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EFFECT OF THE CYP3A5 GENETIC POLYMORPHISM ON BLOOD LEVEL TO DOSE RATIO OF CYCLOSPORINE IN THAI RENAL ALLOGRAFT RECIPIENTS

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ABSTRACT

This study concentrated on the effect of *CYP3A5* polymorphism on cyclosporine (CsA) pharmacokinetics in Thai renal allograft recipients. A prospective descriptive study design was used. Thirty-four renal transplant outpatients who were on microemulsion CsA (Neoral®) and have had stable renal allograft function for at least 3 months were recruited. CsA dose and general demographic data of the patients were recorded. The CsA concentrations at C_0 and C_2 were determined in whole blood using the chemiluminescent microparticle immunoassay (CMIA). *CYP3A5* genotyping was determined by real-time PCR technique. The results obtained indicated that *CYP3A5* polymorphism was correlated with CsA dosage requirement in Thai renal transplant patients. The weight-adjusted dose was significantly higher in the *CYP3A5*1/*1* group as compare to *CYP3A5*1/*3* and *CYP3A5*3/*3* group (2.66±0.49 vs 2.07±0.53 mg/kg/day, p=0.028) while the dose-adjusted C_0 and C_2 showed tendency to be lower in the *CYP3A5*1/*1* group as compare to the other group.

Keywords: Cyclosporine, *CYP3A5* polymorphism, Dose, Relationship, Renal transplantation

INTRODUCTION

Cyclosporine (CsA) is a potent immunosuppressant drug widely used in organ transplantation and some autoimmune disease. CsA was first introduced for the prevention of graft rejection since 1970's and has had a major impact on the result of solid organ transplantation.[1-5] However, dosage of CsA is complicated by intra- and inter-individual variability of its pharmacokinetics and by the narrow therapeutic range to avoid unadequated immunosuppression and toxicity, for this reason, attention to the CsA blood concentration is essential for optimization. Because of the blood concentration of CsA reflect motality, efficacy, adverse reactions and infections thereby pharmacokinetics studies based on therapeutic drug monitoring (TDM) have been conducted for many years. However, this population pharmacokinetic model was shown to have only limited predictive value with regard to explaining the variability of CsA dose/drug concentration. In addition, a fundamental limitation of traditional TDM is that it can only be started when an immunosuppressant is administered, and so, cannot be used for the prediction of individualized initial dosage.

Therefore, an alternative is required for post-transplant management using these immunosuppressants, especially the initial setting of dose. The clinical application of pharmacogenomic provides an option for improving the large variation in individualized medication including immunosuppressive therapy after organ transplantation. Several studies have demonstrated that some genetic information is related to the inter- and intra-individual variation in the pharmacokinetics

of CsA.[6-10] CsA is mainly metabolized by the liver via CYP450. Among the CYP3A subfamily, CYP3A4 and CYP3A5 are the most abundant and important enzymes with an amino acid sequence identity of approximately 85% and largely overlapping substrates.[11] Attempting to link the polymorphism of the *CYP3A4* gene with functional effect on drug pharmacokinetics shows mostly negative results. Genetic polymorphism of *CYP3A5* has been found to be associated with more significant pharmacokinetic effects on immunosuppressive drug than those of *CYP3A4*. It has been reported that only people with at least one *CYP3A5*1* (A at position 6986) allele actually express CYP3A5 protein.[12]

A single nucleotide polymorphism (SNP) in intron 3 (*3, 6986 A>G) was found in the *CYP3A5* gene, which causes a slicing error and aberrantly spliced mRNA with a premature stop codon result in an absence of enzymatic activity, and therefore, the expression of CYP3A5 enzyme is polymorphic. In Thai population the allele frequency of *CYP3A5*3* was 66% and *CYP3A5*1* was 34%, that is similar to other Asian population but is significantly different from Caucasian and African American.[13-14] However, there has never been study about the effect of *CYP3A5* polymorphism on CsA pharmacokinetic in Thai renal allograft patients. Knowledge about the effect of *CYP3A5* polymorphism on CsA pharmacokinetics may be useful in therapeutic plans to avoid serum drug concentration-related adverse effect and reduce inappropriate dosage.

MATERIALS AND METHODS

Study design: A prospective descriptive study design was used. The protocol (no. TQC.E.001/2554) has been approved by the Ethic Committee of the Praram 9 Hospital (Bangkok, Thailand) and written informed consent was obtained from all patients.

