Eur J Clin Pharmacol (2015) 71:1091–1097
DOI 10.1007/s00228-015-1901-4

PHARMACOKINETICS AND DISPOSITION

Effect of *CYP3A5* and *ABCB1* polymorphisms on the interaction between tacrolimus and itraconazole in patients with connective tissue disease

Masaru Togashi[1] · Takenori Niioka[2] · Atsushi Komatsuda[1] · Mizuho Nara[1] · Shin Okuyama[3] · Ayumi Omokawa[4] · Maiko Abumiya[2] · Hideki Wakui[5] · Naoto Takahashi[1] · Masatomo Miura[2]

Received: 9 May 2015 / Accepted: 2 July 2015 / Published online: 17 July 2015

Abstract
Purpose The aim of this study was to investigate the effect of itraconazole (ITCZ), a potent inhibitor of CYP3A4 and P-glycoprotein, on the blood concentration 12 h after tacrolimus administration (C_{12h}) in relation to *CYP3A5* 6986A>G and *ABCB1* 3435C>T genotype status in patients with connective tissue disease (CTD).
Methods Eighty-one CTD patients taking tacrolimus (Prograf®) once daily at night (2100 hours) were enrolled in this study. Whole blood samples were collected 12 h after tacrolimus administration at steady state.
Results The dose-adjusted tacrolimus C_{12h} with or without ITCZ co-administration was significantly higher in patients with *CYP3A5*3/*3* than in those with the *CYP3A5*1* allele [*CYP3A5 *1/*1* vs. **1/*3* vs. **3/*3* = 1.67 vs. 2.70 vs. 4.83 ng/mL/mg ($P = 0.003$) and 0.68 vs. 0.97 vs. 2.20 ng/mL/mg ($P < 0.001$), respectively], but differences were not observed for *ABCB1* genotypes. However, there was no difference in the increase rate of the dose-adjusted C_{12h} of tacrolimus between *CYP3A5* or *ABCB1* genotypes ($P = 0.378$ and 0.259). On the other hand, reduction of the estimated glomerular filtration rate exhibited a correlation with the C_{12h} of tacrolimus after ITCZ co-administration ($r = -0.482$, $P = 0.009$).
Conclusions In *CYP3A5*3/*3* patients, because the metabolic pathway for tacrolimus occurs only through CYP3A4, the combination with ITCZ seems to lead to a higher risk of acute renal dysfunction. Therefore, we suggest that the target blood tacrolimus concentration be set as low as possible through dose-adjustment for patients with the *CYP3A5*3/*3* allele.

Keywords Itraconazole · Tacrolimus · *CYP3A5* polymorphism · Drug-drug interaction · Connective tissue disease

Masaru Togashi and Takenori Niioka contributed equally to this work.

Electronic supplementary material The online version of this article (doi:10.1007/s00228-015-1901-4) contains supplementary material, which is available to authorized users.

✉ Atsushi Komatsuda
komatsud@med.akita-u.ac.jp

[1] Department of Hematology, Nephrology, Rheumatology, Akita University Graduate School of Medicine, 1-1-1 Hondo, Akita 010-8543, Japan

[2] Department of Pharmacy, Akita University Hospital, Akita, Japan

[3] Center for Kidney Disease and Transplantation, Akita University Hospital, Akita, Japan

[4] Department of General Internal Medicine and Clinical Laboratory Medicine, Akita University Graduate School of Medicine, Akita, Japan

[5] Department of Life Science, Graduate School of Engineering and Resource Science, Akita University, Akita, Japan

Introduction

Tacrolimus is used for patients with connective tissue disease (CTD), which includes rheumatoid arthritis and systemic lupus erythematosus, to control disease activity [1–4]. In Japan, an oral twice-daily formulation of tacrolimus (Prograf®, Astellas, Tokyo, Japan) was approved for use in CTD patients. Although organ transplant recipients take tacrolimus (Prograf®) twice daily [5], CDT patients take a single daily dose of Prograf® after the evening meal [2–6]. Since the blood concentration 12 h after tacrolimus administration (C_{12h}) can be measured during outpatient visits at the hospital the following morning, C_{12h} monitoring is particularly convenient.

The antifungal agent itraconazole (ITCZ) is used as a therapeutic or preventive drug for superficial mycosis, including candidiasis and trichophytia [7–9], and is often administered to CTD patients. Since ITCZ potently inhibits the activity of P450 (CYP) 3A and P-glycoprotein, which is encoded by the ATP-binding cassette subfamily B member 1 (ABCB1) [10–13], the blood concentration of tacrolimus, which is metabolized by CYP3A and transported by ABCB1, increases following ITCZ administration [14–16]. Therefore, clinicians should pay particular attention to tacrolimus-induced side effects when co-administered with ITCZ. In addition to inhibiting CYP3A, ITCZ is also metabolized stereoselectively by CYP3A4 [17, 18]. The metabolites of ITCZ, hydroxy-ITCZ, keto-ITCZ, and *N*-desalkyl-ITCZ, contribute to CYP3A4 inhibition [13]. The persistent inhibition of CYP3A4 after ITCZ dosing is related to the effects of inhibitory metabolites with long half-life [13].

