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EVALUATION OF TACROLIMUS ABBREVIATED AREA-UNDER-THE-CURVE MONITORING IN RENAL TRANSPLANT PATIENTS WHO ARE POTENTIALLY AT RISK FOR ADVERSE EVENTS

Yuen Yi Hon, Pharm.D.^a, Christine E. Chamberlain, Pharm.D.^a, David E. Kleiner, M.D.^b, Michael S. Ring, M.D.^c, Douglas A. Hale, M.D.^{c,*}, Allan D. Kirk, M.D., Ph.D.^{c,†}, and Roslyn B. Mannon, M.D.^{c,#}

^a Pharmacy Department, Clinical Center, National Institutes of Health, Bethesda, MD

^b Laboratory of Pathology, National Cancer Institute, National Institutes of Health, Bethesda, MD

^c Transplantation Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD

Abstract

In a cohort of 32 renal transplant patients who are potentially at risk for adverse events, we compared tacrolimus (TAC) abbreviated AUC values calculated by a method developed in Asians (AUC_w) with those derived for Caucasians (AUC_a). The relationships between TAC trough (C₀), abbreviated AUC, and biopsy results were also assessed. Forty-eight AUCs and 15 associated biopsies were evaluated. For AUCs obtained from Caucasian patients only, median AUC_w value was lower than that of AUC_a (104 vs. 115 ng*h/mL, n=29, p<0.0001). AUCs obtained from both methods for all patients correlated with C₀ ($r_s > 0.72$, n=48, p<0.0001). Median AUC_w (72.9 vs. 174 ng*h/mL, p=0.043) and AUC_a (81.0 vs. 203 ng*h/mL, p=0.043) were lower in patients experiencing biopsy-proven acute rejection (AR) than those with normal histology. C₀ tended to be lower in biopsies showing AR > 6 months post transplant (5.80 vs. 11.0 ng/mL, p=0.110). Thus, lower abbreviated AUCs were obtained for Caucasians using a method developed in Asians. C₀ correlated well with abbreviated AUCs. Lower C₀ and AUC appeared to be associated with biopsy-proven AR > 6 months post transplant. Further prospective evaluation of TAC AUC and C₀ monitoring in a larger cohort of patients is warranted.

Keywords

tacrolimus immunosuppression; trough concentration; abbreviated AUC; biopsy-proven acute rejection; therapeutic drug monitoring

Introduction

Tacrolimus (TAC) is a potent calcineurin inhibitor which has been shown to be efficacious in prophylaxis of renal allograft rejection. It shares a similar adverse reaction profile with the other calcineurin inhibitor cyclosporine; similar rates of impaired renal function,

Name and address for correspondence: Christine Yuen-Yi Hon, Pharm.D., Clinical Pharmacokinetics Research Laboratory, Clinical Center Pharmacy Department, National Institutes of Health, Bldg 10, Room 1N-257, MSC-1196, 10 Center Drive, Bethesda, MD 20892, 301-496-0967 (W), 301-496-0210 (F) chon@cc.nih.gov.

*University of Florida, Jacksonville, FL,

†Emory University, Atlanta, GA, and

#University of Alabama at Birmingham, Birmingham, AL

gastrointestinal disorders, and neurological complications (headache, insomnia, and dizziness) were reported in patients receiving TAC or cyclosporine maintenance therapy (1). However, the incidences of hypertension and hypercholesterolemia were lower and those of tremor, paresthesia, thrombosis, and post transplant diabetes mellitus were higher in patients receiving TAC compared to those receiving cyclosporine (1–3).

