Impact of single nucleotide polymorphisms on tacrolimus pharmacokinetics in liver transplant patients after switching to once-daily dosing

Jangho Park (khumedicaljang@hanmail.net)
Osan Hankook Hospital https://orcid.org/0000-0002-4471-3657
Kwang-Woong Lee
Seoul National University College of Medicine
Seung Cheol Oh
Seoul National University College of Medicine
Min Young Park
Seoul National University College of Medicine
Jeong-Moo Lee
Seoul National University College of Medicine
Su Young Hong
Seoul National University College of Medicine
Suk Kyun Hong
Seoul National University College of Medicine
YoungRok Choi
Seoul National University College of Medicine
Nam-Joon Yi
Seoul National University College of Medicine
Kyung-Suk Suh
Seoul National University College of Medicine

Research Article

Keywords: CYP3A5, multidrug resistance-1 gene, ABCC2, P450 oxidoreductase*28, liver transplant recipient, tacrolimus, once-daily dosing, pharmacokinetics, dose-adjusted trough level, polymorphism

Posted Date: April 19th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1553480/v1

Abstract

Background: The effects of multidrug resistance-1 (*MDR1*), *ABCC2*, and P450 oxidoreductase (POR)*28 gene polymorphisms on tacrolimus metabolism following a switch to once-daily dosing have not been elucidated. We investigated the effects of recipient and donor *CYP3A5*, *MDR1*, *ABCC2*, and *POR*28* polymorphisms on tacrolimus pharmacokinetics following a switch to once-daily tacrolimus dosing.

Methods: Eighty-seven liver transplant recipients who were switched from twice- to once-daily tacrolimus dosing following living-donor liver transplantation and 81 matched donors were genotyped for *CYP3A5*, *MDR1* (1236C>T, 2677G>T/A, and 3435C>T), *ABCC2* (-24C>T, 1249G>A, and 3972C>T), and *POR*28*. Tacrolimus dose-adjusted trough levels (C0/dose) before and after the switch were determined and calculated based on past medical records. Recipients were divided into two groups, one group constituted of 38 patients with a C0/dose decrease of less than 30% following conversion (group 1) and the other constituted of 49 patients with a C0/dose decrease of ≥30% (group 2).

Results: CYP3A5 *1/*3 and *3/*3 were more frequent in recipients in group 1 (60.5% vs. 36.8%), while CYP3A5 *1/*1 was more frequent in group 2 (59.2% vs. 32.7%) (p = 0.016). The proportions of donor ABCC2 1249G>A genotypes AA and AG were higher in group 2 than in group 1 (20.4% vs. 5.3%; p = 0.042).

Conclusion: Recipient CYP3A5 polymorphism and donor ABCC2 1249G>A polymorphism affected tacrolimus pharmacokinetics following the switch to once-daily dosing. Dose adjustment to maintain therapeutic tacrolimus levels following the switch to once-daily dosing should be considered based on polymorphisms in both the recipient and donor.

Introduction

Tacrolimus, a calcineurin inhibitor, is usually administered twice daily following solid organ transplantation, guided by therapeutic drug monitoring. Maintaining drug concentrations within the required range is essential as out-of-range drug concentrations can result in graft rejection or tacrolimus-induced nephrotoxicity. The pharmacokinetics of tacrolimus depend mainly on the activities of cytochrome P450 (CYP) 3A5, a predominant metabolic enzyme in the intestines, and P-glycoprotein (ABCB1), an efflux transporter located in enterocyte membranes.[1] As the pharmacokinetics of tacrolimus vary with race, many studies have been conducted on several genes encoding CYP3A5 and ABCB1.

