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Influence of Rabeprazole and Lansoprazole on the Pharmacokinetics of Tacrolimus in Relation to CYP2C19, CYP3A5 and MDR1 Polymorphisms in Renal Transplant Recipients

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ABSTRACT: The objective of this study was to evaluate whether genetic polymorphisms of CYP2C19, CYP3A5 and *MDR1* significantly impact the interaction between tacrolimus and rabeprazole or lansoprazole. Seventy-three recipients were randomly assigned after renal transplantation to receive repeated doses of tacrolimus for 28 days with a regimen of either 20 mg of rabeprazole or 30 mg of lansoprazole. Blood concentrations of tacrolimus were measured by microparticle enzyme immunoassay. The mean daily dose and the dose-adjusted area under the plasma concentration-time curves from 0 to 12 h (AUC_{0-12}) of tacrolimus coadministered with rabeprazole or lansoprazole were the lowest and highest, respectively, in CYP2C19 poor metabolizers (PMs) having the *CYP3A5* * *3*/* *3* genotype (0.084 and 0.112 mg/kg/day and 1.269 and 1.033 ng · h/ml/mg/kg, respectively). On the other hand, the mean dose-adjusted AUC_{0-12} of tacrolimus coadministered with rabeprazole or lansoprazole were the highest in CYP2C19 PMs having the *MDR13435CC+CT* genotype, but not significantly.

The present study indicates that there are significant interactions between tacrolimus and rabeprazole or lansoprazole in CYP2C19 PM renal transplant recipients bearing the *CYP3A5* * *3*/* *3* genotypes. For recipients having these genetic polymorphisms, lower dosages of tacrolimus are required to achieve the target therapeutic index. Copyright © 2007 John Wiley & Sons, Ltd.

Key words: tacrolimus; rabeprazole; lansoprazole; CYP2C19; CYP3A5; MDR1C3435T

Introduction

Rabeprazole and lansoprazole are proton pump inhibitors (PPIs) that inhibit gastric acid secretion through interaction with the H^+/K^+-ATPase in gastric parietal cells [1–4]. These PPIs are typically administered with tacrolimus, an immunosuppressive agent, in renal transplant recipients suffering from gastric ulcer disease. Whereas lansoprazole is extensively metabolized by two cytochrome P450 (CYP) enzymes, CYP2C19 and CYP3A4 [5–7], rabeprazole is primarily converted non-enzymatically to rabeprazole-thioether and is only slightly metabolized by CYP2C19 and CYP3A4 [8–11]. Therefore, compared with lansoprazole, CYP2C19 and CYP3A4 contribute less to the metabolism of rabeprazole. However, it was recently reported that CYP3A4 and CYP2C19 oxidize rabeprazole-thioether back to the parent compound rabeprazole and desmethylrabeprazole-thioether, respectively [12]. In recipients bearing mutations in exon 5 and 4 of CYP2C19, lansoprazole reportedly inhibits tacrolimus metabolism via CYP3A4,

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thereby increasing the blood tacrolimus concentration [13,14]. Therefore the drug interaction between tacrolimus and rabeprazole also cannot be denied. This is especially true in patients that have the so called CYP2C19 poor metabolizer (PM) status. In these patients, the metabolism of tacrolimus, a substrate for CYP3A4 [15], is assumed to be affected by lansoprazole and rabeprazole, because the metabolic pathway of lansoprazole and rabeprazole-thioether, a primary catabolite of rabeprazole is shifted from CYP2C19 to CYP3A4. Thus in CYP2C19 PM patients, CYP3A4 is an important metabolizing enzyme for lansoprazole and rabeprazole. Generally, CYP3A4 and the related protein CYP3A5 have similar catalytic specificities, although CYP3A5 has less activity than CYP3A4 [16,17]. CYP3A5 expression levels are strongly correlated with a single nucleotide polymorphism, A6986G within intron 3 of CYP3A5, which is designated *CYP3A5* * 3 [18]. In our previous study, renal transplant recipients who were *CYP3A5* * *3*/* *3* required a significantly lower dose of tacrolimus than *CYP3A5* * *1* carriers [19]. Therefore, CYP3A5 polymorphisms also may affect the drug-interaction between tacrolimus and lansoprazole or rabeprazole.