The largely inter-individual variability in the pharmacokinetics of tacrolimus can be explained by a single nucleotide polymorphism (SNP) in intron 3 of *CYP3A5* 6986A>G. An association between the *CYP3A5* genotype and tacrolimus pharmacokinetics is well established [19–21], i.e., the blood concentrations of tacrolimus are higher for patients with *CYP3A5*3/*3* than for those with the *CYP3A5*1* allele [19–21]. On the other hand, the functional significance of *ABCB1* 3435C>T expression and function remains unclear [19, 22]. Therefore, the drug interaction between tacrolimus and ITCZ might differ in magnitude among *CYP3A5* and *ABCB1* genotypes [13]. To the best of our knowledge, however, no study has evaluated the magnitude of drug-drug interactions and safety based on the C_{12h} of tacrolimus and *CYP3A5* or *ABCB1* polymorphisms in CTD patients co-administered ITCZ.

Therefore, the aim of this study was to investigate the effect of *CYP3A5* and *ABCB1* polymorphisms on the interaction between tacrolimus and ITCZ in CTD patients.

Methods

Patients and protocols

A single-institute, retrospective study was conducted to evaluate the drug-drug interaction between orally administered ITCZ and tacrolimus (Prograf®, Astellas, Tokyo, Japan) in patients being treated for CTD (as shown in Table 1) at Akita University Hospital. ITCZ (50–200 mg/day) was administered to CTD patients to prevent fungal infection, such as superficial mycosis. CTD patients were administered Prograf® once daily at night, 2100hours, and they were not allowed to consume drugs or food affecting CYP3A and ABCB1 activity, with the exception of ITCZ. Patients with a serum creatinine >2.0 mg/dL or creatinine clearance <30 mL/min (n = 2) and patients who did not have their tacrolimus blood concentration monitored (n = 5) were excluded from this study. The study was conducted according to the

Table 1 Clinical characteristics of 81 patients with connective tissue disease

Sex	
Males	13 (16.0 %)
Females	68 (84.0 %)
CYP3A5 genotypes	
**1/*1*	4 (4.9 %)
**1/*3*	33 (40.8 %)
**3/*3*	44 (54.3 %)
ABCB1 (3435C>T) genotypes	
C/C	26 (32.1 %)
C/T	39 (48.1 %)
T/T	16 (19.8 %)
Age (year)	46.4 ± 17.6 (16–77)
Body weight (kg)	55.2 ± 11.3 (35.9–96.0)
Body surface area (m^2)	1.55 ± 0.17 (1.16–2.00)
Laboratory values at tacrolimus initiation	
Aspartate transaminase (IU/L)	21.2 ± 10.8 (6.0–71.0)
Alanine transaminase (IU/L)	23.1 ± 20.5 (7.0–118.0)
Hemoglobin (g/dL)	12.6 ± 1.5 (9.6–15.6)
Serum albumin (g/dL)	3.8 ± 0.5 (2.6–4.9)
Serum creatinine (mg/dL)	0.6 ± 0.2 (0.3–1.5)
Potassium (mEq/L)	4.0 ± 0.4 (3.1–5.2)
Estimated glomerular filtration rate (mL/min)	112.0 ± 39.5 (36.6–218.6)
Diagnosis	
Systemic lupus erythematosus	51 (63.0 %)
Rheumatoid arthritis	20 (24.7 %)
Vasculitis	3 (3.7 %)
Behcet's disease	3 (3.7 %)
Mixed connective tissue disease	2 (2.5 %)
Dermatomyositis	1 (1.2 %)
Chronic inflammatory demyelinating polyneuropathy	1 (1.2 %)
Patients with itraconazole	35 (43.2 %)
Daily dose of itraconazole (mg/day)	
50 mg	5 (14.3 %)
100 mg	23 (65.7 %)
200 mg	7 (20.0 %)

Data presented as mean ± standard deviation (range) or number (%)

Body surface area (BSA) (m^2) = body weight $(kg)^{0.425}$ * body height $(cm)^{0.725}$ * 0.007184

eGFR = 194 * serum creatinine $(mg/dL)^{-1.094}$ * $Age^{-0.287}$ * BSA (m^2)/1.73 (* 0.739 for female)

eGFR estimated glomerular filtration rate

Declaration of Helsinki principles. The study protocol was approved by the Ethics Committee of Akita University Hospital, and all patients gave written informed consent.