Similar to cyclosporine, TAC has a narrow therapeutic index and its pharmacokinetics exhibits high intra- and inter-subject variability, necessitating the use of therapeutic drug monitoring to optimize efficacy and minimize toxicity. While monitoring parameters such as concentration at 2 hours following the dose or the first 4 hours of the concentration-versus-time curve (AUC) have been well established for cyclosporine (4,5), these parameters have not been clearly defined for TAC (5). Typically, TAC therapeutic drug monitoring in renal transplantation is done by measuring predose trough concentration (C₀). Target whole blood trough concentrations range from 5 – 15 ng/mL immediately after transplantation, followed by a lower range of 5 – 12 ng/mL late post transplant (6). The use of other monitoring parameters such as full 12-hour and abbreviated AUCs have also been advocated by others (7–9). However, these methods are not widely used because of limited practicality and the lack of definitive association between AUC measurement and clinical outcome. In spite of a high correlation between C₀ and AUC as indicated in the package insert ($r = 0.93$) (10), it remains questionable in the clinical setting whether the trough level correlates with systemic exposure.

Beginning in year 2000, we performed TAC abbreviated AUC monitoring in a selected cohort of renal transplant recipients for non-compliance, questionable bioavailability, increased serum creatinine levels, and clinical signs and symptoms of drug toxicity and graft rejection. This cohort was overrepresented by patients who might have experienced adverse events as a result of under- and over-immunosuppression. The abbreviated AUCs being used for the monitoring were calculated using the equation from Wong et. al. (11), which was the first and the only regression equation available for calculating TAC abbreviated AUC at that time. This equation used four concentrations and was developed for Asian population; its application in other populations has not been validated yet. In 2005, an equation utilizing only three concentrations was validated by Armendariz et. al. for European Caucasians (12).

Since two thirds of the patients in our cohort were Caucasians, we sought to compare the AUC values obtained from the two regression equations and determined whether the method by Wong et al. could be used in Caucasian population. Additionally, we evaluated the relationships of C₀ and abbreviated AUC with biopsy results in an attempt to reveal any important information for monitoring those adverse events experienced by our patients. Finally, examination of the correlation between C₀ and abbreviated AUC was performed as well.

Patients and Methods

Data Collection and Calculation

Between August 2000 to December 2006, 83 TAC abbreviated AUCs were performed for renal transplant recipients at our institution. All of the patients consented to participate and be monitored in one of our transplant treatment protocols. Clinical data including patient demographics, type and date of transplantation, induction and maintenance immunosuppression therapies, whole blood TAC concentrations at 0 (C₀, trough), 1, 2, and 4 hours (C₁, C₂, and C₄) after the morning dose of twice-daily TAC were collected. In patients who were maintained on a stable TAC regimen, biopsies performed at the time of AUC or within a 3-day time period were also obtained. Exclusion criteria for data analysis included alternate day dosing, non-steady-state TAC level, incomplete concentration time

points for AUC calculation, the use of concomitant sirolimus (SRL) maintenance therapy, and the measurements of TAC concentrations by high performance liquid chromatography-tandem mass spectrometry.

Predicted 12-hour AUCs were calculated using the regression equations as reported by Wong et al. (11) (AUC_w, equation 1) and Armendáriz et. al. (12) (AUC_a, equation 2) as follows:

$$\text{AUC}_w = 10 + 1.4 \cdot C_0 + 0.8 \cdot C_1 + 1.6 \cdot C_2 + 5.5 \cdot C_4 \quad (1)$$

$$\text{AUC}_a = 8.90 + 4.0 \cdot C_0 + 1.77 \cdot C_1 + 5.47 \cdot C_4 \quad (2)$$

The actual partial 2- and 4-hour AUCs (AUC₀₋₂ and AUC₀₋₄) were determined by the linear trapezoid rule using SigmaPlot (Systat Software, Inc., San Jose, CA). Dose normalized (DN-) C₀ and -AUCs were calculated by dividing trough concentration and the predicted AUCs (AUC_w and AUC_a) by half of the total daily dose, respectively.