The impact of CYP 3A5 on drug pharmacokinetics has been extensively studied in heart, kidney, and liver transplantation patients.[2] The presence of the wild-type CYP3A5 polymorphism, CYP3A5*1, was found to be related to reduced tacrolimus therapeutic levels in liver transplant patients.[3–7] The relationship between ABCB1, encoded by the multidrug resistance-1 (MDR1) gene, and tacrolimus pharmacokinetics has also been evaluated in kidney and liver transplant patients; however, the results obtained have been controversial.[2, 5, 8–11] In addition, another transporter, multidrug resistance-associated protein 2

(MRP2), encoded by *ABCC2*, was found to exert various effects on tacrolimus pharmacokinetics in kidney transplant patients[12–15]; however, no study has evaluated its effects on tacrolimus pharmacokinetics following liver transplantation. Furthermore, the effects of P450 oxidoreductase (POR), a CYP enzyme modulator encoded by the POR*28 gene, on tacrolimus pharmacokinetics have been evaluated mainly following kidney transplantation, and the results obtained have been controversial.[14, 16–18]

Once-daily extended-release tacrolimus administration was introduced to promote patient compliance and increase graft survival. It has been reported to be safe and feasible, and its effects were found not to be inferior to those of conventional tacrolimus dosing in liver transplant patients.[19–21] However, it has been reported that tacrolimus levels decrease after switching from twice- to once-daily dosing; thus, dose adjustment is necessary to restore drug concentrations to the therapeutic range.[21, 22] Recently, Kim et al. reported a decrease in tacrolimus levels in recipients who were expressers of CYP3A5 (*1/*1 or *1/3) following the switch from twice- to once-daily dosing after liver transplantation; however, this study was limited by a relatively small sample size and a short follow-up period following the switch.[23] Previously, Miyata et al.[24] reported a decrease in tacrolimus levels in patients who had received donor livers with the CYP3A5 *1 allele following the switch to once-daily dosing. However, tacrolimus was administered intravenously rather than orally and the time to switch dosing was relatively short, i.e., 14 days after transplantation.

Although several studies have evaluated the pharmacokinetics of tacrolimus following twice-daily administration, studies carried out on its pharmacokinetics following once-daily administration are few. Moreover, the most investigated genes affecting tacrolimus pharmacokinetics following all types of transplantation are *CYP3A5* and *MDR1*, and most studies on *ABCC2* or *POR*28* have been performed mainly in kidney transplant patients. Thus, we hypothesized that these genes might affect the pharmacokinetics of tacrolimus following once-daily dosing. This study, therefore, sought to determine whether *CYP3A5*, *MDR1*, *ABCC2*, and *POR*28* polymorphisms in donors or recipients could affect tacrolimus dose-adjusted trough level in liver transplant patients following the switch to once-daily dosing.

Methods

Study design

This was a single-center, retrospective study that analyzed prospectively collected patient samples. DNA was extracted from patient blood samples or paraffin blocks stored in a cancer tissue bank. This study was approved by the Institutional Review Board of Seoul National University Hospital, Korea (1908-172-1059).

Patients & immunosuppressants

This study was conducted in patients who had been regularly followed up after having been transplanted living-donor livers between March 1999 and January 2018; these included patients who had consistently

been treated with tacrolimus (Tacrobell®, Chong Kun Dang Pharma, Seoul, Korea or Prograf®, Astellas Pharma, Tokyo, Japan) following liver transplantation by twice-daily dosing and then switched to once-daily dosing (Advagraf®, Astellas Pharma, Inc., Deerfield, IL, USA) at the same total daily dose. A triple regimen (tacrolimus, mycophenolate mofetil, and corticosteroids) was administered to the patients following liver transplantation. Corticosteroids were tapered and discontinued within 6 months. Donors for each recipient were also included in the study. Patients were enrolled in the study after voluntarily consenting for their tissues to be used as human research material. Patients who did not consent to the use of their tissues as human research material were not enrolled.

Data collection

Three microliters of blood was collected from recipients and donors enrolled in this study during outpatient visits within the study period, for DNA extraction; this was carried out after they had voluntarily consented for their tissues to be used as material for human research. In case of difficulty in obtaining recipient or donor blood samples, DNA was extracted from their paraffin blocks of liver tissues stored in a cancer tissue bank following surgery to confirm single-nucleotide polymorphisms (SNPs) and CYP3A5, MDR1, ABCC2, and POR*28 genotypes. In addition, ABCC2 haplotypes were determined and analyzed as described by Pulk et al.[14] Haplotypes were classified into three groups, the high expression (H1/H2 and H2/H2) group, the wild/average expression (H1/H1, H2/H10, and H2/H12) group, and the low expression (H1/H9, H1/H10, H1/H12, H9/H12, and H12/H12) group. The medical records of each patient were reviewed for the determination of serum tacrolimus levels, as well as its administered dosage before and after the switch to once-daily dosing.