Data extraction, sample collection, and analytical methods

CTD patient information including disease name, clinical characteristics, prescription history, and laboratory values were obtained from the medical care information system in Akita University Hospital. The follow-up period was from October 2007 to September 2014. Consequently, data for 81 Japanese patients were available. Whole blood samples were collected 12 h after tacrolimus administration. The median of multiple tacrolimus C_{12h} values for each patient was used (supplementary document 2, Tables 2 and 3). For patients who had added ITCZ during tacrolimus therapy ($n = 28$), the tacrolimus C_{12h} in the first week after ITCZ combination was excluded from this study (Figs. 1, 2 and 3). Blood concentrations of tacrolimus were determined by the chemiluminescence magnetic microparticle immunoassay on the Architect-i1000 ® system (Abbott Laboratories; Abbott Park, IL) according to the manufacturer's instructions. The total imprecision was 7.0, 5.7, and 4.8 % at the three target concentrations of tacrolimus (3.2, 8.5, and 15.9 ng/mL), respectively [23]. The limit of detection and limit of quantitation (LOQ) of the Architect-i1000® method were 0.25 and 0.5 ng/mL, respectively [23].

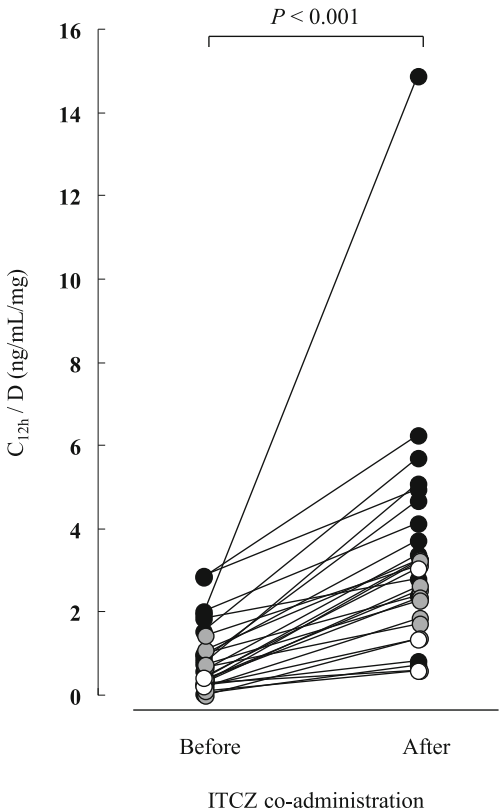

Fig. 1 Changes in the dose-adjusted C_{12h} of tacrolimus before and after concomitant use of itraconazole (ITCZ) in each patient. C_{12h} blood concentration at 12 h after tacrolimus administration. *White circle*, *CYP3A5 *1/*1*; *gray circle*, **1/*3*; *black circle*, **3/*3*

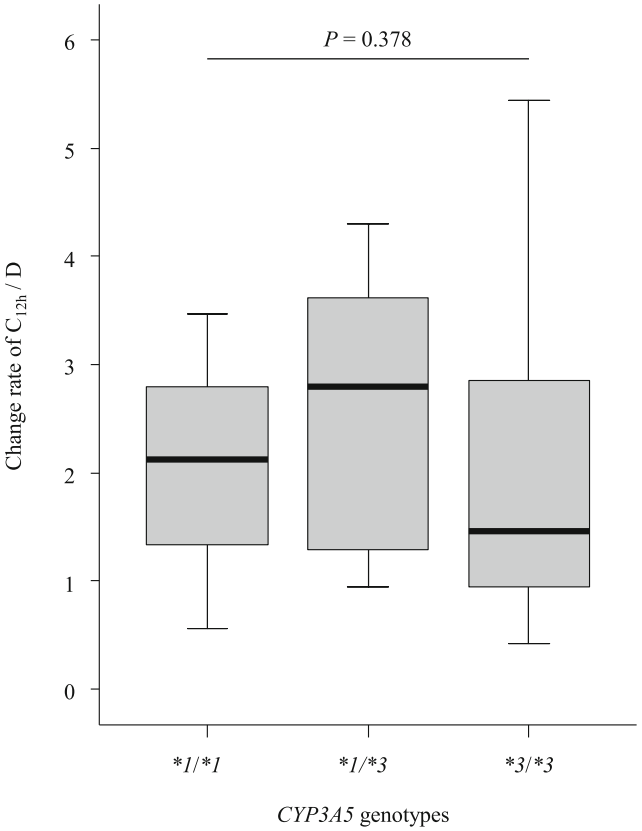

Fig. 2 Comparisons of change rate of dose-adjusted C_{12h} (C_{12h}/D) of tacrolimus with ITCZ administration between *CYP3A5* genotype groups. Change rate = (C_{12h}/D after co-administration of ITCZ–C_{12h}/D before beginning ITCZ)/C_{12h}/D before beginning ITCZ. Graphical analysis was performed using an SPSS box and whiskers plot. The box spans data between two quartiles (IQR), with the median represented as a *bold horizontal line*. The ends of the whiskers (*vertical lines*) represent the smallest and largest values that were not outliers. C_{12h} blood concentration 12 h after tacrolimus administration

Genotyping

DNA was extracted from a peripheral blood sample using a QIAamp Blood Kit (Qiagen, Hilden, Germany) and was stored at −80 °C until being analyzed. For genotyping the *CYP3A5* 6986A>G (**3*) allele, the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was used [24]. Genotyping procedures to identify the C and T alleles in exon 26 of the *ABCB1* 3435C>T were also performed with the PCR-RFLP method [25]. The analysis results obtained from PCR-RFLP were confirmed using a fully automated single nucleotide polymorphism (SNP) detection system (prototype i-densy®, Arkray Inc., Kyoto, Japan).