Tacrolimus is also a substrate of the efflux transporter P-glycoprotein [20]. P-Glycoprotein is encoded by the *MDR1* gene and is highly expressed in the small intestine and kidney. *In vitro* studies have found that whereas lansoprazole is also a substrate of P-glycoprotein [21], rabeprazole is not [22]. Therefore, polymorphisms in the *MDR1* gene may affect the drug interaction between tacrolimus and lansoprazole. Interestingly, a polymorphism in exon 26 of the human *MDR1* gene (C3435T) has been associated with changes in the expression level and function of P-glycoprotein in the intestine [23,24]. Until now it has not been clearly established whether the drug interaction between tacrolimus and lansoprazole in humans is affected by differences in the P-glycoprotein function due to polymorphism of *MDR1*.

The aim of this investigation was to examine the impact of CYP3A5 and *MDR1* (C3435T) polymorphisms on the drug interaction between tacrolimus and rabeprazole or lansoprazole in relation to CYP2C19 genotype status: homozygous extensive metabolizers (homEMs), heterozygous EMs (hetEMs) and PMs.

Materials and Methods

Patients and protocols

Seventy-three Japanese renal transplant recipients were selected to participate in this study. The eligibility criteria in the study required that the patients: (1) had a first living-donor transplantation, (2) be on an identical immunosuppressive regimen including tacrolimus (Prograf®, Astellas Co. Ltd, Tokyo, Japan), mycophenolate mofetil (MMF; Cellcept®, Chugai Pharmaceutical Co. Ltd, Tokyo, Japan), and steroid, (3) be not ABO incompatible, (4) be on an identical drugs administration regimen including candesartan cilexetil, sulfamethoxazole-trimethoprin and PPI, (5) had no previous marked clinical episodes of chronic rejection, (6) be nonsmokers, (7) had no history of hepatic impairment or gastric ulcer disease. The study protocol was approved by the Ethics Committee of Akita University Hospital, and all recipients gave written informed consent. Seventy-three recipients were randomly assigned after renal transplantation to receive repeated doses of one of the following two regimens for 28 days: tacrolimus and MMF as combination immunosuppressive therapy together with either 20 mg of rabeprazole (Pariet®, Eisai, Tokyo, Japan) ($n = 33$) or 30 mg of lansoprazole (Takepron®, Takeda Pharmaceutical Co. Ltd, Osaka, Japan) ($n = 40$). Tacrolimus and MMF (1.5 g/day) were given in equally divided doses every 12 h at a designated time (09:00 and 21:00). Regardless of CYP2C19, CYP3A5 and MDR1 genetic polymorphisms, the daily tacrolimus dose was adjusted according to the clinical state of the patient, the whole blood trough target level being 15–20 ng/ml up to 2 weeks, 10–15 ng/ml up to 4 weeks and less than 10 ng/ml thereafter. Methylprednisolone was given concomitantly: a dose of 500 mg on the day of surgery, tapered to 40 mg/day during the first week, 20 mg/day of prednisolone in the second week, 15 mg/day of prednisolone in the third week and 10 mg/day thereafter in all 73 recipients. Rabeprazole or lansoprazole was taken orally once daily at 08:00

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(30 min after breakfast). Meals were served at 07:30, 12:30 and 18:00 daily. The meal content (Japanese food) was varied each day and for each patient, but the energy, fat, protein and water content were standardized (energy 1700–2400 kcal, protein 70–90 g, fat 40–50 g and water 1600–2000 ml) depending on body weight. On day 28 after renal transplantation, whole blood samples (5 ml) were collected by vein puncture just prior to and at 1, 2, 3, 4, 6, 9, 12 h after oral tacrolimus administration. Blood concentrations of tacrolimus were measured by microparticle enzyme immunoassay. The compliance of rabeprazole and lansoprazole in each recipient was confirmed by measuring the plasma concentration [25,26]. The demographic and clinical characteristics of the recipients are listed in Table 1.