Patients: Thirty-four (19 men and 15 women) renal transplant outpatients at the transplantation clinic who had a successful renal transplant for at least 3 months were recruited to participate in the present study. Mean patients age was 56.47±10.76 years and mean patients body weight was 67.31±14.07 kg. The authors included only renal transplants who were on microemulsion CsA (Neoral®) and have had stable renal allograft function for at least 3 months (the difference of 3 points of serum creatinine within 60 days were not more exceed than 0.3mg/dl). The data were then analyzed for relationship between *CYP3A5* genotype and level to dose ratio of CsA. Patients taking medication known to interact with CsA, such as calcium channel blockers (diltiazem, verapamil and nicardipine), antimycotics (fluconazole and ketoconazole), antiepileptics (phenytoin and carbamazepine) and macrolide antibiotics (erythromycin and clarithromycin) were not eligible for entry into the study.

Blood Sampling and Assay: Blood sample was usually obtained from forearm. Blood sample drawn in the morning before drug intake was identified as C_0 while blood sample obtained at 2-hour post dose was known as C_2. Blood sample at predose (C_0) was obtained as a part of routine monitoring. However, after they were recruited into the study, blood sample at 2 hour post dose (C_2) was obtained in their next visit in place of C_0.

Determination of CSA blood concentration: The CSA C_0 and C_2 values were determined in whole blood with the chemiluminescent microparticle immunoassays (CMIA) according to the manufacturers' instruction (The Architect I® System, Abbott Laboratories, Chicago, IL, USA) which the measurement range of these assays is 30.0 ng/ml to 1500.0 ng/ml. Dose-adjusted C_0 and C_2 were calculated by dividing the C_0 and C_2 by the corresponding 24-hour dose on milligrams per kilogram basis.

Determination of CYP3A5 Genotypes: Whole blood in EDTA tube for *CYP3A5* genotyping was prepared as buffy coat by centrifuge at 2,500 g for 10 minutes at room temperature. After centrifugation, 3 different fractions are distinguishable: the upper clear layer is plasma; the intermediate layer is buffy coat, containing concentrated leukocytes; and the bottom layer contains concentrated erythrocytes.The 200 mcl of buffy coat were stored in freezer at -20°C until extracted for DNA by QIAmp® DNA Blood Mini kit (QIAGEN Laboratories). *CYP3A5* genotyping was identified using specific primers and TaqMan® minor groove binder (MGB) probes, which had a reporter dye of either FAM™and VIC® at the 5' end and a nonfluorescent quencher at 3' end. These assays were purchased from ABI and they were using TaqMan® PCR. Each primer and probe set was used in the TaqMan® SNP Genotyping Assay (ABI) in accordance with the information on the Applied Biosystems website (http://www.appliedbiosystems.com). Alleles were detected using an Allelic Discrimination Assay (Steponeplus, Sequence Detection System (SDS), Applied Biosystems, Foster, CA). Genotype was determined visually based on the dye-component fluorescent emission data depicted in the X-Y scatter-plot of the SDS software.

Data analysis: The data were analyzed using the computer software SPSS for Windows (Ver. 17.0; SPSS Co., Ltd., Bangkok, Thailand). The demographic data were determined and presented as mean and standard deviation, percentage or frequency. The quantitative parameter variables were expresses as the mean and standard deviation. Quantitative parameters were determined for normality of distribution using Kolmogorov-Smirnov test and determined for homogeneity of variance using Levene's test. Dose-adjusted C_0 and C_2 as well as daily dose were compared among individuals according to allelic status of *CYP3A5* using the 1-way ANOVA (Kruskal-Wallis test), followed by the Schffe post hoc test for multiple comparisons or T-test as appropriated. A *P* value of ≤ 0.05 was considered statistically significant.