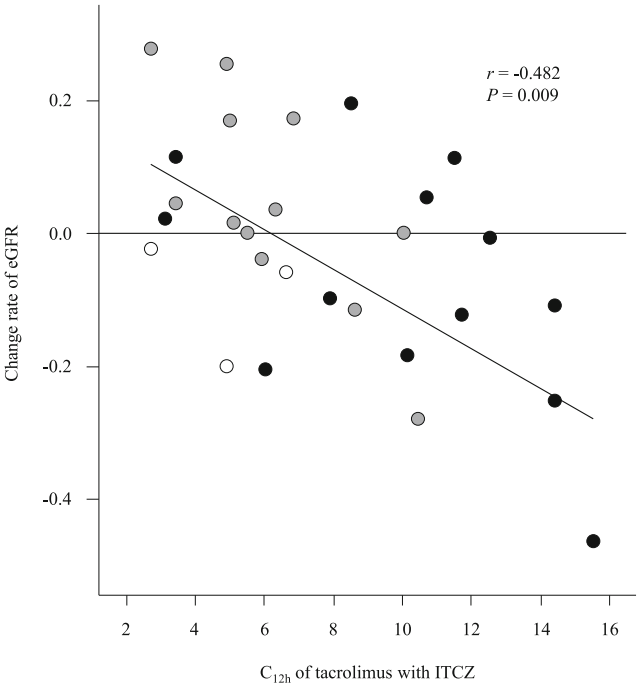

Fig. 3 Correlation between change rate of the estimated glomerular filtration rate (eGFR) and tacrolimus C_{12h} after itraconazole administration. *White circle*, *CYP3A5 *1/*1*; *gray circle*, **1/*3*; *black* circle, **3/*3*; C_{12h} blood concentration 12 h after tacrolimus administration. Change rate = (eGFR after co-administration of ITCZ − eGFR before beginning ITCZ)/eGFR before beginning ITCZ

Statistical procedures

In our previous studies on the pharmacogenomics of CYP3A5 [26, 27], 10 patients were the necessary sample size of one genotype to obtain $\alpha = 0.05$ and $\beta = 0.2$ (power of 80 %). To allow for stratification by genotype, more than 10 patients for each *CYP3A5* genotype were targeted for enrollment in this study. On the other hand, since the functional significance of *ABCB1* 3435C>T expression and function remains unclear, a sample size calculation for those examinations was not performed. The Shapiro-Wilk test was used to assess distribution. The characteristics of CTD patients were expressed as the mean ± standard deviation (range). The parameters of tacrolimus and laboratory test values were expressed as medians (quartile 1–quartile 3). The Kruskal-Wallis test or Mann-Whitney *U* test was used to determine the difference in continuous values between groups. The Wilcoxon signed-rank test was used to determine the difference in continuous values within each patient. Spearman's rank correlation coefficient test was used to assess correlations with the C_{12h} of tacrolimus, and all results were expressed as a correlation coefficient of determinant (*r*). Stepwise multiple linear regression analysis was performed to determine the effect of factors with a *P* value of <0.2 in univariate analysis. For each patient, the *CYP3A5* and *ABCB1* genotypes were replaced with dummy variables (1 and 0, 0 and 1, and 0 and 0, respectively). The percent of variation that can be explained by the multiple regression equation was expressed as a coefficient of determination (R^2). The estimated glomerular filtration rate (eGFR) was calculated for each CTD patient according to the following formula: eGFR = 194 * serum creatinine (mg/dL) $^{-1.094}$ * age $^{-0.287}$ * body surface area (m^2)/1.73 (* 0.739 for female). The change rate of the eGFR and dose-adjusted C_{12h} (C_{12h}/D) of tacrolimus were calculated for each CTD patient according to the following formula: Change rate = (value after co-administration of ITCZ − value before beginning ITCZ)/value before beginning ITCZ. A *P* value less than 0.05 was considered statistically significant. Statistical analysis was performed with the program, SPSS 20.0 for Windows (SPSS IBM Japan Inc., Tokyo, Japan).