Genotyping

DNA was extracted from a peripheral blood sample using a QIAamp Blood kit (Qiagen, Hilden, Germany) and was stored at -80°C until analysis. Genotyping procedures to identify the CYP2C19 wild-type gene and two mutant alleles, *CYP2C19*2* in exon 5 and *CYP2C19*3* in exon 4, were performed with a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method [27]. For genotyping of the *CYP3A5*3* allele, the PCR-RFLP method described by Fukuen *et al*. [28] was used. Genotyping procedures identifying the C and T alleles in exon 26 of the MDR1 gene (C3435 T) were performed using the PCR-RFLP method described by Cascorbi *et al*. [29].

Table 1. Demographic and clinical characteristics of renal transplant recipients

Study group	with Rabeprazole ($n = 33$)	with Lansoprazole ($n = 40$)
Age (year)	46.3 ± 12.7	43.7 ± 11.2
Weight (kg)	54.8 ± 10.5	58.7 ± 13.3
MMF (mg/kg/day)	27.9 ± 5.3	29.2 ± 7.8
AST (IU/l)	16.7 ± 7.8	14.4 ± 7.4
ALT (IU/l)	19.4 ± 16.7	18.9 ± 18.0
Serum albumin (mg/dl)	4.2 ± 0.3	4.1 ± 0.5
Serum ceatinine (mg/dl)	1.3 ± 0.5	1.6 ± 1.2

Data are mean values ±SD. MMF, Mycophenolate mofetil.

Pharmacokinetic analysis

Pharmacokinetic analysis of tacrolimus was carried out with a standard non-compartmental method using WinNonlin (Pharsight Co., CA, version 4.0.1). The elimination half-life was obtained using log-linear regression of the terminal phase of the concentration-time data for at least three sampling points (elimination half-life $= \ln 2/ke$; $ke =$ elimination rate constant). The total area under the observed plasma concentration-time curve (*AUC*) was calculated using the linear trapezoidal rule. The maximum plasma concentration (C_{max}) and time required to reach the peak (t_{max}) were directly obtained from the profile.

Statistical analysis

All results were expressed as mean values ± SD. Statistical comparisons of parameters were supplemented with the multiple comparison procedure of the Mann-Whitney U test in the Stat View program (SAS Institute, Cary, NC, version 5.0). *P* values of less than 0.05 were considered significant.

Results

No significant differences were observed in age, weight or biochemical data (AST, ALT, albumin and serum creatinine) between the two groups (Table 1).

Effect of CYP3A5 polymorphism

The CYP2C19 **1/*1*, **1/*2*, **1/*3*, **2/*2*, **2/*3* and **3/*3* genotypes were detected in 31 (42.5%), 14 (19.2%), 15 (20.5%), 5 (6.8%), 6 (8.2%) and 2 (2.7%) of the 73 recipients, respectively, whereas the *CYP3A5 *1/*1*, **1/*3* and **3/*3* genotypes were 6 (8.2%), 28 (38.3%) and 39 (53.4%).

The kinetic parameters of tacrolimus coadministered with rabeprazole or lansoprazole as they relate to CYP3A5 polymorphisms in the three different CYP2C19 genotype groups are shown in Table 2. The mean required dose of tacrolimus per body weight coadministered with rabeprazole was the lowest in CYP2C19 PMs having the *CYP3A5 *3/*3* genotype (0.084 mg/kg/day).

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Table 2. Pharmacokinetic parameters of tacrolimus in CYP2C19 and CYP3A5 genotype groups

