Pilot Study Comparing the Efficacy, Safety, Convertibility, and Tacrolimus Trough Levels of Twice-Daily Tacrolimus (Prograf) to Once-Daily Tacrolimus (Advagraf) Among Standard-Risk Kidney Transplant Patients at the National Kidney and Transplant Institute

Romina A. Danguilan*, Arlene Lamban, and Glenda Eleanor P. Pamugas

Department of Adult Nephrology, National Kidney and Transplant Institute, Quezon City, Philippines

ABSTRACT

Background. Recently, a once-daily formulation of tacrolimus (Advagraf) was released in the Philippines. Studies have shown that these 2 formulations are bioequivalent at a 1:1 conversion. This study aims to determine the efficacy, safety, convertibility, and tacrolimus trough level of once-daily tacrolimus at the end of 6 months post transplant.

Methods. This is a randomized study among standard-risk primary kidney transplant patients performed at the National Kidney and Transplant Institute, Philippines. A total of 40 patients completed the 6-month follow-up. Patients in Group A who failed to meet the criteria for conversion to once-daily tacrolimus were considered to have reached the end of the study, while patients who satisfied the conversion criteria will be followed up for an additional 6 months.

Results. Baseline characteristics were similar in both groups. The area under the curve, maximum concentration, time to achieve the maximum concentration, and the coefficient of variation were similar. The twice-daily tacrolimus (Prograf) group patients had significantly higher mean tacrolimus trough levels than the Group B once-daily tacrolimus patients. An increase of a once-daily tacrolimus mean dose of 8% was required to achieve a therapeutic drug level post conversion. The graft and patient survival were 100%. There was no biopsy-proven acute rejection noted either both group.

Conclusion. In conclusion, conversion from twice-daily tacrolimus to once-daily tacrolimus in kidney transplant in both de novo and converted patients after KT is safe, ensuring greater stability of drug blood concentrations than the standard form. The results also suggest an 8% increase when converting stable KT patients from twice-daily tacrolimus to once-daily tacrolimus.

RECENTLY, a once-daily formulation of tacrolimus (Advagraf) was released in the Philippine market. Studies have shown that the tacrolimus (Prograf) and tacrolimus prolonged-release (Advagraf) formulations are bioequivalent at a 1:1 conversion [1]. The once-daily tacrolimus fulfills the criteria of the European Medicines Agency and US Food and Drug Administration for bioequivalence; however, recent trials have shown lower tacrolimus exposure, especially in the early post-transplant period. Doses of once-daily tacrolimus had to be increased by up to 50% in some patients until 6 months post transplant and showed that the doses of once-daily tacrolimus had to be increased by 20% to 50% in some patients to achieve similar minimum concentration values [2]. Thus,

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*Address correspondence to Romina A. Danguilan, MD, Department of Adult Nephrology, National Kidney and Transplant Institute, East Ave, Diliman, Quezon City, Philippines 1101. Tel: 6329810300 loc 4430; Fax: 6329810368. E-mail: dr.radanguilan@gmail.com or melhatraarakama@gmail.com

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higher doses of once-daily tacrolimus compared with twice-daily tacrolimus were required to achieve similar minimum concentration values.

One important feature of once-daily tacrolimus is its once-daily formulation is considered an advantage especially in promoting compliance of medication intake. Among American adult renal transplant patients, the median rate of nonadherence is about 22%, is associated with acute rejection, and results in 36% of all graft losses [3]. Bloom found that compliance decreases by 6% when you give a twice-daily medication compared with a sustained-release, once-daily dosing regimen [4].

This study aims to determine the efficacy, safety, and convertibility of prolonged-release tacrolimus among Filipino patients at the National Kidney and Transplant Institute (NKTI). This is an investigator-initiated trial with partial financial assistance from Astellas Philippines for financial support.

METHODOLOGY

This is a randomized controlled study among patients who underwent kidney transplant in NKTI. The inclusion criteria for the study were age of 18 years, primary kidney transplant with a living donor with standard immunologic risk (negative panel-reactive antibody screen, or panel-reactive antibody specific $< 20\%$, at least 1 donor-recipient match), initial prescription of standard doses of induction therapy with either basiliximab or rabbit antithymocyte globulin, and signed informed consent.

Randomization was done by drawing lots for the first patient for Group A (twice-daily tacrolimus) then alternately until we reached 20 participants for each group. They were followed up for a total duration of 9 months for Group A (twice-daily tacrolimus) and 6 months for Group B (once-daily tacrolimus). Patients in Group A who had a stable graft function with creatinine clearance of not less than 60 mL/min; had no current active infection, drug intolerance, or hematologic problems; and were compliant with drug intake and follow-up schedules were converted to once-daily tacrolimus. Patients who failed to meet the criteria for conversion to once-daily tacrolimus were considered to have reached the end of the study, while patients who satisfied the conversion criteria were followed up for an additional 6 months while they were taking once-daily tacrolimus.

