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ORIGINAL ARTICLE

Pharmacokinetic study of once-daily formulation of tacrolimus (Advagraf) in stable Chinese kidney transplant recipients

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KEYWORDS
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Abstract *Background/Purpose:* The objective of this study is to determine whether tacrolimus trough level is appropriate for therapeutic drug monitoring (TDM) of Advagraf in stable Chinese kidney transplant recipients (KTRs).

Methods: In this single-center pharmacokinetic study, stable adult Chinese KTRs on Advagraf were recruited and their blood tacrolimus levels measured at 12 time points within 24 hours. Trough level was defined as predose drug level (C_0). The pharmacokinetic parameters were calculated using standardized noncompartmental methods. Drug exposure, defined as 24-hour area under the curve (AUC_{0-24}), was calculated using the linear trapezoidal method. Whole blood tacrolimus level measurement was performed by high-performance liquid chromatography/tandem mass spectrophotometry.

Results: Fourteen patients (8 males; mean age, 47.1 ± 9.2 years; mean duration of transplant, 8.3 ± 3.6 years) completed the study. The mean C_0 was 4.4 ± 1.9 ng/mL, and the mean AUC_{0-24} was 143.8 ± 57.0 ng h/mL. The mean maximum concentration (C_{max}) was 10.2 ± 3.9 ng/mL, and the median time to C_{max} was 2.0 hours (interquartile range, 1.0–3.0 hours). There was a strong correlation between C_0 and AUC_{0-24} ($r = 0.90$, $p < 0.001$). Patients receiving diltiazem had higher mean AUC_{0-24} (153.0 ± 55.3 ng h/mL vs. 110.1 ± 60.1 ng h/mL) despite a lower dose (mean tacrolimus dose, 0.039 ± 0.022 mg/kg/d vs. 0.054 ± 0.021 mg/kg/d), although both differences did not reach statistical significance. Apart from C_0, tacrolimus level obtained from 6 hours to 12 hours (C_6 to C_{12}) also had good correlation with AUC_{0-24}.

Conclusion: Tacrolimus trough level is a good surrogate marker for TDM of Advagraf in stable Chinese KTRs. The role of C_6 to C_{12} in TDM remains to be determined.

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背景 / 目的: 本研究旨在調查在病情穩定的華裔腎臟移植接受者 (KTRs) 間,Cmin 是否適用於藥物血中濃度監測 (TDM)。
方法: 在這一項單中心藥物動力學研究中,對象為病情穩定的華裔 KTRs,在 24 小時內 12 個時間點接受了動脈血的取樣,谷值的定義為服藥前藥物濃度 (C0)。藥物動力學參數的計算是採用標準化無房室模式,AUC0—24 的計算採用線性梯形方式。全血 tacrolimus 濃度的測量儀器,則是採用高效能液相色層分析串聯質譜儀 (HPLCMS/MS)。
結果: 本研究共納入 14 位服用 Advagraf® 的病人,平均 C0 為 4.4 ± 1.9 ng/ml,平均 AUC0—24 為 143.8 ± 57.0 ng·h/ml,平均最高濃度 Cmax 為 10.2 ± 3.9 ng/ml,達到 Cmax 的時間中位數 tmax 則為 2.0 小時 (四分位數間距 1.0—3.0 小時);C0 與 AUC0—24 存在明顯的相關性 ($r = 0.90$、$p < 0.001$)。在接受 diltiazem 的病人中,平均 AUC0—24 較高 (153.0 ± 55.3 ng·h/ml vs. 110.1 ± 60.1 ng·h/ml),即使他們服用較低的 tacrolimus 劑量 (平均劑量 0.039 ± 0.022 mg/kg/day vs. 0.054 ± 0.021 mg/kg/day);這兩種差異未達統計學意義。除了 C0 之外,6 至 12 小時 (C6 to C12) 之 tacrolimus 濃度亦與 AUC0—24 存在顯著的相關性。
結論: 對於病情穩定的華裔 KTRs,tacrolimus 谷值乃 AUC0—24 的一個良好替代指標;至於 C6 to C12 的角色則仍有待證實。