Statistical Analyses

The distribution of continuous data was assessed by the Shapiro-Wilk test prior to subsequent statistical analyses. The correlations among various parameters were determined by Spearman rank correlation. The differences between AUC_w and AUC_a values in Caucasians were determined by Wilcoxon signed-rank test. The differences in various parameter values between early (<6 months) and late (>6 months) post transplant periods were determined by Mann Whitney U test. In order to account for the effect of time after transplantation on TAC pharmacokinetics, blocked Wilcoxon Rank Sum test was used to analyze the differences in DN-parameters between patients with or without steroids. One-sided Mann Whitney U Test was used to analyze the differences in C₀ and AUCs between the normal biopsy and the acute rejection groups. Statistical significance was set at p value ≤ 0.05. All analyses were performed using the statistical software Statistica 6.1 (StatSoft, Tulsa, OK).

Results

A total of 48 TAC abbreviated AUCs in 32 patients with kidney or kidney-pancreas transplantation were used and evaluated in this study. All TAC concentrations were determined by the IMx TacrolimusII microparticle enzyme immunoassay (Abbott Laboratory, Abbott Park, IL). Thirteen and 35 of the 48 AUCs were performed at <6 and >6 months post transplant, respectively. The Median (range) age of the patients was 37 (17–66) years. Eighteen and 11 patients received depletion (rabbit antithymocyte globulin or alemtuzumab) and non-depletional (daclizumab) induction, respectively, with intraoperative steroid therapy. Two patients received induction with steroids alone, while one patient received an investigational monoclonal antibody for induction therapy. All patients received maintenance TAC immunosuppression with or without mycophenolate mofetil (MMF) and prednisone (Pred). Summary of demographics and the immunosuppressive therapies being used for all of the patients are depicted in Table 1.

A wide range of TAC daily doses was seen in our patients with renal transplantation. The median daily dose was 5 mg, with a range of 1 to 20 mg. These doses resulted in variable TAC concentration at various time points, as well as predicted and partial AUCs. As depicted in Table 2, median C₀, C₁, C₂, and C₄ were 8.15, 12.1, 13.9, and 11.8 ng/mL, respectively. Median AUC₀₋₂ and AUC₀₋₄ were 23.7 and 48.4 ng·h/mL, respectively.

Predicted AUCs were significantly correlated with C0 (Figure 1) and partial actual AUCs (Table 3). AUCw and AUCa correlated better with AUC0-4 than AUC0-2.

Significant lower values of TAC concentrations, AUCs, and DN-parameters were observed in patients during late (> 6 months) compared to early post transplant (< 6 months) (Table 2). After accounting for this time effect, the median DN-C0 (4.08 vs. 2.34 ng/mL/mg, $p < 0.05$), -AUCw (57.4 vs. 34.6 ng*h/mL/mg, $p < 0.01$), and -AUCa (61.9 vs. 38.2 ng*h/mL/mg, $p < 0.01$) were found to be higher in patients who received TAC and TAC/MMF (n=23) compared to those who received TAC/Pred and TAC/MMF/Pred (n=25).

Among the 48 AUC measurements, only 29 of them were obtained from Caucasian patients and were used to compare the two abbreviated AUC methods. As depicted in Figure 2, AUCw was highly correlated with AUCa ($r_s = 0.986$, $p < 0.0001$). Median AUCw was significantly lower than that of AUCa [104 (54.8 – 222) vs. 115 (67.4 – 223) ng/mL, $p < 0.0001$]. Likewise, median DN-AUCw was lower [47.6 (20.2 – 123) vs. 54.9 (22.3 – 128) ng/mL, $p < 0.0001$].

Fifteen biopsy reports associated with the AUC monitoring were collected and analyzed; these biopsies were evaluated according to the 1997 revised Banff classification (13). Histology for 5 of these biopsies was unremarkable and was considered to be normal. Changes associated with acute rejection (AR) and chronic allograft nephropathy were seen in 4 and 2 biopsies, respectively. For the biopsy samples showing AR, all of them were obtained at > 6 months post transplantation (6.3, 10.1, 12.1, and 13.9 months). Pathological changes consistent with BK virus infection and/or calcineurin inhibitor toxicity with or without positive BK virus immunohistochemical staining were observed in four samples. Two of them were positive for BK virus, one for tacrolimus toxicity, and one for both BK virus and drug toxicity.