	CYP2C19 Homozygous EMs		CYP2C19 Heterozygous EMs		CYP2C19 PMs	
Study group	CYP3A5 ** 1/* 1 + *1/* 3*	CYP3A ** 3/* 3*	CYP3A5 ** 1/* 1 + * 1/* 3*	CYP3A ** 3/* 3*	CYP3A5 ** 1/* 1 + *1/* 3*	CYP3A ** 3/* 3*
With rabeprazole						
Patients (male/female)	4 (3:1)	7 (3:4)	8 (4:4)	7 (4:3)	3 (2:1)	4 (3:1)
Age (year)	55.5 ± 6.4	43.0 ± 7.1	47.6 ± 12.2	45.8 ± 18.9	58.3 ± 0.6	38.5 ± 12.4
Weight (kg)	55.7 ± 4.7	53.4 ± 9.5	55.6 ± 12.0	51.5 ± 5.4	48.5 ± 9.0	59.0 ± 10.3
Dose (mg/kg/day)	0.180 ± 0.015	0.164 ± 0.030§	0.198 ± 0.064	0.132 ± 0.022	0.188 ± 0.027*	0.084 ± 0.030
C_{max} (ng/ml)	26.7 ± 4.0	18.3 ± 4.7	19.5 ± 7.8	19.8 ± 3.9	18.2 ± 9.0	18.4 ± 3.1
Dose adjusted C_{max} (ng/ml/mg/kg)	147.4 ± 9.8	116.4 ± 42.4§	102.2 ± 40.1	158.2 ± 64.4	105.8 ± 49.8*	231.4 ± 49.6
C_0 (Trough) (ng/ml)	11.4 ± 2.3	9.7 ± 1.8	7.8 ± 4.8	8.6 ± 1.4	9.6 ± 2.1	10.8 ± 3.7
Dose adjusted C_0 (ng/ml/mg/kg)	62.6 ± 7.6	60.5 ± 11.2§	41.1 ± 23.9	66.0 ± 10.0§	50.8 ± 28.5*	131.2 ± 25.2
$AUC_{(0-12)}$/D (ng h/ml/mg/kg)	0.726 ± 0.177	0.723 ± 0.366	0.531 ± 0.213	0.940 ± 0.333	0.703 ± 0.163	1.269 ± 0.469
With lansoprazole						
Patients (male/female)	10 (5:5)	10 (5:5)	7 (2:5)	7 (4:3)	2 (1:1)	4 (3:1)
Age (year)	46.2 ± 9.6	42.5 ± 15.8	43.0 ± 7.1	42.4 ± 9.4	37.5 ± 10.6	46.8 ± 13.2
Weight (kg)	53.2 ± 8.7	67.4 ± 20.5	53.4 ± 9.5	56.0 ± 4.3	51.5 ± 3.5	63.9 ± 11.7
Dose (mg/kg/day)	0.231 ± 0.074*	0.130 ± 0.028	0.267 ± 0.071	0.164 ± 0.073	0.271 ± 0.036	0.112 ± 0.024
C_{max} (ng/ml)	25.2 ± 10.1	21.7 ± 5.6	22.4 ± 10.4	20.8 ± 7.1	20.6 ± 5.0	24.2 ± 4.6
Dose adjusted C_{max} (ng/ml/mg/kg)	115.2 ± 43.6	172.1 ± 52.3	91.5 ± 53.9	136.0 ± 43.8	77.9 ± 29.0	219.6 ± 38.6
C_0 (Trough) (ng/ml)	14.3 ± 4.2	13.6 ± 3.6	12.9 ± 2.0	12.1 ± 2.1	10.7 ± 2.5	14.5 ± 3.8
Dose adjusted C_0 (ng/ml/mg/kg)	67.7 ± 25.2	111.5 ± 46.8	51.2 ± 15.5	83.9 ± 33.1	39.4 ± 4.0	128.2 ± 10.2
$AUC_{(0-12)}$/D (ng h/ml/mg/kg)	0.650 ± 0.175	0.748 ± 0.263	0.555 ± 0.157	0.788 ± 0.323	0.458 ± 0.078	1.033 ± 0.493

The values are shown as the mean ±SD. C_{max}, maximum plasma concentration; $AUC_{(0-12)}$, area under the plasma concentration-time curve from 0 to 12 h; D, dose.
EM, extensive metabolizer; PM, poor metabolizer.
§$p < 0.05$ compared with the CYP2C19PM group, *$p < 0.05$ compared with the *CYP3A5 * 3/ * 3* group.