Introduction

Tacrolimus, a calcineurin inhibitor (CNI), is commonly used in solid organ transplantation. The latest Kidney Disease: Improving Global Outcomes clinical practice guideline for the care of kidney transplant recipients (KTRs) suggested tacrolimus to be used as the first-line CNI.[1] Tacrolimus was first developed as a twice-daily oral formulation (tacrolimus-BID; Prograf, Astellas Pharma Hong Kong Co., Ltd., Hong Kong, China). Once-daily tacrolimus (tacrolimus-OD; Advagraf, Astellas Pharma) was developed with an aim to improve drug compliance and lower pill burden. In KTRs, there are no significant differences between the two formulations in terms of biopsy-proven acute rejection rate, patient survival, and graft survival at 12 months.[2] Tacrolimus-OD has also been shown to be associated with better patient compliance,[3] gastrointestinal tolerability,[4] and possibly lower overall treatment cost per patient.[5]

Tacrolimus has a narrow therapeutic index and requires therapeutic drug monitoring (TDM) in order to optimize clinical outcome. Traditionally, area under the curve (AUC) measurement is regarded as the gold standard of measuring tacrolimus exposure.[6] Nevertheless, routine AUC measurement is both time-consuming and costly in daily clinical practice. Tacrolimus trough level (C_{min}) is usually used as a surrogate indicator of drug exposure. However, the reported correlation between C_{min} and 12-hour AUC (AUC_{0-12}) was highly variable for tacrolimus-BID.[7] In particular, the C_{min} of tacrolimus-BID did not have a significant correlation with AUC_{0-12} in stable Chinese KTRs, leading to theoretical concerns of extrapolating such recommendation to TDM of tacrolimus-OD.[8] In other population pharmacokinetic (PK) studies, there was up to 50% variation in 24-hour AUC (AUC_{0-24}) for the same C_{min} in patients receiving tacrolimus-OD.[9–11] This has led to the suggestion of using drug levels at 0 hours, 1 hour, and 3 hours after dose (C_0, C_1, and C_3, respectively) for better estimation of the AUC_{0-24}.[9–11]

Given the paucity of evidence regarding the best method of TDM and unique genetic background of the Chinese population, the objective of this study was to determine whether C_{min} is a good surrogate marker for TDM of Advagraf in stable Chinese KTRs.

Methods

Patient selection

This was a prospective, single-center PK study involving stable Chinese KTRs who were followed up in Prince of Wales Hospital and taking tacrolimus-OD (Advagraf; Astellas Pharma Hong Kong Co., Ltd.) as part of their maintenance immunosuppressive regimen. Inclusion criteria included adult KTRs aged $\geq$ 18 years, kidney transplant for more than 1 year, stable renal function (defined as <25% change in serum creatinine) over the past 6 months, and no change of tacrolimus dosage in the previous 1 month. Exclusion criteria included significant liver impairment (defined as elevated serum alanine aminotransferase level more than 2 times the upper limit of normal), severe gastrointestinal disorder that may affect drug absorption, and pregnancy. Clinical records of recruited patients were reviewed for the collection of baseline demographic and clinical data. The study was approved by the local ethics committee, and all study procedures were in compliance with the Declaration of Helsinki.

Sample collection and tacrolimus assay

After written informed consent was obtained, a 24-hour PK study was performed for each patient. The study was carried out in an outpatient setting on the day of the scheduled clinic follow-up. All patients were instructed to take the drug on an empty stomach and swallow the whole capsule with water in order to achieve maximal absorption. Blood sampling was performed at 12 time points within 24 hours: 0 minute (i.e., before dose), 20 minutes, 40 minutes, 1 hour, 1.5 hour, 2 hours, 3 hours, 4 hours, 6 hours, 9 hours, 12 hours, and 24 hours. At each time point, 3 mL of venous blood was drawn and stored in separate ethylenediaminetetraacetic acid (EDTA) bottles. Venous blood sampling was performed by a research nurse in a hospital day ward. After blood taking for tacrolimus levels from 0 minute to 12 hours, patients were allowed to go home. Patients were then instructed to come back the next morning for blood taking to measure tacrolimus level at

24 hours (C_{24}). Whole blood tacrolimus level measurement was performed using high-performance liquid chromatography/tandem mass spectrophotometry.