The induction therapy, concurrent maintenance immunosuppressive agents, and TAC C0 and AUCs for the different biopsy groups were summarized in Table 4. Comparisons of TAC exposure showed that median AUCw (72.9 vs. 174 ng*h/mL, $p = 0.043$) and AUCa (81.0 vs. 203 ng*h/mL, $p = 0.043$) were significantly lower in patients experiencing acute rejection than those with normal histology. Additionally, C0 tended to be lower in biopsies showing rejection > 6 months post transplant (5.80 vs. 11.1 ng/mL, $p = 0.110$).

Discussion

With the assumption that TAC AUC values obtained from the equation of Armendáriz et. al. (12) (i.e. AUCa) were representative of the true actual 12-hour AUCs, we found that AUCw values were significantly underestimated by 10.6% in Caucasians. Likewise, AUC values calculated by another regression equation that was derived from a Thai population (14) were underestimated as well (data not shown). These small differences, albeit statistical significant, did not appear to affect our results significantly and may not be clinically relevant.

We found differences in a number of parameters between early and late post transplant periods, with TAC concentrations (C2 and C4) and predicted 12-hour AUCs approximately 50–85 % higher and DN-parameters twice as high for samples collected within the 6 months after transplantation. These observations are in line with the use of clotrimazole prophylaxis in our patients within the first 6 months and the general clinical practice of targeting a higher range of trough concentrations early post transplant, when the requirement of immunosuppression is the highest. However, previous reports showed that there was a trend for body clearance to decline, and DN-AUCs were increased over the course of one year after transplantation (8,15). Presumably, these changes were attributed to the withdrawal of

corticosteroids during the first 6 months after transplantation. It is noteworthy that AUCs were determined at pre-defined selected time points in these previous studies, whereas AUCs were monitored sporadically in our patients based on clinical situation.

Interactions between TAC and other immunosuppressants have been reported previously. TAC AUCs were decreased during concomitant administration of SRL (16–18), whereas DN-C0 and AUCs were increased after steroid withdrawal (19). On the contrary, co-administration of MMF did not affect TAC C0 and AUC (20,21). We found that lower DN-parameters were achieved in patients receiving prednisone in addition to maintenance TAC therapy (either alone or in combination with MMF), suggesting that TAC metabolism was enhanced as a result of p-glycoprotein and cytochrome P450 3A enzyme induction by corticosteroids (22,23).

The use of predose trough level in routine monitoring of TAC is based on the premise that there exists a good correlation between C0 and AUC. The correlation coefficients for C0-actual AUC relationship were found to range from 0.78 – 0.98 in several studies (14,24–27), although a few others reported lower correlation coefficients ranging from 0.34 – 0.60 (11,12,28). Our study showed Spearman correlation coefficients of approximately 0.75 between C0 and abbreviated AUCs, showing that TAC trough level correlates well with and is a good indicator of systemic exposure, although the correlations were not as strong as that indicated in the package insert for actual AUC (10). If further work continues to show significant correlation between C0 and AUC, then maybe the more expensive AUC monitoring can be eliminated.

Biopsy reports associated with AUC monitoring were available in about one third of the AUC measurements and pathological changes were found in about two thirds of these biopsies. This reflects the fact that AUC monitoring in this study was performed in a selected cohort of patients, who had questionable pharmacokinetics and clinical signs and symptoms suggestive of acute rejection and drug toxicity. Therefore, our results may not necessarily be applicable to all kidney transplant recipients, but are more closely related to patients who may experience adverse events related to under- and over-immunosuppression. Interestingly, with the exception of two samples, all of our biopsies were obtained > 6 months after transplantation.