Results

Clinical characteristics of the CTD patients are listed in Table 1. The allele frequencies for *CYP3A5*1* and **3* were 25.3 and 74.7 % and for *ABCB1* C3435T C and T were 56.2 and 43.8 %, respectively. The most common diagnosis for all CTD patients, at 63.0 %, was systemic lupus erythematosus. None of the patients had serious renal or hepatic dysfunction. Clinical findings of worsening active CTD, such as fever, dehydration, and change of medication, were not encountered for any of the patients. Thirty-five of the 81 CTD patients were administered ITCZ during tacrolimus therapy, and 28 of the 35 patients administered ITCZ began receiving ITCZ during tacrolimus therapy (supplementary document 1). The C_{12h} and dose of tacrolimus between *CYP3A5* or *ABCB1* genotypes are listed in supplementary document 2. Although there was no difference in the dose of tacrolimus between *CYP3A5* or *ABCB1* genotypes in each group with or without ITCZ, the tacrolimus C_{12h} with or without ITCZ was significantly higher for patients with *CYP3A5*3/*3* than for those with the *CYP3A5*1* allele [*CYP3A5 *1/*1* vs. **1/*3* vs. **3/*3*; 2.7 vs. 6.6 vs. 7.7 ng/mL ($P = 0.001$) and 1.7 vs. 2.2 vs. 4.9 ng/mL ($P < 0.001$), respectively]. The comparison and correlation with C_{12h}/D of tacrolimus and clinical characteristics of CTD patients with or without ITCZ are listed in Table 2. There was no difference in the C_{12h}/D of tacrolimus according to the daily dose of ITCZ. The tacrolimus C_{12h}/D with or without ITCZ was significantly higher for patients with *CYP3A5*3/*3* than for those with the *CYP3A5*1* allele [*CYP3A5*1/*1* vs. **1/*3* vs. **3/*3* = 1.67 vs. 2.70 vs. 4.83 ng/mL/mg ($P = 0.003$) and 0.68 vs. 0.97 vs. 2.20 ng/mL/mg ($P < 0.001$), respectively]. In addition, there were significant correlations between the C_{12h}/D of tacrolimus and patient age in each group with or without ITCZ ($r = 0.360$, $P = 0.036$ and $r = 0.404$, $P < 0.001$, respectively). The stepwise selection multiple linear regression analysis of explanatory variables for C_{12h}/D of tacrolimus in CTD patients with or without ITCZ is listed in Table 3. The *CYP3A5* genotype (**3/*3*) and patient age affected the C_{12h}/D

Table 2 Comparison and correlation with the dose-adjusted C_{12h} of tacrolimus and clinical characteristics in patients with or without itraconazole

	Without itraconazole (n = 74)		With itraconazole (n = 35)	
	Median (quartile 1–quartile 3)	P value	Median (quartile 1–quartile 3)	P value
Sex		0.127		0.803
Males	0.97 (0.63–2.25)		4.13 (2.37–4.70)	
Females	1.40 (0.99–2.35)		3.37 (2.33–5.02)	
CYP3A5 genotypes		<0.001		0.003
**1/*1*	0.68 (0.57–0.88)		1.67 (1.30–2.51)	
**1/*3*	0.97 (0.70–1.23)		2.70 (2.05–3.48)	
**3/*3*	2.20 (1.30–3.07)		4.83 (3.77–6.05)	
ABCB1 (3435C>T) genotypes		0.109		0.392
C/C	2.17 (1.03–3.07)		4.57 (3.35–5.10)	
C/T	1.33 (0.73–2.05)		3.45 (2.60–5.20)	
T/T	1.14 (0.85–1.86)		2.55 (2.07–3.49)	
Daily dose of itraconazole		–		0.936
50 mg	–		3.60 (2.10–4.13)	
100 mg	–		3.36 (2.60–4.83)	
200 mg	–		2.13 (1.37–6.50)	
	Correlation coefficient (r)	P value	Correlation coefficient (r)	P value
Age	0.404	<0.001	0.360	0.036
Body weight	−0.097	0.406	0.024	0.895
Body surface area	0.228	0.074	0.354	0.064
Laboratory values at tacrolimus initiation				
Aspartate transaminase	0.096	0.411	0.116	0.512
Alanine transaminase	−0.065	0.577	−0.009	0.958
Hemoglobin	−0.167	0.153	−0.103	0.561
Serum albumin	0.031	0.793	−0.286	0.118
Serum creatinine	0.000	0.998	0.207	0.240
Potassium	0.256	0.026	0.071	0.689
Estimated glomerular filtration rate (eGFR)	−0.265	0.037	−0.278	0.161

The values are expressed as median (quartile 1–quartile 3) (ng/mL/mg) or correlation coefficient

C_{12h}/D dose-adjusted blood concentration at 12 h after tacrolimus administration in stable state

Table 3 Stepwise selection multiple linear regression analysis of explanatory variable for the dose-adjusted C_{12h} of tacrolimus in patients with or without itraconazole

Explanatory variable	Slope	SE	SRC	P value	R^2
Without itraconazole					0.466
Age	0.023	0.006	0.367	<0.001	
*CYP3A5*3/*3* (=1)	1.156	0.193	0.530	<0.001	
Intercept = −0.017		0.279			
With itraconazole					0.284
Age	0.050	0.023	0.327	0.039	
*CYP3A5*3/*3* (=1)	2.063	0.750	0.418	0.010	
Intercept = 2.695		1.746			