Data and statistical analysis

PK parameters were calculated using standardized non-compartmental methods. Maximum concentration (C_{max}) and time to reach C_{max} (t_{max}) were obtained directly from the blood concentration—time curves. Trough level was defined as the predose concentration at 0 minute (C_0). The AUC_{0-24} was calculated using the linear trapezoidal method. Statistical analysis was performed using SPSS for Windows software version 17.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as mean ± standard deviation, unless otherwise specified. Correlation between blood concentrations measured at different time points and AUC_{0-24} was assessed with the nonparametric Spearman's rank correlation coefficient (ρ). A p value < 0.05 was considered statistically significant.

Results

A total of 17 patients were identified, which represented all KTRs receiving Advagraf in our center. Two patients refused to participate in the study. One patient was excluded because of history of gastrectomy. Fourteen patients were recruited and completed the study. The baseline demographic and clinical characteristics are shown in Table 1. No patients suffered from adverse events throughout the study.

The mean maintenance dose of tacrolimus was 0.042 ± 0.022 mg/kg/d. Tacrolimus exposure in each patient, expressed in form of whole-blood tacrolimus concentration—time curve, is shown in Figure 1. The PK

Table 1 Baseline demographic and clinical characteristics.

Total number of patients	14
Male/female	8/6
Age (y)	47.1 ± 9.2
Body height (cm)	163.2 ± 11.1
Body weight (kg)	70.8 ± 16.1
Systolic blood pressure (mmHg)	130 ± 17
Diastolic blood pressure (mmHg)	76 ± 14
Diabetes	3 (21.4%)
Hypertension	14 (100%)
Duration of kidney transplant (y)	8.3 ± 3.6
Dosage of Advagraf (mg/kg/d)	0.042 ± 0.022
Hemoglobin (g/dL)	12.9 ± 1.8
Serum creatinine (μmol/L)	162 ± 136
Serum albumin (g/L)	42.6 ± 2.4
Total cholesterol (mmol/L)	4.9 ± 0.9
LDL cholesterol (mmol/L)	2.7 ± 0.8
HDL cholesterol (mmol/L)	1.6 ± 0.4
Total triglyceride (mmol/L)	1.3 ± 0.6
Fasting glucose (mmol/L)	5.2 ± 0.9
Concomitant medications	
Prednisolone + Advagraf + mycofenolate[a]	7 (50%)
Prednisolone + Advagraf + azathioprine	5 (35.7%)
Prednisolone + Advagraf	2 (14.3%)
Diltiazem	11 (78.6%)
Beta-blocker	8 (57.1%)
Angiotensin converting enzyme inhibitor	1 (7.1%)
Angiotensin receptor blocker	5 (35.7%)
Histamine-2 receptor blocker	3 (21.4%)

HDL = high-density lipoprotein; LDL = low-density lipoprotein.
[a] Three patients were on mycophenolic acid delayed-release (Myfortic), and four patients were on mycophenolate mofetil.

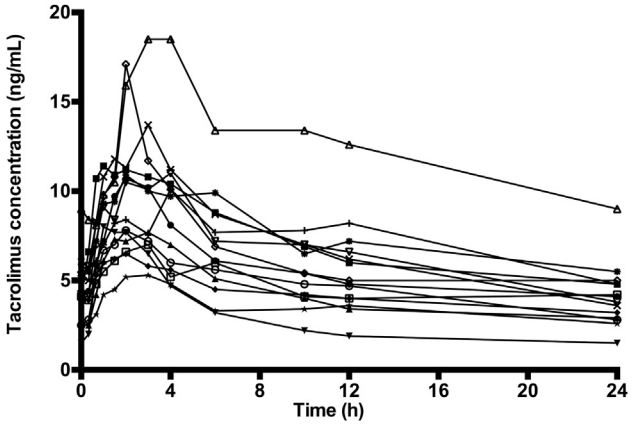

Figure 1 Pharmacokinetic profile of once-daily tacrolimus expressed in the form of blood concentration time curve.