Our results demonstrated that biopsy-proven AR appeared to be associated with low TAC exposure, both in terms of predose trough concentration and predicted 12-hour AUCs. The median C0 in our acute rejection group was 5.80 ng/mL, which is similar to an average median C0 of 5.57 ng/mL for patients who experienced rejection during the first month after kidney transplant (29), and is consistent with a suggested target range of 5 – 15 ng/mL that seemed to optimize efficacy and minimize toxicity for up to 42 days post transplantation (30). In addition, 75% of our biopsy-proven rejection episodes were associated with predicted AUC values < 85 ng*h/mL, suggesting that TAC AUC may be a useful marker for AR and an exposure of at least 85 ng*h/mL may be necessary to avoid this adverse event. Although patients greater than 6 months out are not likely to reject, our findings suggest that an appropriately high C0 or AUC may still be needed to control AR. Hence, it is important to further evaluate TAC C0 and AUC prospectively in a large cohort of kidney transplant recipients, to better define the exposure-response relationships and assess the usefulness of C0 and AUC monitoring.

The retrospective nature and the small number of biopsy results pose major limitations to this study. Additionally, AUC monitoring was performed only in a subset of our patients. The use of abbreviated AUC provides estimates of actual TAC exposure. However, this

method is less costly and laborious than the full 12-hour AUC, making it more useful in the clinical setting.

Conclusion

Lower TAC abbreviated AUC values were obtained for Caucasians by using the equation from Wong et al. (11) but the small AUC differences may not be clinically relevant. C₀ correlated well with abbreviated AUCs, and if further work continues to point this out, then maybe the more expensive AUC monitoring can be eliminated. In this small study, lower C₀ and AUC appeared to be associated with acute rejection in patients who had received kidney transplant for at least six months. Further prospective evaluation of TAC C₀ and AUC monitoring, in a larger cohort of patients, is warranted to answer some of the questions brought to light by this research.

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Figure 1.
Correlations between (a) C0 and AUCw and (b) C0 and AUCa in all subjects.

Figure 2.
Correlation between AUCw and AUCa measurements in Caucasians.

Table 1

Summary of demographics and immunosuppressive therapies for all the patients

Total number of patients (percent)	32 (100%)
Type of transplantation	
Kidney	30 (93.8%)
Kidney-pancreas	2 (6.2%)
Sex	
Male	18 (56.3%)
Female	14 (43.7%)
Age at transplantation	
Median (range)	37 (17 – 66)
Race	
White	21 (65.6%)
Black	8 (25.0%)
Asian	2 (6.3%)
Hispanic	1 (3.1%)
Induction therapy	
Depletional with intraoperative steroids	18 (56.2%)
Daclizumab with intraoperative steroids	11 (34.4%)
Steroids alone	2 (6.3%)
Investigational monoclonal antibody	1 (3.1%)
Maintenance immunosuppressive regimen at the time of AUC monitoring	
TAC	14 (29.2%)
TAC/Pred	5 (10.4%)
TAC/MMF	9 (18.8%)
TAC/MMF/Pred	20 (41.7%)

TAC, tacrolimus; Pred, prednisone; MMF, mycophenolate mofetil

Table 2

Summary of tacrolimus dose, concentration at various time points, and the predicted 12-hour and partial actual AUCs for all the measurements

