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Letter to the Editors

Impact of *CYP3A5* genetic polymorphism on pharmacokinetics of tacrolimus in healthy Japanese subjects

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Tacrolimus (TAC), a calcineurin inhibitor, is an important immunosuppressive agent for treating autoimmune disease, including myasthenia gravis and rheumatoid arthritis, as well as for preventing allograft rejection in organ transplantation [1]. Since the therapeutic range of blood TAC is narrow, current interest focused on this drug is to maintain optimal blood concentrations in therapeutic drug monitoring (TDM) based on pharmacogenomic data, such as *CYP3A5* and *MDR1* gene polymorphisms [2]. Fukudo *et al.* [2] have reported that both *CYP3A5* genotype and MDR1 mRNA expression were important factors affecting TAC pharmacokinetics in paediatric living related liver transplantation. Choi *et al.* [3] have revealed the impact of *CYP3A5* genotype on TAC pharmacokinetics in healthy Koreans, where the area under the concentration–time curve (AUC) of TAC in subjects with *CYP3A5*3/*3* was 2.5-fold higher compared with *CYP3A5*1* carriers. We have examined the impact of *CYP3A5* and *MDR1* genetic polymorphism on TAC pharmacokinetics in healthy Japanese by using population pharmacokinetics (PPK) analysis. This study was approved by the Ethical Committee of University of Tsukuba (Tsukuba, Japan) and written informed consent was obtained in each case.

Twenty healthy subjects received a single dose of oral TAC (2 mg; Prograf; capsule Astellas Pharma Inc., Tokyo, Japan). Venous blood samples for determining blood TAC were collected before and 1, 2, 4 and 8 h after the administration. Blood TAC was determined by microparticle enzyme immunoassay. Since the blood TAC concentration at 8 h after dose was as low as the detection limit for this method (1.5 ng ml^{-1}), we did not measure the concentration after 8 h. PPK analysis was performed using WinNonMix (Version 2.0; Pharsight, Mountain View, CA, USA) with a one-compartment model to calculate apparent clearance (CL/*F*) and volume of distribution (*V*/*F*). The absorption rate constant (k_a) was fixed to a reported value (4.5 h^{-1}) [4]. Age, body weight, sex, and *CYP3A5* and *MDR1* genotypes were evaluated as the covariates by conducting a forward and backward stepwise regression analysis. Genome DNA was isolated from peripheral blood by using the QIAamp DNA Mini Kit (Qiagen GmbH, Hilden, Germany). The genotyping of *CYP3A5* and *MDR1* at the position of 1236C→T, 2677G→A/T and 3435C→T, was conducted by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method [5, 6]. *MDR1*–1517a T→C polymorphism, which was reported by Takane *et al.* [7] as the predictive factor of the expression level of MDR1 mRNA (NCBI dbSNP ID: rs28381796), was also genotyped by using a PCR-RFLP method developed in our laboratory.

TAC pharmacokinetic parameters are summarized in Table 1. The AUC_{0-8h} in subjects with *CYP3A5*3/*3* were 1.8-fold higher than that in *CYP3A5*1* carriers ($P = 0.03$), which agreed with the report of Choi *et al.* [3]. *MDR1*–1517a T/C genotype ($n = 4$) tended to have lower AUC_{0-8h} compared with –1517a T/T genotype ($n = 10$) (20.8 ± 11.1 *vs.* 29.2 ± 8.2 ng h ml^{-1}) in *CYP3A5*1* carriers, although the difference was not statistically significant because of insufficient power.

We conducted PPK analysis to estimate the contribution of *CYP3A5* genotype on individual variations of TAC pharmacokinetics. Among the covariates, body weight affected the *V*/*F* and CL/*F*, and *CYP3A5*1* allele only affected CL/*F* (Table 2). The estimated CL/*F* in subjects with *CYP3A5*1* carriers was 1.5 times higher than that in subjects with *CYP3A5*3/*3* (Table 2), which was comparable to measured values. The interindividual variability in CL/*F* with final model 4 was reduced from that with model 3 including no genetic covariates (22.4% to 9.7%, base model 1; 40.3%). These results suggest that approximately 32% of the interindividual variation of TAC CL/*F* can be explained by *CYP3A5* polymorphism in healthy Japanese. This value is greater than the 9% and 23% reported, which were obtained in paediatric [2] and adult [8] liver transplantation situations, respectively. The liver transplantation is very complex in estimating the efficacy of *CYP3A5* polymorphism on TAC pharmacokinetics, because of several issues such as the

Table 1

Effect of *CYP3A5* polymorphism on tacrolimus pharmacokinetics in healthy Japanese

CYP3A5	*n* (M/F)	Age (years)	Weight (kg)	AUC_{0-8h} (ng h ml^{-1})	*CL/F* ($l\ h^{-1}\ kg^{-1}$)
***1* carrier**	14 (13/1)	35.6 ± 8.0	66.2 ± 11.0	26.8 ± 9.5 (21.8, 31.7)	1.33 ± 0.61 (1.01, 1.64)
3/*3	6 (5/1)	26.2 ± 1.3	66.2 ± 11.8	48.0 ± 21.9 (30.5, 65.6)	0.73 ± 0.25 (0.53, 0.93)
***P*-value†**	–	0.009	–	0.032	0.032

†Mann–Whitney *U*-test. Values are given as number of subjects or mean ± SD. Values in parentheses represent the 95% confidence interval.

Table 2

Summary of analysis models estimating for pharmacokinetic parameters of tacrolimus

Models	ΔOFV†	Interindividual variability *V/F*	Interindividual variability CL/*F*
1 $V/F = \theta_1 \cdot e^{\eta_i}$, $CL/F = \theta_2 \cdot e^{\eta_i}$	–	32.6%	40.3%
2 $V/F = \theta_1 \cdot BW \cdot e^{\eta_i}$, $CL/F = \theta_2 \cdot e^{\eta_i}$	8.46	21.0%	36.1%
3 $V/F = \theta_1 \cdot BW \cdot e^{\eta_i}$, $CL/F = \theta_2 \cdot BW \cdot e^{\eta_i}$	7.90	23.1%	22.4%
4 $V/F = \theta_1 \cdot BW \cdot e^{\eta_i}$, $CL/F = \theta_2 \cdot BW \cdot \theta_3^{CYP3A5*1} \cdot e^{\eta_i}$	7.48	26.7%	9.7%

BW, body weight; CL/*F*, apparent clearance; OFV, objective function value; ΔOFV, difference in OFV; *V/F*, apparent volume of distribution. Parameter of model 4 is described by the following equations: $V/F = 3.24 \cdot BW$, $CL/F = 0.55 \cdot BW \cdot 1.49^{CYP3A5*1}$ (if the subject was a *CYP3A5*1* allele carrier, then *CYP3A5*1* = 1, otherwise 0). †ΔOFV greater than 3.84 (d.f. = 1) was accepted as statistically significant ($P < 0.05$).

mismatch in genotype between recipients and donors and change in enzyme activities due to liver function, which may explain the discrepancy between the present and reported values. Because these factors associated with liver transplantation do not affect TAC pharmacokinetics in patients with myasthenia gravis and rheumatoid arthritis as well as healthy subjects, it is considered that the impact of *CYP3A5* genotype on TAC TDM for autoimmune diseases is important. We therefore suggest that it would be useful to include *CYP3A5* genotyping in TAC therapy for autoimmune diseases, especially in the Asian population, which frequently carry the *CYP3A5*1* allele.

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