RESULTS

Demographic data: Data were included for analysis from the total of 34 patients. Twenty-one patients received cadaver while 13 patients received living-related renal transplant. The mean time after transplantation (range) was 7.53±4.87 years (ranged from 1 year 7 months to 17 years 5 months). All patients were treated with triple drug regimen (CsA, Mychophenolate mofietil and prednisolone) for immunosuppression. The CsA dose was range from 50 to 200 mg/day with a mean value of 141.91±32.98 mg/day. The demographic characteristics of the patients are shown in **Table 1.**

Population allelic frequencies: Genotyping of *CYP3A5* was obtained for all 34 patients. When characterized the patients into 3 groups by *CYP3A5* genotyping, there were 5 patients (14.7%) with homozygous **1/*1*, 13 patients (38.2%) with heterozygous **1/*3* and 16 patients (*47.1%*) with homozygous **3/*3*. The allele frequency of *CYP3A5*1* was 33.8% and *CYP3A5*3* was 66.2% which were in Hardy-Weinberg Equilibrium. Patient's gender and body weight were not significantly different while the patient's age was different among the 3 groups of different genotypes. The demographic characteristics of patients when categorized patients into 3 groups based on *CYP3A5* genotypes are shown in **Table 2.**

Effect of CYP3A5 genotypes on CsA blood concentrations at trough (C_0) and at 2 hour post dose (C_2): The weight-adjusted dose was significantly higher in the *CYP3A5*1/*1* group when compare to *CYP3A5*3/*3* group (post hoc; p = 0.021) while the dose-adjusted C_0, dose-adjusted C_2, CsA C_0 and CsA C_2 were not significantly different. However, the mean dose-adjusted C_0 showed an increasing trend in the patients with non-expressor alleles (**3*). This result showed the higher dose requirement in patients with *CYP3A5*1/*1* genotype. The comparisons of CsA dose, CsA C_0, CsA C_2, dose-adjusted CsA C_0 and dose-adjusted CsA C_2 among the renal transplant patients with different of *CYP3A5* genotype are shown in **Table 3**.

When we categorized patients into 2 groups based on *CYP3A5* genotypes by included *CYP3A5*1/*3* into the same group as *CYP3A5*3/*3*; the weight-adjusted dose in *CYP3A5*1/*1* group was significantly higher while the dose-adjusted C_0 and dose-adjusted C_2 of the *CYP3A5*1/*1* group showed the tendency to be lower than the other group even though these differences did not reach the statistically significant level at œ = 0.05 (p= 0.070 and p= 0.066, respectively). The comparisons of CsA dose, CsA C_0, CsA C_2, dose-adjusted CsA C_0 and dose-adjusted CsA C_2 when categorized patients into 2 groups (*CYP3A5*1/*1* versus *CYP3A5*1/*3* + *CYP3A5*3/*3* genotype) are shown in **Table 4.**

DISCUSSION

The clinical use of CsA is complicated by their narrow therapeutic index and highly variable and unpredictable pharmacokinetic in individual patients. CsA absorption is slow, incomplete and highly variable after oral administration, bioavailability range from 5 to 90 % with a mean of 30%. In an effort to improve considerable variability in pharmacokinetics a new formulation of CsA (Microemulsion CsA, Neoral®) has been developed. Microemulsion CsA is more quickly absorbed and exhibits, on average, a 29% higher bioavailability. In addition, Micro-emulsion CsA produces a more uniform exposure to CsA throughout the day, and from day to day on maintenance regimen.[15]

Although, therapeutic drug monitoring is routinely performed, both acute and chronic toxicity occur in everyday clinical practice. The most significant adverse effect of CsA is nephrotoxicity which is a major drawback of CsA therapy. Other side effects are hirsutism, gingival hyperplasia, and a variety of neurologic syndromes such as headaches, tremors, and paresthesias can occur. Moreover, some patients do not reach target concentrations with the recommended starting dose and therefore have an increase risk of underimmunosuppression and acute rejection.[16] CsA is metabolized by CYP3A4/5 in both liver and enterocyte.[17-19] CYP3A5 is a hepatic, intestinal and kidney drug-metabolizing enzyme that

is closely relate in structure and function to CYP3A4.[20] One of the *CYP3A5* polymorphism, *CYP3A5*3* allele that has SNP in intron3 (A6986G) and causes alternative splicing and protein truncation, thereby affecting CYP3A5 expression.[21-23] The functional defect in CYP3A5 enzyme cause the interindividual variability in the disposition of calcineurin inhibitors.