Table 2 Pharmacokinetic parameters of Advagraf.

Mean 24-h area under the curve, AUC_{0-24} (ng h/mL)	143.8 ± 57.0
Mean maximum concentration, C_{max} (ng/mL)	10.2 ± 3.9
Mean trough concentration, C_0 (ng/mL)	4.4 ± 1.9
Median time to maximum concentration, t_{max} (h)	2.0 (1.0—3.0)

AUC_{0-24} = 24-hour area under the curve; C_0 = predose drug level; C_{max} = mean maximum concentration; t_{max} = time to reach C_{max}.

Table 3 Correlation between tacrolimus concentration at different time points and 24-hour drug exposure.

Time point	Spearman ρ (p)
0 min	0.90 ($p < 0.001$)
20 min	0.92 ($p < 0.001$)
40 min	0.78 ($p = 0.001$)
60 min	0.70 ($p = 0.007$)
90 min	0.69 ($p = 0.008$)
2 h	0.77 ($p = 0.002$)
3 h	0.74 ($p = 0.004$)
4 h	0.86 ($p < 0.001$)
6 h	0.98 ($p < 0.001$)
10 h	0.94 ($p < 0.001$)
12 h	0.97 ($p < 0.001$)
24 h	0.85 ($p < 0.001$)

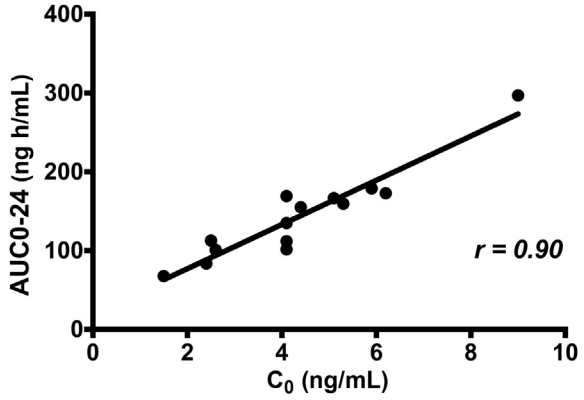

Figure 2 Correlation between tacrolimus trough level, C_0, and 24-hour area under curve (AUC_{0-24}).

parameters are shown in Table 2. A target AUC_{0-24} of 125 ng h/mL has been recommended using the mean population-based PK parameters of tacrolimus-BID, which corresponds to a C_{min} of 7.5 ng/mL (range, 5–15 ng/mL).[12] The mean AUC_{0-24} of our patients was 143.8 ± 57.0 ng h/mL, which corresponded to mean C_0 of 4.4 ± 1.9 ng/mL. Patients receiving diltiazem had higher mean AUC_{0-24} (153.0 ± 55.3 ng/mL vs. 110.1 ± 60.1 ng h/mL) despite a lower dose of tacrolimus (0.039 ± 0.022 mg/kg/d vs. 0.054 ± 0.021 mg/kg/d), although both differences did not reach statistical significance. There was also a trend toward higher C_0 in patients receiving diltiazem (4.4 ± 1.7 ng/mL vs. 3.2 ± 2.1 ng/mL). The correlation between tacrolimus level at each time point and AUC_{0-24} is shown in Table 3. There was a good correlation between C_0 and AUC_{0-24} ($r = 0.90$, $p < 0.001$). A graphical representation is shown in Figure 2. Apart from C_0, the tacrolimus level obtained from 6 hours to 12 hours (C_6 to C_{12}) also had good

Table 4 Pharmacokinetic studies of once-daily tacrolimus in solid organ transplant recipients.