C_{12h}/D dose-adjusted blood concentration at 12 h after tacrolimus administration in stable state, *SRC* standardized regression coefficient

of tacrolimus in each group with or without ITCZ (P = 0.010 for **3/*3*, P = 0.039 for age, R^2 = 0.284 and P < 0.001 for **3/*3*, P < 0.001 for age, R^2 = 0.466, respectively). Changes in the C_{12h}/D of tacrolimus before and after ITCZ administration in each patient are shown in Fig. 1. The C_{12h}/D of tacrolimus in all patients increased with ITCZ administration (P < 0.001), particularly for patients with *CYP3A5*3/*3* allele. Compared with before ITCZ administration, the C_{12h}/D of tacrolimus for patients co-administered ITCZ reached over six times at the maximum. On the other hand, as shown in Fig. 2, there was no significant difference in the change rate of the C_{12h}/D of tacrolimus with ITCZ administration between *CYP3A5* genotypes (P = 0.378). Similarly, there was no significant difference in the change rate of the C_{12h}/D of tacrolimus with ITCZ administration between *ABCB1* 3435C>T genotypes

(P = 0.259). A correlation between the change rate of the eGFR and C_{12h} after ITCZ administration is shown in Fig. 3. As the tacrolimus C_{12h} with ITCZ increased, the change rate of eGFR decreased (r = −0.482, P = 0.009). On the other hand, there were no significant differences in the change rate of eGFR between *CYP3A5* or *ABCB1* 3435C>T genotypes (P = 0.116 or 0.255).

Discussion

To the best of our knowledge, this study is the first to report the effects of ITCZ on the tacrolimus C_{12h} among CTD patients with respect to *CYP3A5* genotype. In the present study, no significant difference in the change rate of C_{12h}/D of tacrolimus with ITCZ co-administration was observed among the *CYP3A5* genotypes. In an in vitro study using recombinant human CYP3A5/CYP3A4 microsomes, the inhibitory potency (IC_{50}) ratio for midazolam by ITCZ was reported to be 8.8–9.6 [28]. Namely, the inhibitory potency by ITCZ for CYP3A4 was approximately ninefold greater than for CYP3A5. In the present study, therefore, an inhibition of CYP3A4 rather than CYP3A5 by ITCZ might have an effect on the increase of the C_{12h}/D of tacrolimus with ITCZ. On the other hand, Chandel et al. have reported that the dose-adjusted trough concentrations (C_{0h}/D) of tacrolimus increased with ketoconazole (KCZ) co-administration in all *CYP3A5* genotypes [29]. According to their results, the magnitudes of the increase from baseline were 112 and 79 % in patients with the *CYP3A5*3/*3* and *CYP3A5*1* alleles, respectively (P < 0.001) [29]. The inhibitory effect of KCZ was significantly higher in *CYP3A5*3/*3* microsomes than in *CYP3A5*1/*1* microsomes [28]. A difference in the results obtained from Chandel et al. and our present study could be caused by the difference in inhibition potency for CYP3A5 between KCZ and ITCZ.

In the present study, the inter-individual variation in the change rate of C_{12h}/D of tacrolimus with ITCZ co-administration was quite large. Lin et al. have reported that the CYP3A4 content in liver microsomal proteins and jejunal homogenate protein were 5–376 and 0.5–32.8 pmol/mg, respectively [30]. This large individual difference in CYP3A4 content in liver microsomal proteins and jejunal homogenate protein might affect the change rate of the C_{12h}/D of tacrolimus with ITCZ.

The change rate of eGFR exhibited a negative correlation with the C_{12h} of tacrolimus with ITCZ. In *CYP3A5*3/*3* patients, the tacrolimus C_{12} at baseline before ITCZ co-administration was high, and in combination with ITCZ seemed to lead to a higher risk of acute renal dysfunction. Correlations between blood concentration and toxicity of tacrolimus have been found for organ transplant patients [31]. Until now, although the target blood concentration of tacrolimus at C_{12h} has not been clarified, blood tacrolimus concentrations in CTD patients should be kept as low as possible in patients with the *CYP3A5*3/*3* allele. Since CTD patients are mainly treated as outpatients and ITCZ therapy may be added during tacrolimus therapy, the C_{12h} of tacrolimus might maintain a high value until the next consultation day, such as the patient with a very high C_{12h}/D in Fig. 1. Therefore, for patients with the *CYP3A5*3/*3* genotype taking tacrolimus and also taking ITCZ, clinicians should have a greater awareness of providing more prudent therapeutic drug monitoring.

There were significant correlations between the C_{12h}/D of tacrolimus and age in each group with or without ITCZ co-administration. Although expression of CYP3A proteins does not appear to change with age [32, 33], elderly patients may exhibit altered clearance of CYP3A substrates for a variety of reasons, including disease, altered tissue perfusion, and reduced first-pass metabolism in the intestine [34]. Therefore, patient age must be an independent factor associated with the C_{12h}/D of tacrolimus, unrelated to CYP3A expression. On the other hand, *ABCB1* genotypes did not influence the change rate of the eGFR and the C_{12h}/D of tacrolimus. More recently, Tavira et al. have reported that eGFR values at 2 weeks and 1, 3, 6, and 12 months after renal transplant surgery were lower for recipients who received a kidney from *ABCB1* 3435T carriers than from donors with 3435C/C [35]. In addition, Naito et al. have reported that rheumatoid arthritis patients carrying the *ABCB1* 3435T/T allele had a lower eGFR and higher blood concentrations of tacrolimus [36]. Although these reports were quite fascinating, the same results were not obtained in our study with CTD patients. The impact of *ABCB1* 3435C>T on eGFR might depend on the stage and type of disease. Since the genetic basis of tacrolimus-induced toxicity remains unclarified [19], further examination of this supposition is necessary.