Although the effect of *CYP3A5* polymorphism on tacrolimus is clear that *CYP3A5*3/*3* patients has a higher dose-adjusted C_0 and required lower tacrolimus dose to achieved the target level when compare to *CYP3A5*1* carriers, the effect of this SNP on CsA pharmacokinetic is controversial. Whereas correlations between the *CYP3A5* genotype and dose-adjusted CsA concentration was found by some studies,[24-25] these effect were not observed by other studies.[26-27] Besides, these conflicting finding may be due to differences in the frequencies of *CYP3A5*1* and *CYP3A5*3* variants, the examined pharmacokinetic parameters, the low power of the test due to small numbers of patients participated in the study especially those patients in *CYP3A5*1/*1* group. Some studies have use CsA trough level, whereas other examines CsA exposure using area under the concentration-time curves.

In the present study, we determined the frequency of the *CYP3A5*3* allele in Thai kidney transplant recipients. Our finding indicate that the frequency of the *CYP3A5*3* allele was similar to previous study in Thai population and in all Asians, including Chinese, Indian, Malaysians and Japanese populations,[13-14,28] but are different from those report to other populations, including Caucasian and African-American populations.[12,29] Moreover, we explored the effect of *CYP3A5* genotype polymorphism on CsA dose-adjusted C_0 and dose-adjusted C_2 in the Thai renal transplant recipients. The findings show that the CsA weight-adjusted dose in patients with *CYP3A5*1/*1* genotype was highest while the dose-adjusted C_0 and dose-adjusted C_2 was lowest due to the fact that CYP3A5*1/*1* express larger amount of CYP3A5 enzyme.

This implies that *CYP3A5* polymorphism was correlated with CsA dosage requirement; thus, the patients with the *CYP3A5*1/*1* genotype could require a higher dose of CsA to achieve target CsA blood concentrations than those with the *CYP3A5*1/*3* and *CYP3A5*3/*3* genotype.
The mean dose-adjusted CsA C_0 show an increasing trend in the patients with non-expressor allele (36.87±11.98, 48.96±14.47, 52.26±17.03 ng/ml per mg/kg/day, respectively) even though not reaching the statistically different level (p=0.169) which might due to the small number of patients in each group.

Comparisons of CsA daily dose, C_0, C_2 ,dose-adjusted C_0 and dose-adjusted C_2 when categorized the 34 patients into 2 groups of different genotypes *CYP3A5*1/*1* VS *CYP3A5*1/*3* and *CYP3A5*3/*3*, showed statistically significantly higher in weight-adjusted daily dose while the dose-adjusted C_0 and dose-adjusted C_2 were nearly statistically significantly lower in patients with *CYP3A5*1/*1* compare to the group of patients with *CYP3A5*1/*3* or *CYP3A5*3/*3* genotypes. We found that dose-adjusted C_0 and dose-adjusted C_2 were approximately 1.4 fold higher in *CYP3A5*3/*3* patients than in *CYP3A5*1/*1* patients. These results is similar with the report by Haufroid et al,[24] they reported that dose-adjusted CsA C_0 was 1.6 fold higher in *CYP3A5*3/*3* patients than in *CYP3A5*1/*3* patients. However, this different did not reach statistically significant level which might due in part to the low power of the test since the number of patients in the *CYP3A5*1/*1* group was so small while the variation within the same genotype was quite high. Since this group of patients was routinely monitoring for C_0 and the dosage of CsA was adjusted accordingly, the level of C_0 was nearly equal in all genotypes. After the patients were recruited into this study, C_2 was monitored in place of C_0 in their next visit for research observation. C_2 and dose-adjusted C_2 showed tendency to be lower in the *CYP3A5*1/*1* group as compare to *CYP3A5*1/*3* and *CYP3A5*3/*3* groups. This result indicated that if C_2 is proposed to be monitoring in place of C_0 (due to its higher correlate to clinical outcome), higher than present dosage of CsA may be required in the *CYP3A5*1/*1* group which will enlarge the significant difference in CsA dosage requirement among different CYP3A5 genotypes.

Note: In this study the age of patients in CYP3A5*1/*1* group was significantly lower than the other group; this might confound the results obtained. Further study in larger number of patients which rule out this confounding effect is required.