This mean daily dose of tacrolimus in CYP2C19 PMs having *CYP3A5 * 3/ * 3* was significantly lower than that in CYP2C19 homEMs having the *CYP3A5 * 3/ * 3* genotype (0.084 vs 0.164 mg/kg/day, $p < 0.05$). The mean dose-adjusted $AUC_{(0-12)}$ of tacrolimus coadministered with rebeprazole was the highest in CYP2C19 PMs having the *CYP3A5 * 3/ * 3* genotype (1.269 ng · h/ml/mg/kg) and was higher than that for CYP2C19 homEMs having the *CYP3A5 * 3/ * 3* genotype and CYP2C19 PMs having the *CYP3A5 * 1/ * 1 + * 1/ * 3* genotype (0.723 and 0.703 ng · h/ml/mg/kg, respectively). There were no significant differences in the C_{max} and trough concentration (C_0) of tacrolimus coadministered with rabeprazole among the six different groups. However, the dose-adjusted C_{max} and C_0 of tacrolimus in CYP2C19 PMs having the *CYP3A5 * 3/ * 3* genotype were significantly higher than those in CYP2C19 homEMs having the *CYP3A5 * 3/ * 3* genotype and CYP2C19 PMs having the *CYP3A5 * 1/ * 1 + *1/ * 3* genotype (231.4 and 131.2 vs 116.4 and 60.5, and 105.8 and 50.8 ng/ml/mg/kg, respectively).

In all three CYP2C19 genotype groups, the mean required dose of tacrolimus per body weight coadministered with lansoprazole in recipients having the *CYP3A5 * 3/ * 3* genotype was lower than in those having the *CYP3A5 * 1/ * 1 + * 1/ * 3* genotype. Among CYP2C19

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homEMs, there were significant differences in the tacrolimus dosage between the *CYP3A5 * 1/ * 1 + * 1/ * 3* and *CYP3A5 * 3/ * 3* genotypes (0.231 *vs* 0.130 mg/kg/day, $p < 0.05$). The mean dose-adjusted $AUC_{(0-12)}$ of tacrolimus coadministered with lansoprazole was the highest in CYP2C19 PMs having *CYP3A5 * 3/ * 3* genotype (1.033 ng · h/ml/mg/kg), but not significantly. Additionally, there were no significant differences in the C_{max}, and C_0 of tacrolimus coadministered with lansoprazole among the six different groups. However, the dose-adjusted C_{max} and C_0 of tacrolimus for the *CYP3A5 * 3/ * 3* genotype were higher than those of *CYP3A5 * 1/ * 1 + * 1/ * 3* in all of different CYP2C19 genotype groups, but not significantly.

Effect of MDR1 polymorphism

For the MDR1 C3435 T polymorphism, the *CC*, *CT* and *TT* genotypes were detected in 25 (34.2%), 27 (37.0%) and 21 (28.8%) of the 73 recipients.

The kinetic parameters of tacrolimus coadministered with rabeprazole or lansoprazole in recipients with the *CC*, *CT* and *TT* genotypes at position 3435 of the *MDR1* gene are shown in Table 3. There were no significant differences in the pharmacokinetic parameters of tacrolimus coadministered with rabeprazole among the six different genotypes. Similar to the results of tacrolimus coadministered with rabeprazole, lansoprazole did not affect the pharmacokinetic parameters of tacrolimus in all of the six different groups. However, the mean dose-adjusted $AUC_{(0-12)}$ of tacrolimus coadministered with rabeprazole or lansoprazole were the highest in CYP2C19 PMs of the *MDR13435CC + CT* genotype groups (1.142 and 1.000 ng · h/ml/mg/kg, respectively), although they were not significantly different.

CYP2C19, CYP3A5 and MDR1C3435T genotype information for recipients having high dose-adjusted AUC_{0-12} of tacrolimus is shown in Table 4. The dose-adjusted $AUC_{(0-12)}$ value of tacrolimus was high in three recipients, patients

Table 3. Pharmacokinetic parameters of tacrolimus in CYP2C19 and MDR1C3435 T genotype groups