The patients were given tacrolimus 1 day prior to the transplant. Group A patients were given twice-daily tacrolimus at 0.08 to 0.1 mg/kg in 2 divided doses while Group B patients received once-daily tacrolimus at a dose of 0.08 to 0.1 mg/kg once a day. Administration of induction was according to center protocol using standard doses of either basiliximab or rabbit antithymocyte globulin. Both patient groups were placed on standard doses of mycophenolate and prednisone as per hospital practice. Routine prophylactic antibiotics were given, such as trimethoprim-sulfamethoxazole 800/160 mg 3 times a week for 4 months, isoniazid 300 mg once a day for 6 months, valacyclovir 500mg, and nystatin (Mycostatin) 5 cc gargle and swallow 3 times a day for 1 month.

The Group A (twice-daily tacrolimus) patients were followed up weekly on the first month, then fortnightly thereafter until the third month. Patients who fulfilled the criteria for conversion were shifted to once-daily tacrolimus with the same equivalent dose at 1:1 conversion at 3 months post kidney transplant given once a day. Patients who did not qualify for conversion to once-daily tacrolimus were considered to have reached the end of the study at 3 months, while patients who were converted to once-daily tacrolimus were followed up similar to the de novo once-daily tacrolimus patients (Group B) for an additional 6 months. The Group B (once-daily tacrolimus) patients were followed up weekly during the first month of surgery then fortnightly until the sixth month post transplant.

The area under the curve (AUC), maximum concentration (Cmax), and time to achieve the maximum concentration (Tmax) were determined. The abbreviated AUC was measured by obtaining a 3-point blood level determination using C0 (trough), C2, and C4. This finding was shown by Wong et al to have a 93% correlation with the full AUC [5]. An abbreviated AUC profile was done on day 2 post transplant using C0, C2, and C4 determinations for all the patients.

The tacrolimus dose for both groups was adjusted to maintain a C0 (trough) level of 3 to 7 ng/mL as recommended by Eckberg et al (Symphony Trial) for patients given induction [6]. Therapeutic drug monitoring using C0 (trough) levels with appropriate dose adjustments were done weekly for the first month, then every 2 weeks for the second and third months, and as clinically indicated. Patients converted to once-daily tacrolimus after the third month had tacrolimus trough monitoring every 2 weeks for the first month then fortnightly for 5 more months. Any adverse reactions were noted and addressed. Graft biopsy was performed for suspected acute rejection or as required by the physician.

Graft outcomes were monitored monthly throughout the study period. Graft biopsy was performed as indicated and was treated as per protocol. Any adverse reaction to the drugs (twice-daily tacrolimus and once-daily tacrolimus) were managed appropriately. Serious adverse reactions known to occur with tacrolimus use, such as seizures, severe anemia, leukopenia, thrombocytopenia, or microangiopathy, were monitored for each group.

This is a single-center study that received institutional review board approval (NKTI-IRB-2013−56); recruitment took place at NKTI.

Statistical Analysis

Statistical analyses were made of descriptive statistics: means and standard deviations for quantitative variables and the frequency and percentage for qualitative variables. The McNeman χ^2 test was used to compare the survival, incidence of rejection, and incidence of adverse events between the twice-daily tacrolimus and once-daily tacrolimus groups. The Wilcoxon signed-rank test was used to compare the graft function between the 2 groups. Intention to treat analysis principle was adopted. For the estimation of bioequivalence, a comparative estimate was used by measuring the mean and the confidence interval.

RESULTS

Patient Population

A total of 42 patients were screened and randomized for participation in the study. There were 22 patients who were randomized to Group A (twice-daily tacrolimus) and 20 to Group B (once-daily tacrolimus). Forty patients completed the study and were included in the safety analyses. There were 2 patients who were lost to follow-up in week 16 and week 22. Both patients left the country for work. Baseline characteristics were similar in both groups: mean age of 42.6 and 41.1 years and predominantly male; most of the patients had chronic glomerulonephritis as their native kidney

