%) of the total daily dosage of Tac bid. Mean tacrolimus level after switching decreased by 16.3% (SD, 19.4%). Percentage of change of daily dosage of tacrolimus and mean tacrolimus level of all patients at 3 months are shown in Fig 1. At 6 months after conversion, mean daily Adv dosage was 120.29% (SD, 20.49%) of the Tac bid dose.

Patients receiving CYPinh had a lower increase in tacrolimus dosage compared with those in the no CYPinh group (123.3% [SD, 50.5%] vs 162.0% [SD, 62.4%] of total daily dosage of Tac bid; $P = .04$). Eight of 10 patients (80%) in the no CYPinh group required dose escalation, with the highest increment of 166.67% of Tac bid dose in 2 patients. Patients receiving only diltiazem tended to need more dose increment than patients receiving fluconazole or ketoconazole but without statistical significance (134.6% [SD, 46.1%] vs 112.8% [SD, 49.8%] of total daily dosage of Tac bid; $P = .15$). However, dose increment was significantly higher among patients receiving azole than those in the no CYPinh group ($P = .02$). Eleven of 19 patients (57.9%) in the diltiazem alone group and 9 of 24 patients (37.5%) receiving fluconazole or ketoconazole required higher daily tacrolimus dose after conversion.

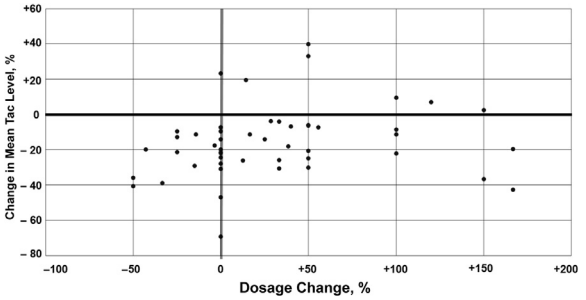


**Fig 1.** Scatter plot between percentage of dosage change and percentage of change in mean tacrolimus level of all enrolled patients after conversion for 3 months. Most patients needed higher daily dosage of Adv but lower tacrolimus trough level after conversion. Adv, once-daily tacrolimus (Advagraf).

Intrapatient variability tended to decrease after conversion but without statistical significance (Tac 17.46% [SD, 11.25%] vs Adv 14.83% [SD, 6.78%]; $P = .11$). The IPV of all enrolled patients is shown in Fig 2. Change of IPV after conversion did not significantly differ between patients who received CYPinh and those in the no CYPinh group (−1.48% [SD, 10.22%] vs −7.54% [SD, 16.78%], respectively; $P = .15$). After dividing patients in 2 groups using mean IPV of Tac bid as a cutoff, 22 patients had IPV > 17% and 31 patients had IPV ≤ 17%. Fourteen of 22 patients with IPV > 17% preconversion (63.6%) had significant reduction of IPV to ≤ 17% after conversion. In addition, 8 of 31 patients with IPV ≤ 17% before conversion (25.8%) increased IPV to > 17% post conversion; IPV significantly decreased after conversion among patients having IPV > 17% compared with those in the lower IPV group (−10.95% [SD, 12.91%] vs +3.29% [SD, 6.08%], respectively; $P < .001$).

The conversion was clinically well tolerated. Serum creatinine remained stable over a 1-year period after conversion (1.52 [SD, 0.54] mg/dL vs 1.46 [SD, 0.46] mg/dL; $P = .24$). There was no newly diagnosed biopsy-proven acute rejection during the study period. One patient died of serious infection at 9 months after conversion.

## DISCUSSION

Once-daily tacrolimus has an advantage in better drug adherence, which may reduce rejection and result in superior allograft outcome. The conversion ratio of 1:1 is recommended for stable KT patients, but several studies showed a significantly reduced tacrolimus trough level after conversion with this ratio [4,5,10]. Lower target trough level of extended-released tacrolimus was associated with a later significant increase in incidence of acute rejection, subclinical allograft inflammation, and occurrence of donor-specific antibodies [12]. Although duration of insufficient tacrolimus level after conversion might not be as long as in this study [12], close monitoring and adjusting trough level post conversion was required. Our study revealed a 30% increase in daily dosage of tacrolimus despite lower mean tacrolimus level after conversion, similar to a study in an Asian population [13]. However, unlike the related study showing no difference in dose increment between the patients with and without diltiazem [3], our larger scale of patients receiving CYPinh (especially ketoconazole or fluconazole) needed less increase in tacrolimus dosage after conversion.