	CYP2C19 Homozygous EMs		CYP2C19 Heterozygous EMs		CYP2C19 PMs	
Study group	*CC + CT*	*TT*	*CC + CT*	*TT*	*CC + CT*	*TT*
With rabeprazole						
Patients (male/female)	9 (5:4)	2 (1:1)	7 (4:3)	8 (4:4)	5 (3:2)	2 (1:1)
Age (year)	44.0 ± 9.3	48.0 ± 17.0	42.2 ± 16.0	50.1 ± 13.7	42.6 ± 14.1	58.0 ± 1.4
Weight (kg)	55.4 ± 9.8	59.2 ± 25.6	56.5 ± 13.7	52.1 ± 6.0	54.2 ± 6.1	55.4 ± 22.8
Dose (mg/kg/day)	0.158 ± 0.049	0.150 ± 0.029	0.148 ± 0.042	0.186 ± 0.068	0.125 ± 0.059	0.137 ± 0.095
C_{max} (ng/ml)	20.3 ± 7.1	14.8 ± 2.7	21.9 ± 9.5	18.1 ± 1.9	20.6 ± 5.6	16.1 ± 1.9
Dose adjusted C_{max} (ng/ml/mg/kg)	128.5 ± 39.6	102.3 ± 37.1	152.2 ± 75.5	106.5 ± 32.9	162.0 ± 81.6	147.7 ± 88.4
C_0 (Trough) (ng/ml)	9.8 ± 2.8	9.0 ± 1.0	8.4 ± 4.7	8.0 ± 3.2	10.9 ± 3.3	8.7 ± 0.1
Dose adjusted C_0 (ng/ml/mg/kg)	61.8 ± 8.2	61.7 ± 19.0	55.3 ± 20.5	48.7 ± 25.3	87.4 ± 56.9	82.9 ± 56.5
$AUC_{(0-12)}$/D (ng h/ml/mg/kg)	0.737 ± 0.308	0.658 ± 0.356	0.698 ± 0.315	0.704 ± 0.336	1.142 ± 0.504	0.737 ± 0.118
With lansoprazole						
Patients (male/female)	16 (8:8)	4 (2:2)	12 (5:7)	2 (1:1)	3 (2:1)	3 (2:1)
Age (year)	44.4 ± 13.6	44.7 ± 13.6	42.9 ± 8.6	43.5 ± 4.9	44.3 ± 13.2	43.0 ± 14.1
Weight (kg)	57.9 ± 10.4	69.7 ± 33.8	54.1 ± 7.1	58.3 ± 8.8	58.0 ± 14.7	61.5 ± 9.4
Dose (mg/kg/day)	0.179 ± 0.075	0.172 ± 0.083	0.210 ± 0.084	0.251 ± 0.135	0.148 ± 0.086	0.181 ± 0.100
C_{max} (ng/ml)	22.6 ± 8.5	27.6 ± 3.1	21.4 ± 9.2	23.0 ± 5.2	24.1 ± 2.8	21.8 ± 6.5
Dose adjusted C_{max} (ng/ml/mg/kg)	136.9 ± 46.2	189.2 ± 90.2	113.7 ± 51.4	114.0 ± 82.4	196.7 ± 21.8	148.1 ± 81.0
C_0 (Trough) (ng/ml)	13.0 ± 3.5	18.2 ± 2.5	12.5 ± 2.2	12.1 ± 0.2	11.8 ± 4.4	14.7 ± 3.0
Dose adjusted C_0 (ng/ml/mg/kg)	84.6 ± 38.1	123.6 ± 63.9	69.3 ± 30.9	57.0 ± 31.6	98.9 ± 55.0	98.3 ± 48.9
$AUC_{(0-12)}$/D (ng h/ml/mg/kg)	0.719 ± 0.248	0.582 ± 0.181	0.686 ± 0.280	0.588 ± 0.296	1.000 ± 0.662	0.682 ± 0.272

The values are shown as the mean ± SD. C_{max}, maximum plasma concentration; $AUC_{(0-12)}$, area under the plasma concentration-time curve from 0 to 12 h; D, dose.

EM, extensive metabolizer; PM, poor metabolizer.

$^{\S}p < 0.05$ compared with the CYP2C19PM group, $^{*}p < 0.05$ compared with the MDR13435TT group.