Study	Year of publication	Patients	Number of patients	Ethnicity	Correlation between C_{min} and AUC_{0-24}
Hardinger et al[18]	2004	Stable KTRs > 6 mo	18	Caucasians (89%), African American (11%)	Day 14, $r^2 = 0.77$
Alloway et al[19]	2005	Stable KTRs > 6 mo	66	Caucasian (80.3%), African American (18.2%), Asian (1.5%)	Day 14, $r = 0.92$; Day 21, $r = 0.86$
van Hooff et al[20]	2012	Stable KTRs ≥ 6 mo	60	Caucasian (75.0%), Black (1.7%) Asian (13.3%), others (10%)	Day 28, $r = 0.89$; Day 56, $r = 0.82$
van Boekel et al[21]	2015	Stable KTRs	26	Caucasian (100%)	$r = 0.83$
Wlodarczyk et al[22]	2009	*De novo* KTRs	34	Caucasian (96.7%), others (3.3%)	Days 1, 14, and 42 (combined), $r = 0.83$
Cabello et al[23]	2010	*De novo* KTRs aged ≥ 55	14	White (100%)	Day 3, $r = 0.87$; Day 21, $r = 0.83$
Wlodarczyk et al[24]	2012	*De novo* KTRs	17	White (94.1%), other (5.9%)	Days 1, 3, 7, and 14 (combined), $r = 0.87$
Niioka et al[25]	2012	*De novo* KTRs	25	Japanese (100%)	Day 28, $r = 0.64$
Tsuchiya et al[26]	2013	*De novo* KTRs	50	Japanese (100%)	Day 14, $r = 0.94$
Satoh et al[27]	2014	*De novo* KTRs	24	Japanese (100%)	Prior to transplant, $r^2 = 0.70$; 1 mo, $r^2 = 0.71$; 1 y, $r^2 = 0.86$
Florman et al[28]	2005	LTRs > 6 mo with stable renal and liver function	62	Caucasian (91.9%), African American (6.5%), Pacific Islander (1.6%)	Day 28, $r = 0.90$; Day 56, $r = 0.88$
Zhang et al[29]	2011	LTRs 6–24 mo with stable renal and liver function	83	Chinese (100%)	Day 1, $r = 0.94$; Day 84, $r = 0.90$
Fischer et al[30]	2011	*De novo* LTRs	45	Caucasian (100%)	Days 1, 14, and 42 (combined), $r = 0.92$
Sugwara et al[31]	2011	*De novo* LTRs	9	Japanese (100%)	Day 7, $r = 0.49$
Alloway et al[32]	2011	Stable heart transplant patients > 6 mo	45	White (91.1%), Black (8.9%)	Days 14 and 21 (combined), $r = 0.94$
Méndez et al[33]	2014	Stable lung transplant patients > 6 mo	19	Not mentioned	Days 14–28, $r = 0.96$

KTRs = kidney transplant recipients; LTRs = liver transplant recipients; C_{min} = tacrolimus trough level; AUC_{0-24} = 24-hour area under the curve.

correlation with the AUC_{0-24}. As shown in Figure 1, tacrolimus levels were relatively stable from 6 hours to 12 hours.

Discussion

Tacrolimus-OD is increasingly used in solid organ transplant recipients in recent years. It has a longer t_{max} than tacrolimus-BID, but AUC_{0-24} is similar.[13,14] Apart from potentially better drug compliance and lower pill burden, tacrolimus-OD has been shown to be associated with improved graft outcome, glucose tolerance, and lipid profile.[15–17] Tacrolimus has a narrow therapeutic index. Underdosing is associated with an increased risk for graft rejection, whereas overdosing is associated an increased risk for CNI toxicity. Therefore, a reliable method of TDM is of paramount importance to optimize clinical outcome.