Table 1. Baseline Characteristics

	Group A Twice-Daily Tacrolimus (n = 22)	Group B Once-Daily Tacrolimus (n = 20)	Significance
Age, mean (SD), y	42.6 (11.4)	41.1 (12.8)	0.6827
Sex, No. (%)			
Female	10 (45.5)	5 (25)	0.1670
Male	12 (54.5)	15 (75)	
Weight, mean (SD), kg	61.3 (16.6)	57 (12.4)	0.3422
Native kidney disease, No. (%)			
CGN	13 (59.1)	15 (75)	
DMN	3 (13.6)	3 (15)	
HPNNS	3 (13.6)	1 (5)	
Others	3 (13.6)	4 (20)	
Living Donor Kidney Donation	22 (100)	20 (100)	1.00
HLA-A, -B, -DR mismatch, mean (SD), No.	2.5 (1.1)	2.5 (1.4)	0.6268
HLA-DR match, mean (SD), No.	1.2 (0.4)	1.1 (0.4)	0.1752
Negative tissue crossmatch, No. (%)	22 (100)	20 (100)	1.00
PRA screen class I negative, No. (%)	22 (100)	20 (100)	1.00
PRA screen class II negative, No. (%)	22 (100)	20 (100)	1.00
**Induction, No. (%)			
Basiliximab	13 (65)	13 (65)	1.0000
rATG	7 (35)	7 (35)	

Abbreviations: CGN, chronic glomerulonephritis; DMN, ; HPNNS, ; PRA, panel-reactive antibody; rATG, rabbit antithymocyte globulin.
*Significant at 0.05 level of significance.

disease; most were similar in sex and number of HLA mismatches; and 65% received basiliximab as induction (Table 1).

The AUC, Cmax, and Tmax were determined. The abbreviated AUC was measured by obtaining a 3-point blood level determination using C0 (trough), C2, and C4 measurements in both groups. The AUC was similar in both groups with no significant difference between the 2. The Cmax achieved by both formulations were similar and peaked at 2 hours (Tmax) after intake. The Tmax and Cmax between Group A twice-daily tacrolimus and Group B once-daily tacrolimus did not differ statistically ($P = .23$ and $P = .89$, respectively).

Tacrolimus Dose and Trough Levels

The mean C0 concentrations of once-daily tacrolimus (4.9 [SD, 2.3] ng/dL) were significantly ($P = .02$) lower than twice-daily tacrolimus (6.9 [SD, 2.9] ng/dL) at week 1 post KT. The mean concentration of C0 remained stable until week 12. The twice-daily tacrolimus group patients had a significantly higher mean tacrolimus trough level than the Group B (once-daily tacrolimus) patients ($P = .02$) and were maintained within the target range throughout the study (Table 2).

The mean total daily doses of both Group A (twice-daily tacrolimus) and Group B (once-daily tacrolimus) remained stable during the study. The tacrolimus dose per day was statistically higher in the Group B (once-daily tacrolimus) throughout the study (Table 2).

Patients who were initially prescribed twice-daily tacrolimus were all converted to once-daily tacrolimus on week 12 after kidney transplant. There was a mean increase of 1.23 mg/d (8.3%) of tacrolimus dose after conversion on week 12 post KT. There was a mean decrease of 1.19 ng/mL (20%) in tacrolimus trough level after conversion to once-daily tacrolimus. There was a decrease in tacrolimus trough level on the seventh day after conversion from twice-daily tacrolimus to once-daily tacrolimus.

Table 2. Mean Tacrolimus Dose and Trough Level Until Week 12 After Kidney Transplant

	Tacrolimus Dose				Tacrolimus Trough Level			
After kidney transplant	n	Twice-daily tacrolimus dose per day, mean (SD), mg/d	n	Once-daily tacrolimus dose per day, mean (SD), mg/d	*P* Value	n	Twice-daily tacrolimus trough, mean (SD), ng/mL	n	Once-daily tacrolimus trough, mean (SD), ng/mL	*P* Value
Day 2	22	4.3 (1.3)	20	4.9 (1.5)	.15	22	6.9 (3.5)	20	6.7 (3.9)	.86
Week 1	22	3.8 (1.7)	20	5.3 (2.4)	.03	22	6.9 (2.9)	20	4.9 (2.3)	.02
Week 2	22	3.5 (1.6)	20	5.4 (2.1)	.002	22	6 (1.9)	20	5.4 (2.1)	.35
Week 3	22	3.7 (1.6)	20	5.2 (2.3)	.02	22	6.2 (2.3)	20	5.2 (1.4)	.09
Week 4	22	3.4 (1.7)	20	5.1 (2.1)	.007	22	5.6 (2.1)	20	4.8 (1.6)	.19
Week 6	22	3.3 (1.5)	20	4.9 (2.3)	.01	22	5.6 (2)	20	5.1 (1.7)	.39
Week 8	22	3.7 (1.8)	20	4.6 (2.5)	.16	22	6.4 (2.5)	20	5.7 (2.2)	.31
Week 10	22	3.5 (1.8)	20	4.8 (2.3)	.046	22	6.3 (1.4)	20	5.8 (1.8)	.37
Week 12	22	3.4 (1.8)	20	4.6 (2.4)	.08	22	5.6 (1.3)	20	5.4 (2)	.63

There was no significant difference between coefficient of variation between Group A (twice-daily tacrolimus) and Group B (once-daily tacrolimus) at the 5% significance level ($P = .43$).