Parameters	All (n = 48)	Time post transplantation	
		< 6 months (n = 13)	> 6 months(n = 35)
Daily dose (mg)	5 (1 – 20)	4 (2 – 12)	6 (1 – 20)
Concentration (ng/mL)			
C0	8.15 (1.40 – 14.4)	9.10 (5.10 – 14.4) ^a	7.60 (1.40 – 13.2) ^a
C1	12.1 (2.10 – 62.0)	12.4 (6.40 – 38.5)	11.9 (2.10 – 62.0)
C2	13.9 (1.90 – 30.0)	22.7 (11.0 – 30.0) ^a	12.2 (1.90 – 28.6) ^a
C4	11.8 (2.90 – 27.4)	16.1 (9.90 – 27.4) ^b	9.70 (2.90 – 21.6) ^b
Predicted 12-hour AUC (ng*h/mL)			
AUCw	117 (32.6 – 246)	175 (103 – 246) ^b	104 (32.6 – 211) ^b
AUCa	128 (34.1 – 258)	172 (101 – 258) ^a	113 (34.1 – 241) ^a
Partial actual AUC (ng*h/mL)			
AUC0-2	23.7 (3.75 – 79.7)	28.4 (16.1 – 54.1)	23.2 (3.75 – 79.7)
AUC0-4	48.4 (8.55 – 126)	76.5 (40.7 – 108) ^a	45.0 (8.55 – 126) ^a
Dose-normalized (DN) parameters			
DN-C0 (ng/mL/mg)	2.92 (0.38 – 11.3)	5.40 (1.28 – 9.07) ^a	2.75 (0.38 – 11.3) ^a
DN-AUCw (ng*h/mL/mg)	44.4 (8.29 – 151)	77.0 (31.2 – 133) ^b	38.7 (8.29 – 152) ^b
DN-AUCa (ng*h/mL/mg)	47.3 (8.63 – 172)	86.2 (25.2 – 142) ^a	42.9 (8.63 – 172) ^a

Data are presented as medians (ranges)

^{a,b} Differences between early and late post transplant;

^a p < 0.01;

^b p < 0.001

C0, C1, C2, and C4, TAC concentration at time 0, 1, 2, and 4 hours post dose; AUCw, area under the concentration-time curve predicted by equation 1;(11) AUCa, area under the concentration-time curve predicted by equation 2;(12) AUC0-2, actual area under the concentration-time curve from 0 to 2 hours; AUC0-4, actual area under the concentration-time curve from 0 to 4 hours

Table 3

Correlations between the predicted 12-hour AUCs with tacrolimus daily dose and partial actual AUCs.

Spearman Rank Correlation Coefficient (r_s)		
Parameter	AUC_w	AUC_a
Daily dose	0.248	0.264
AUC ₀₋₂	0.837*	0.833*
AUC ₀₋₄	0.937*	0.902*

*
p<0.0001

Abbreviations are defined as in footnotes of Table 2

Table 4

Induction therapy, concurrent maintenance immunosuppressive agents, and tacrolimus trough concentration (C0) and abbreviated areas-under-the-curves (AUCs) for the different biopsy groups.

Biopsy Group	Case Number	Time Post Transplant (months)	Induction	Concurrent Maintenance	Immuno- suppressants	C0 (ng/mL)	AUC _w (ng ^h /mL)	AUC _a (ng ^h /mL)
N	5	0.97	rATG	None		11.0	222	223
	22	12.3	rATG	MMF-pred		11.1	106	132
	25	0.47	Daclizumab	MMF		14.4	174	203
	39	12.2	Daclizumab	MMF-pred		8.1	186	206
	45	6.6	Daclizumab	Pred		4.7	73.6	83.9
AR	6	10.1	rATG	None		5.5	77.5	84.4
	11	12.1	Daclizumab	MMF-pred		8.2	136	150
	21	13.9	rATG	MMF-pred		5.7	68.3	77.6
CAN	31	6.6	Steroid	MMF-pred		5.9	51.8	67.4
	8	12.3	Daclizumab	MMF-pred		8.7	107	116
	34	6.2	rATG	MMF-pred		12	193	229
BK	4	37.4	Daclizumab	MMF-pred		10	121	135
T	41	34.8	rATG	Pred		8.3	101	113
	28	12.3	Steroid	MMF		6.4	89.8	97.0
BKT	48	10.2	Daclizumab	MMF-pred		6.8	211	241

N, normal; AR, acute rejection; CAN, chronic allograft nephropathy; BK, BK virus infection; T, tacrolimus toxicity; BKT, BK virus infection with tacrolimus toxicity; rATG, rabbit antithymocyte globulin; MMF, mycophenolate mofetil; pred, prednisone