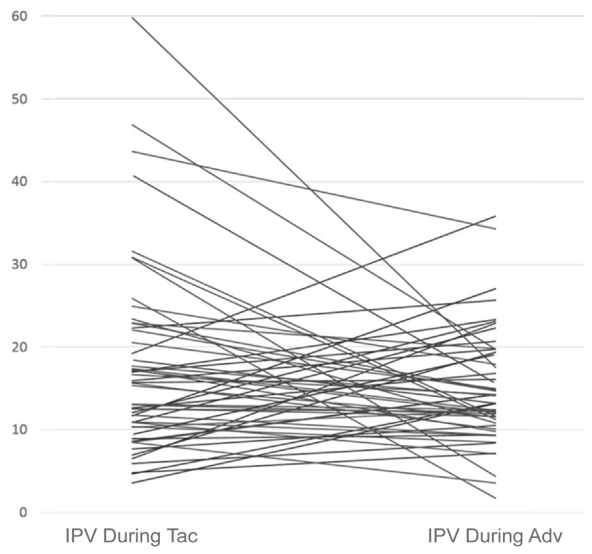


**Fig 2.** IPV of all enrolled patients compared between receiving Tac bid and Adv.Adv, once-daily tacrolimus (Advagraf); IPV, intrapatient variation; Tac bid, standard release twice-daily tacrolimus.

Difference in dose increment according to CYPinh might indicate that CYP plays a role in change of dosage after conversion. Even though tacrolimus is principally metabolized by CYP3A4 genetic variation, which mainly affected tacrolimus trough level in Asian populations, it is a polymorphism of CYP3A5. The presence of the *CYP3A5*1* allele (*1/*1 or *1/*3) is associated with abundant production of functional enzyme, leading to a faster rate of metabolism and lower tacrolimus trough level than *CYP3A5*3* carriers. The frequency of the *CYP3A5*1* allele is higher in Thai than in white populations (47% vs 10%) [14].

From our study, concomitant use of CYPinh, which impeded drug metabolism by both CYP3A4 and CYP3A5, may contribute to a lower dose increment after conversion. Thus, patients receiving ketoconazole or fluconazole, which constitute the most potent inhibitors, had the lowest dose increment. The percentage of dosage increase in the no CYPinh group, which was as high as 62%, may also have been caused by CYP expression. Despite no use of CYPinh, total daily Tac bid dosage was quite equal; therefore, patients in this group may possibly have *CYP3A5*3/*3* alleles. Wehland et al reported a significant decline in tacrolimus trough level after conversion in *CYP3A5*3/*3* carriers, and this group of patients required 153% of Tac bid dose to achieve the same target level, which is relatively comparable with our study [11].

The benefit of Adv as once-daily formulation in drug adherence should be demonstrated by better IPV. Wu et al [9] reported a significant reduction in IPV from 14% to 8.5% among 129 stable KT patients after conversion. However, Shuker et al revealed no difference in IPV after conversion in a larger scale of patients (17% vs 16%; $P = .31$) [10]. The possible cause of such dissimilarity might be from the difference in the number of trough levels used in calculating IPV between pre- and postconversion in the study of Wu et al [9]; more samples in the postconversion phase could have determined more accurate IPV.

Our study demonstrated no significant change in mean IPV, which was calculated from a median of 5 consecutive samples both pre- and post phase. However, conversion to Adv still improved IPV among patients with high IPV while

receiving Tac bid after ensuring their adherence. Better IPV in this group of patients may have resulted from reduced drug interaction with food intake or have enhanced the compliance. However, some patients with low IPV while receiving Tac bid had a significant increase in IPV after conversion, mostly caused by a meaningful drop in trough level after switching, requiring several adjustments in dosages. Hence, conversion at a ratio of 1:1.3 may be more appropriate to avoid lower trough level in Asian populations.

Data regarding change of IPV among patients receiving CYPinh are limited. Concomitant use of CYPinh increases the complexity of the drug regimen, which may result in poorer compliance. Nevertheless, because dosage formulation of tacrolimus in Thailand is available at only **1.0** mg per tablet, use of CYPinh still decreased the total daily number of pills, which might be helpful for good compliance. Our study revealed no different change of IPV after conversion whether the patients received CYPinh or not.

Our study is the first to demonstrate the effect of CYPinh, especially in the azole group, regarding change of tacrolimus dosage and IPV after conversion from Tac bid to Adv. This might confirm the role of CYP3A5 in dosage change post conversion. However, some limitations in our study comprised being a single center, the retrospective nature of the study design, and no result concerning CYP3A5 expression. However, we collected data from all patients in our KT database, which may reflect the real-life clinical practice.

## CONCLUSION

Conversion from Tac bid to Adv among Thai renal transplant recipients required an increment in daily dosage by 30% to achieve the same trough level. Concomitant use of CYPinh significantly reduced tacrolimus dose increase after conversion. A trend was noted toward improved IPV after converting to Adv. For patients with high IPV while receiving Tac bid, change to Adv may result in better IPV; however, long-term benefits should be further elucidated.

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