In conclusion, because the metabolic pathway of tacrolimus in *CYP3A5*3/*3* patients proceeds only through CYP3A4, the combination with ITCZ seems to lead to a higher risk of acute renal dysfunction. Safe and reliable immunosuppressive therapy with tacrolimus can be performed with CTD patients together with ITCZ based on *CYP3A5* genotype.

Acknowledgments This work was supported by a grant (No. 26460189) from the Japan Society for the Promotion of Science, Tokyo, Japan.

Conflict of interest The authors declare that they have no competing interests.

References

1. Lee YH, Woo JH, Choi SJ, Ji JD, Bae SC, Song GG (2010) Tacrolimus for the treatment of active rheumatoid arthritis: a systematic review and meta-analysis of randomized controlled trials. Scand J Rheumatol 39:271–278

2. Takeuchi T, Kawai S, Yamamoto K, Harigai M, Ishida K, Miyasaka N (2014) Post-marketing surveillance of the safety and effectiveness of tacrolimus in 3,267 Japanese patients with rheumatoid arthritis. Mod Rheumatol 24:8–16
3. Tian SY, Feldman BM, Beyene J, Brown PE, Uleryk EM, Silverman ED (2014) Immunosuppressive therapies for the induction treatment of proliferative lupus nephritis: a systematic review and network meta-analysis. J Rheumatol 41:1998–2007
4. Lee YH, Lee HS, Choi SJ, Dai Ji J, Song GG (2011) Efficacy and safety of tacrolimus therapy for lupus nephritis: a systematic review of clinical trials. Lupus 20:636–640
5. Scott LJ, McKeage K, Keam SJ, Plosker GL (2003) Tacrolimus: a further update of its use in the management of organ transplantation. Drugs 63:1247–1297
6. Takahashi S, Hiromura K, Sakurai N, Matsumoto T, Ikeuchi H, Maeshima A, Kaneko Y, Kuroiwa T, Nojima Y (2011) Efficacy and safety of tacrolimus for induction therapy in patients with active lupus nephritis. Mod Rheumatol 21:282–289
7. Lass-Flörl C (2011) Triazole antifungal agents in invasive fungal infections: a comparative review. Drugs 71:2405–2419
8. Viscoli C (2009) Antifungal prophylaxis and pre-emptive therapy. Drugs 69:75–78
9. Boogaerts M, Maertens J (2001) Clinical experience with itraconazole in systemic fungal infections. Drugs 61:39–47
10. Christians U, Jacobsen W, Benet LZ, Lampen A (2002) Mechanisms of clinically relevant drug interactions associated with tacrolimus. Clin Pharmacokinet 41:813–851
11. Isoherranen N, Kunze KL, Allen KE, Nelson WL, Thummel KE (2004) Role of itraconazole metabolites in CYP3A4 inhibition. Drug Metab Dispos 32:1121–1131
12. Shon JH, Yoon YR, Hong WS, Nguyen PM, Lee SS, Choi YG, Cha IJ, Shin JG (2005) Effect of itraconazole on the pharmacokinetics and pharmacodynamics of fexofenadine in relation to the MDR1 genetic polymorphism. Clin Pharmacol Ther 78:191–201
13. Templeton I, Peng CC, Thummel KE, Davis C, Kunze KL, Isoherranen N (2010) Accurate prediction of dose-dependent CYP3A4 inhibition by itraconazole and its metabolites from in vitro inhibition data. Clin Pharmacol Ther 88:499–505
14. Nara M, Takahashi N, Miura M, Niioka T, Kagaya H, Fujishima N, Saitoh H, Kameoka Y, Tagawa H, Hirokawa M, Sawada K (2013) Effect of itraconazole on the concentrations of tacrolimus and cyclosporine in the blood of patients receiving allogeneic hematopoietic stem cell transplants. Eur J Clin Pharmacol 69:1321–1329
15. Enderby CY, Heckman MG, Thomas CS, Keller CA (2014) Tacrolimus dosage requirements in lung transplant recipients receiving antifungal prophylaxis with voriconazole followed by itraconazole: a preliminary prospective study. Clin Transpl 28: 911–915
16. Kramer MR, Amital A, Fuks L, Shitrit D (2011) Voriconazole and itraconazole in lung transplant recipients receiving tacrolimus (FK 506): efficacy and drug interaction. Clin Transpl 25:163–167
17. Kunze KL, Nelson WL, Kharasch ED, Thummel KE, Isoherranen N (2006) Stereochemical aspects of itraconazole metabolism in vitro and in vivo. Drug Metab Dispos 34:583–590
18. Peng CC, Shi W, Lutz JD, Kunze KL, Liu JO, Nelson WL, Isoherranen N (2012) Stereospecific metabolism of itraconazole by CYP3A4: dioxolane ring scission of azole antifungals. Drug Metab Dispos 40:426–435