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Table 4. CYP2C19, CYP3A5 and MDR1 genotype and characteristics of the recipient having more than 1.000 (ng h/ml/mg/kg) for dose-adjusted $AUC_{(0-12)}$ of tacrolimus

Patient no	Gender	PPI	CYP2C19 genotype	CYP3A5 genotype	MDR1 C3435T	Tacrolimus	
						Dose (mg/kg/day)	$AUC_{(0-12)}$/D (ng h/ml/mg/kg)
1	M	Lansoprazole	*1/*3	*3/*3	C/T	0.106	1.103
2	F	Lansoprazole	*1/*2	*3/*3	C/T	0.200	1.481
3	F	Lansoprazole	*1/*1	*3/*3	C/T	0.270	1.011
4	M	Lansoprazole	*3/*3	*3/*3	C/C	0.120	1.753
5	F	Lansoprazole	*1/*2	*3/*3	C/C	0.145	1.000
6	F	Lansoprazole	*1/*1	*3/*3	C/T	0.143	1.151
7	F	Lansoprazole	*1/*2	*3/*3	C/T	0.111	1.074
8	F	Lansoprazole	*1/*1	*3/*3	C/C	0.153	1.000
9	M	Lansoprazole	*1/*1	*3/*3	C/T	0.102	1.155
10	M	Lansoprazole	*1/*1	*3/*3	C/T	0.148	1.120
11	M	Rabeprazole	*1/*2	*3/*3	C/C	0.098	1.132
12	F	Rabeprazole	*2/*2	*3/*3	C/T	0.070	1.682
13	F	Rabeprazole	*1/*1	*3/*3	C/T	0.126	1.234
14	F	Rabeprazole	*2/*2	*3/*3	C/T	0.129	1.581
15	F	Rabeprazole	*1/*3	*3/*3	T/T	0.139	1.410
16	M	Rabeprazole	*1/*2	*3/*3	C/T	0.066	1.160

4, 12 and 14. Each of these three recipients had CYP2C19PM (*2/*2 and *3/*3) and *CYP3A5*3/*3*. Notably, all recipients having high dose-adjusted $AUC_{(0-12)}$ of tacrolimus had *CYP3A5*3/*3*. Furthermore, although there was a single exception (no 15), the dose-adjusted $AUC_{(0-12)}$ of tacrolimus tended to be high in recipients having *MDR13435CC+CT*.

Discussion

The primary objective of this study was to evaluate whether CYP2C19, CYP3A5 and MDR1 genetic polymorphisms had a significant impact on the drug interaction between tacrolimus and rabeprazole or lansoprazole. The present study showed that usual therapeutic doses of rabeprazole and lansoprazole have a clinically significant influence on the dose-adjusted *AUC* of tacrolimus in PMs of CYP2C19 having *CYP3A5*3/*3*. Additionally, the degree of interaction between tacrolimus and rabeprazole in each genotype group was similar to that between tacrolimus and lansoprazole. Itagaki *et al*. have reported that lansoprazole, but not rabeprazole, inhibited tacrolimus metabolism in renal transplant recipients with *CY2C19*1/*2* [14]. In the present study, regardless of CYP2C19 genetic polymorphism, recipients having *CYP3A5*1/*1+*1/*3* did not show significant interactions between tacrolimus and rabeprazole or lansoprazole (Table 4). Although coadministration of rabeprazole and lansoprazole increased the blood concentration of tacrolimus in the CYP2C19 PM recipients, the degree of the drug interaction between tacrolimus and rabeprazole or lansoprazole seems to be influenced by CYP3A5 genetic polymorphisms rather than CYP2C19 genetic polymorphisms. Additionally, as with lansoprazole, coadministration of rabeprazole also seems to inhibit tacrolimus metabolism *via* CYP3A. Though slightly metabolized by CYP2C19, rabeprazole is primarily converted nonenzymatically to rabeprazole-thioether which then is further re-oxidized mainly by CYP3A4 to rabeprazole [12]. Rabeprazole-thioether is a substrate of CYP2C19 and CYP3A. Thus, it is possible that tacrolimus might engage in a drug interaction with rabeprazole-thioether rather than rabeprazole.