Graft and Patient Survival

Both groups had excellent graft function at both 3 and 6 months of once-daily tacrolimus treatment, with differences between the 2 groups being insignificant. Throughout the study, renal function was not significantly different between the 2 treatment groups. The mean estimated glomerular filtration rates (eGFR) were 80.3 (SD, 20.5) mL/min and 76.4 (13.5) mL/min ($P = .47$) for once-daily tacrolimus and twice-daily tacrolimus, respectively. The twice-daily tacrolimus group had a lower eGFR, but it was not statistically significant ($P = .20$). At the end of 6 months, none of the patients in either group experienced acute rejection or severe adverse reactions. Despite the change of tacrolimus C0, no episode of acute rejection occurred during the study period. The eGFR remained unchanged (77–79.8 mL/min).

No patients died or lost graft in both groups during the observation period up to 6 months after kidney transplant. Six-month patient and graft survival were 100% in both groups.

DISCUSSION

Our study showed that de novo once-daily tacrolimus post-transplant patients had lower tacrolimus trough levels and required significantly higher doses to achieve the target trough level even if their baseline demographics were the same. Many studies showed that once-daily tacrolimus needed significantly higher tacrolimus doses per kilogram up to 6 months post-transplant than those on twice-daily tacrolimus: 0.16 vs 0.11 mg/kg; 0.14 vs 0.08 mg/kg; and 0.12 vs 0.08 mg/kg at 1, 3, and 6 months, respectively [2,7]. This is also similar to one multilinear modeling analysis showed that the tacrolimus dose was higher with once-daily tacrolimus than twice-daily tacrolimus on D8 than at M3 and in CYP3A5 expressors ($P < .001$ for all) [7]. In another study, patients on once-daily tacrolimus tended to have lower trough levels and require higher dosages than those taking twice-daily tacrolimus during the early post-transplant period, which is consistent with our study result. Once-daily tacrolimus can be administered with excellent efficacy and safety in de novo renal transplant recipients [8].

The tacrolimus trough levels were lower in both de novo once-daily tacrolimus transplant patients and patients who were converted to once-daily tacrolimus 3 months after stable renal graft function. We observed mean increase of tacrolimus dose of 1.23 mg/d (8.3%) to reach the target trough level. It is important to emphasize that the patients continued to have stable renal function and they reached the target therapeutic level. These findings were consistent with a published study that showed there was a decrease in the therapeutic drug level of the tacrolimus after conversion to once-daily tacrolimus, but it remained on the target level, and there was significant reduction in tacrolimus blood levels that required an increase in tacrolimus daily dose post conversion [9]. Once-daily tacrolimus patients and patients who were converted to once-daily tacrolimus after 3 months had a good eGFR and did not develop acute rejection. These findings were also shown by other published studies stating that once-daily tacrolimus was efficacious in de novo and conversion once-daily tacrolimus since graft function as measured by eGFR did not change significantly at 6 months post KT. Stable renal graft function during conversion has been reported by other studies. Our study, together with other data, showed safety and efficacy in switching from twice-daily tacrolimus to once-daily tacrolimus [10].

The AUC, Cmax, and Tmax of both once-daily tacrolimus and twice-daily tacrolimus showed no significant differences, which is also consistent with the findings of other studies [11,12].

The eGFRs of patients, though not statistically significant, were slightly higher than among patients who were on twice-daily tacrolimus. This finding was also seen in one study of patients who were converted to once-daily tacrolimus who had a clinically significant improvement in kidney graft function on long-term observation. The improvement seemed to be unrelated to changes in tacrolimus blood trough levels [13].

CONCLUSION

In conclusion, conversion from twice-daily tacrolimus to once-daily tacrolimus in kidney transplant in both de novo and converted patients after KT is safe, ensuring greater stability of drug blood concentrations compared with the standard form. The treatment change did not have any effect on transplanted organ function.

Results of the AUC, Cmax, and Tmax of the 2 innovator tacrolimus formulations demonstrated that there are no significant pharmacokinetic differences between twice-daily tacrolimus and once-daily tacrolimus. The results also suggest an 8% increase when converting stable KT patients from twice-daily tacrolimus to once-daily tacrolimus. This information will facilitate achieving target tacrolimus exposure when converting between different tacrolimus formulations, and regular therapeutic drug monitoring is essential when converting patients to once-daily tacrolimus.

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