19. Hesselink DA, Bouamar R, Elens L, van Schaik RH, van Gelder T (2014) The role of pharmacogenetics in the disposition of and response to tacrolimus in solid organ transplantation. Clin Pharmacokinet 53:123–139
20. Staatz CE, Goodman LK, Tett SE (2010) Effect of CYP3A and ABCB1 single nucleotide polymorphisms on the pharmacokinetics and pharmacodynamics of calcineurin inhibitors: part II. Clin Pharmacokinet 49:207–221
21. Staatz CE, Goodman LK, Tett SE (2010) Effect of CYP3A and ABCB1 single nucleotide polymorphisms on the pharmacokinetics and pharmacodynamics of calcineurin inhibitors: part I. Clin Pharmacokinet 49:141–175
22. Terrazzino S, Quaglia M, Stratta P, Canonico PL, Genazzani AA (2012) The effect of CYP3A5 6986A>G and ABCB1 3435C>T on tacrolimus dose-adjusted trough levels and acute rejection rates in renal transplant patients: a systematic review and meta-analysis. Pharmacogenet Genomics 22:642–645
23. De BK, Jimenez E, De S, Sawyer JC, McMillin GA (2009) Analytical performance characteristics of the Abbott Architect i2000 tacrolimus assay; comparisons with liquid chromatography-tandem mass spectrometry (LC-MS/MS) and Abbott IMx methods. Clin Chim Acta 410:25–30
24. Fukuen S, Fukuda T, Maune H, Ikenaga Y, Yamamoto I, Inaba T, Azuma J (2002) Novel detection assay by PCR-RFLP and frequency of the CYP3A5 SNPs, CYP3A5*3 and *6, in a Japanese population. Pharmacogenetics 12:331–334
25. Cascorbi I, Gerloff T, Johne A, Meisel C, Hoffmeyer S, Schwab M, Schaeffeler E, Eichelbaum M, Brinkmann U, Roots I (2001) Frequency of single nucleotide polymorphisms in the P-glycoprotein drug transporter MDR1 gene in white subjects. Clin Pharmacol Ther 69:169–174
26. Miura M, Satoh S, Kagaya H, Saito M, Numakura K, Tsuchiya N, Habuchi T (2011) Impact of the CYP3A4*1G polymorphism and its combination with CYP3A5 genotypes on tacrolimus pharmacokinetics in renal transplant patients. Pharmacogenomics 12:977–984
27. Miura M, Niioka T, Kagaya H, Saito M, Hayakari M, Habuchi T, Satoh S (2011) Pharmacogenetic determinants for interindividual difference of tacrolimus pharmacokinetics 1 year after renal transplantation. J Clin Pharm Ther 36:208–216
28. Shirasaka Y, Chang SY, Grubb MF, Peng CC, Thummel KE, Isoherranen N, Rodrigues AD (2013) Effect of CYP3A5 expression on the inhibition of CYP3A-catalyzed drug metabolism: impact on modeling CYP3A-mediated drug-drug interactions. Drug Metab Dispos 41:1566–1574
29. Chandel N, Aggarwal PK, Minz M, Sakhuja V, Kohli KK, Jha V (2009) CYP3A5*1/*3 genotype influences the blood concentration of tacrolimus in response to metabolic inhibition by ketoconazole. Pharmacogenet Genomics 19:458–463
30. Lin YS, Dowling AL, Quigley SD, Farin FM, Zhang J, Lamba J, Schuetz EG, Thummel KE (2002) Co-regulation of CYP3A4 and CYP3A5 and contribution to hepatic and intestinal midazolam metabolism. Mol Pharmacol 62:162–172
31. Staatz CE, Tett SE (2004) Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. Clin Pharmacokinet 43:623–653
32. Gorski JC, Vannaprasaht S, Hamman MA, Ambrosius WT, Bruce MA, Haehner-Daniels B, Hall SD (2003) The effect of age, sex, and rifampin administration on intestinal and hepatic cytochrome P450 3A activity. Clin Pharmacol Ther 74:275–287
33. Hunt CM, Westerkam WR, Stave GM, Wilson JA (1992) Hepatic cytochrome P-4503A (CYP3A) activity in the elderly. Mech Aging Dev 64:189–199
34. Klotz U (2009) Pharmacokinetics and drug metabolism in the elderly. Drug Metab Rev 41:67–76
35. Tavira B, Gómez J, Díaz-Corte C, Coronel D, Lopez-Larrea C, Suarez B, Coto E (2015) The donor ABCB1 (MDR-1) C3435T polymorphism is a determinant of the graft glomerular filtration rate among tacrolimus treated kidney transplanted patients. J Hum Genet. doi:10.1038/jhg.2015.12
36. Naito T, Mino Y, Aoki Y, Hirano K, Shimoyama K, Ogawa N, Kagawa Y, Kawakami J (2015) ABCB1 genetic variant and its associated tacrolimus pharmacokinetics affect renal function in patients with rheumatoid arthritis. Clin Chim Acta 445:79–84