CONCLUSIONS

The present study has demonstrated that genetic polymorphism of *CYP3A5* at intron 3 was responsible, at least in part, for the marked variability in CsA dosage requirement in Thai renal transplant patients. Patients with the *CYP3A5*1/*1* genotype may need to be given a higher dose of CsA to reach target concentrations compare with the patients that were *CYP3A5*3/*3*. In organ transplantation, the

poor bioavailability and large intra- and inter-individual variability in the administration of immunosuppressive drug limit the postoperative drug therapy, which may subsequently affect the function and lifespan of grafts. It is of great importance to individualize the therapeutic regimens in different patients to balance clinical efficacy and toxicity. Pharmacogenetic detection of *CYP3A5*3* before transplantation is likely to be useful in clinical practice to optimize the initial dose of CsA administered to individual renal transplant patients. However, the clinical applicability of this approach and change in the initial dose of CsA based on the outcome of genotype screening remain to be proven.

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Table 1: Demographical characteristics of the patients (N=34).

Demographical data	Frequency, (Mean ± SD or Median)	Percentage (%)
Gender		
Male	19	55.9
Female	15	44.1
Age (year)	56.47±10.76	
Weight (Kg)	67.31±14.07	
Cause of chronic renal failure		
Diabetic nephropathy	6	17.6
Chronic glomerulonephritis	22	64.8
IgA nephropathy	3	8.8
Others	3	8.8
Follow- up time (Year)	7.53±4.87	
Graphic illustration		
CDKT	21	61.8
LRKT	13	38.2
Concomitant disease*		
Hypertension	29	
Diabetes	11	
Cardiovascular disease	7	
Hypercholesterol	20	
Other	5	

Abbreviations: CDKT: Kidney taken from cadavers; LRKT: Kidney taken from living donors
** Some patients had more than one concomitant disease*

Table 2: Demographic characteristics of patients when categorized patients into 3 groups based on *CYP3A5* genotypes

Demographic data	*CYP3A5*1/*1*	*CYP3A5*1/*3*	*CYP3A5*3/*3*	*P*-value
No. of patients	5	13	16	
Gender (male/female) [a]	2/3	7/6	10/6	0.493
Age (year, Mean±SD) [b]	45±13.56	55.85±9.87	60.56±8.09	0.013
Body weight (kg,Mean±SD) [b]	63.4±15.82	67.99±13.79	67.98±14.5	0.807

[a] *Chi-square test,* [b] *One-way ANOVA.*

Table 3: Comparisons of CsA dose, CsA C_0, CsA C_2, dose-adjusted CsA C_0 and dose-adjusted CsA C_2 among the renal transplant patients with different of *CYP3A5* genotype

Parameter	*CYP3A5*1/*1*	*CYP3A5*1/*3*	*CYP3A5*3/*3*	*P*-value[a]
Number of patients	5	13	16	
CsA daily dose (mg/day, Mean±SD)	165±33.54	142.31±21.37	134.38±38.6	0.197
Weight-adjusted dose (mg/kg/day, Mean±SD)	2.66±0.49*	2.16±0.53	2.00±0.53*	0.067
CsA C_0	98.00±32.91	101.69±21.69	99.50±28.78	0.959
CsA C_2 (ng/ml, Mean±SD)	498.20±230.93	731.54±310.57	530.88±209.35	0.083
Dose-adjusted C_0	36.87±11.98	48.96±14.47	52.26±17.03	0.169
Dose-adjusted C_2 (ng/ml per mg/kg/day, Mean±SD)	188.10±87.93	349.63±158.36	273.85±105.61	0.056

[a] *One-way ANOVA*
**Post-hoc ; p=0.021*

Table 4: Comparisons of CsA dose, CsA C_0, CsA C_2, dose-adjusted CsA C_0 and dose-adjusted CsA C_2 when categorized patients into 2 groups (*CYP3A5*1/*1* versus *CYP3A5*1/*3* + *CYP3A5*3/*3* genotype)

Parameter	*CYP3A5*1/*1*	*CYP3A5*1/*3+CYP3A5*3/*3*	*P*-value[a]
Number of patients	5	29	
CsA daily dose (mg/day, mean±SD)	165±33.54	137.93±31.78	0.090
Weight-adjusted dose (mg/kg/day, mean±SD)	2.66±0.49	2.07±0.53	0.028*
CsA C_0	98.00±32.92	100.48±25.43	0.848
CsA C_2 (ng/ml, mean±SD)	498.20±230.93	620.83±274.10	0.354
Dose-adjusted C_0	36.87±11.98	50.78±15.75	0.070
Dose-adjusted C_2 (ng/ml per mg/kg/day, mean±SD)	188.10±87.93	307.82±134.88	0.066

[a] *t-test*

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