The PK studies of tacrolimus-OD have been conducted in solid organ transplant recipients of different ethnicities. These included stable KTRs,[18–21] *de novo* KTRs,[22–27] stable liver transplant recipients (LTRs),[28,29] *de novo* LTRs,[30,31] stable heart transplant recipients,[32] and stable lung transplant recipients.[33] The key findings of these studies are summarized in Table 4. The reported correlation between C_0 and AUC_{0-24} was variable, with the correlation coefficient ranging from 0.49[31] to 0.96.[33] There was only one PK study in the literature involving Chinese population.[29] In this prospective, open-label, multicenter study, 83 stable LTRs were converted from tacrolimus-BID to tacrolimus-OD on a 1 mg:1 mg basis. Two separate PK studies were conducted after switching to tacrolimus-OD on Day 1 and Day 84. There was a good correlation between C_0 and AUC_{0-24} on both days (Day 1, $r = 0.94$; Day 84, $r = 0.90$).

Our study is the first PK study of tacrolimus-OD in stable Chinese KTRs in a real-life clinical setting. Our patients have been transplanted for a mean of 8.3 years. The mean duration of tacrolimus-OD use was 3.6 years. All patients had stable graft function without recent change of drug dosage. This helped to ensure that the PK profiles were obtained after the establishment of a steady state of drug absorption and metabolism. We found a strong correlation between C_0 and AUC_{0-24}. Compared with the previous study by Zhang et al,[29] our patients received a lower dose of tacrolimus (0.042 ± 0.022 mg/kg/d vs. 0.072 ± 0.035 mg/kg/d), but achieved a higher level of C_0 (4.4 ± 1.9 ng/mL vs. 3.3 ± 1.5 ng/mL) and AUC_{0-24} (143.8 ± 57.0 ng h/mL vs. 113 ± 44 ng h/mL). This may be explained by the high percentage of diltiazem (a potent cytochrome P450 enzyme inhibitor) use in our cohort. In patients not receiving diltiazem in our cohort, the AUC_{0-24} was comparable with that reported by Zhang et al[29] (110.1 ± 60.1 ng h/mL vs. 113 ± 44 ng h/mL).

Using C_{min} for TDM, despite allowing standardized comparison between patients, may not be always practical in a busy clinical setting. van Boekel et al[21] recently performed a prospective, extended PK studies in 26 stable Caucasian KTRs. Instead of the traditional venous sampling method, the investigators used a validated dried blood spot method for sampling and analysis of tacrolimus level. Patients were trained to perform finger prick with an automatic lancet and take their own blood samples at home. Capillary blood sampling was performed at 10 different time points up to 32 hours. The correlation coefficients between drug level taken at 24 hours to 32 hours and AUC_{0-24} ranged from 0.82 to 0.88 ($p < 0.01$ for all). The authors suggested that the use of delayed drug levels could be considered for TDM, especially for patients who have clinic follow-up in the afternoon. However, the effect of delaying tacrolimus intake for the purpose of blood taking could be a potential concern.

In our study, there was excellent correlation between C_6 to C_{12} and AUC_{0-24}. Any delay in taking tacrolimus could be avoided if these time points could be used for TDM. It should be stressed, however, that currently there is no recommendation from the pharmaceutical company or clinical trials on the desirable range of tacrolimus level if time points other than the trough level are used for TDM. The effect on clinical outcome is also uncertain.

There are several limitations in our study. The sample size was small. We included only KTRs who were switched from tacrolimus-BID to tacrolimus-OD, whether using C_{min} is appropriate for TDM in *de novo* Chinese KTRs could be ascertained. The PK profile of tacrolimus is influenced by the patients' cytochrome P450 isoenzymes 3A4 and 3A5 (CYP3A4 and CYPA3A5) genotype status.[34–37] We do not have the data on CYP3A4 and CYP3A5 genetic polymorphisms in our patients. However, even if such information is available, its potential effect on PK profile is grossly confounded because of the high percentage of diltiazem use. We do not have renal biopsy data to correlate the degree of immunosuppression as reflected by tacrolimus AUC_{24} with the presence of subclinical rejection or CNI-induced chronic allograft injury.

Conclusion

This marks the first PK study of Advagraf in stable Chinese KTRs that showed that tacrolimus trough level could be safely used for TDM. Further studies are required to determine the role of TDM using C_6 to C_{12}.

Conflicts of interest

None.

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