On the other hand, although lansoprazole has been shown to be transported by P-glycoprotein *in vitro* [21], no information is available from clinical practice. In the present study, the magnitude of the contribution of *MDR1* C3435T to the

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drug interaction between tacrolimus and lansoprazole appears to be low, because there were no significant differences in the pharmacokinetic parameters of tacrolimus among the six groups divided into CYP2C19 and *MDR1C3435 T* genotypes. However, the dose-adjusted *AUC*, C_{max} and trough concentration of tacrolimus coadministered with lansoprazole and rabeprazole in CYP2C19 PMs having *MDR13435CC + CT* were the highest in the six groups. Because rabeprazole is not a substrate of P-glycoprotein [22], this phenomenon cannot be explained well. However, rabeprazole-thioether might be a substrate of P-glycoprotein. The plasma concentrations of rabeprazole-thioether in CYP2C19 PMs are significantly higher than those in CYP2C19 EMs [30]. Because the *AUC* of tacrolimus was greater in CYP2C19 PMs having *MDR13435CC + CT* than those in CYP2C19 EMs having *MDR13435CC + CT*, coadministration of lansoprazole and rabeprazole was considered to be responsible for the difference between these two groups. However, further studies on the contribution of P-glycoprotein to rabeprazole disposition should be performed.

In addition, in the PMs of CYP2C19, the *AUC* of tacrolimus coadministered with rabeprazole or lansoprazole were slightly greater in recipients with the *3435CC + CT* genotype compared with those with the *3435TT* genotype. Thus, unlike the report of Hoffmeyer *et al*., which showed that white subjects with the *3435TT* genotype had significantly lower intestinal P-glycoprotein levels than those with the *3435CC* genotype [24], our results support the findings of Nakamura *et al*. which showed that *MDR1* mRNA expression was higher in Japanese subjects with the TT genotype than those carrying *C* at position 3435 [23]. Therefore, although there were no significant differences, coadministration of rabeprazole or lansoprazole with tacrolimus apparently tends to increase the blood concentration of tacrolimus in the CYP2C19 PM recipients having the *MDR1C3435T C* allele.

Some weaknesses of our study are that it is based on a small sample size and that there are no data on the pharmacokinetics of tacrolimus alone. The latter problem arises because the existence of ulcers affects the graft survival in living related recipients [31]. Until now, no report has addressed both the CYP2C19 and CYP3A5 genotype groups or both CYP2C19 and MDR1 genotype groups for the pharmacokinetic parameter of tacrolimus alone. Therefore, the discussion is based on the pharmacokinetic data of tacrolimus in patients having both CYP2C19 homEMs and *CYP3A5 * 1* allele or having both CYP2C19 homEMs and MDR1 *3435TT*. Therefore, it could not be completely proved that coadministration of rabeprazole or lansoprazole increased the blood concentration of tacrolimus. Our results must be interpreted within the context of its limitations. The blood tacrolimus concentrations coadministered with rebeprazole or lansoprazole were the highest in CYP2C19 PMs having the *CYP3A5 * 3/ * 3* genotype or having the *MDR1C3435T C* allele. Therefore, further study using pharmacokinetic data of tacrolimus in patients not taking PPI is necessary. In addition, further study is necessary using a bigger sample size.

Identical immunosuppressive regimens including tacrolimus, MMF and steroid were used in this study. Mycophenolic acid, the active metabolite of the pro-drug MMF, has been reported to not affect plasma concentrations of tacrolimus in recipients treated with MMF and tacrolimus [32]. On the other hand, pharmacokinetic interaction occurs between steroids and tacrolimus, because steroids induce both CYP3A and P-glycoprotein activity [33]. However, all combined drugs except tacrolimus were kept a fixed dosage in this study. Therefore, it is thought that there was little influence of a concomitant drug in our results.

The graft survival in living related recipients has been reported to be significantly lower in patients with ulcers than in those without ulcers [31]. Upper gastrointestinal complications have resulted in considerable morbidity and mortality to renal transplant recipients, because they cannot take immunosuppressive agents. Our findings show that rabeprazole and lansoprazole may inhibit tacrolimus metabolism thereby increasing blood concentrations of tacrolimus in CYP2C19 PM recipients having the *CYP3A5 * 3/ * 3* genotype. For these recipients, a lower dosage of tacrolimus is required to achieve the target therapeutic index.

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