DNA sequencing and genotyping

Genomic DNA was extracted from whole blood samples and paraffin blocks using a DNA Extraction Kit (Intron Bio, Sungnam, Korea), according to the manufacturer's instructions. To describe the relationship between detailed genotypes and trough levels, CYP3A5 (6986G > A in intron 3), MDR1 (1236C > T in exon 12, 2677G > T/A in exon 21, and 3435C > T in exon 26), ABCC2 (-24C > T, 1249G > A, and 3972C > T), and POR*28 (1508C > T) expression levels were determined using a TaqMan assay kit (Thermo Fisher Scientific, Applied Biosystems, Waltham, MA, USA). Six SNPs in *MDR1* and *ABCC2* were genotyped by direct sequencing. For the TaqMan assay, the reaction was carried out in a final volume of 10 μL constituted of 5 ng of genomic DNA, 1X TaqMan Genotyping Master Mix, and 20X TaqMan SNP Genotyping Assay solution. Polymerase chain reaction (PCR) was performed in thermal cyclers using Prism 7900HT devices (Applied Biosystems, Foster City, CA, USA). The thermal cycling conditions were as follows: 10 min at 95 ℃, then 40 cycles at 92 ℃ for 15 s, and 60 ℃ for 1 min. Alleles were assigned using the SDS version 2.1 software (Applied Biosystems). Direct sequencing was performed using the ABI Prism Big Dye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems) for comparative sequencing according to the manufacturer's instructions. Sequence variants were verified using the SeqMan version 7.0 software (DNASTAR Inc., Madison, Wisconsin, USA).

Outcomes

The primary endpoint of this study was the determination of the effects of *CYP3A5*, *MDR1*, *ABCC2*, and *POR*28* polymorphisms in recipients and donors on blood tacrolimus trough levels in recipients following the switch to once-daily dosing. The secondary endpoint was the comparison of changes in tacrolimus levels between CYP3A5 expressers and non-expressers, in association with polymorphisms in *MDR1*, *ABCC2*, and *POR*28* that significantly affect tacrolimus levels.

Statistical analysis

In similar previously published multicenter studies, the rate of reduction in tacrolimus concentration following the switch to once-daily dosing was reported to be 28.8 ± 23.5% in the CYP3A5 expression group and 14.2 ± 35.2% in the CYP3A5 non-expression group.[23] Assuming a two-sided type I error of 5% and a power of 80%, 40 patients were drawn from each group. Therefore, at least 80 recipients and 80 donors were required for this study.

The paired t-test and the chi-square test were used to determine factors affecting tacrolimus trough levels following the switch to once-daily dosing; these included patient characteristics and the investigated genes. To compensate for missing data, logistic regression was used to ascertain factors found to significantly affect tacrolimus trough levels through the t- and chi-square tests. The Mann-Whitney U test was used for further analysis. Furthermore, *ABCC2* haplotypes were predictably determined and analyzed based on the findings of previous studies.[12, 14, 25] Statistical analyses were carried out using SPSS Version 28.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Based on patient selection criteria, 91 recipients and donors were eligible for this study. At the end of patient registration, 87 recipients and 81 donors were enrolled and studied. The patients were divided into two groups based on the decrease in tacrolimus dose-adjusted trough levels (C0/dose) as established in a previous study[22] i.e., patients with less than a 30% decrease in C0/dose and patients with a ≥ 30% decrease in C0/dose following the switch to once-daily dosing (Table 1). There were no significant differences in age, sex, or bodyweight between the two groups. Polymorphic genotypes presented with missing data. The median time between transplantation and the switch to once-daily dosing was significantly shorter in group 2 (37.0 months [range, 4–163] vs. 25.0 months [range, 1–161]; p = 0.025).

Table 1
Differences in patient characteristics between groups 1 and 2

			Group 1 (n = 38)	Group 2 (n = 49)	p-value
Age (Years, mean ± SD)			46.8 ± 19.2	50.0 ± 12.8	0.277
Male sex			28 (73.7%)	37 (75.5%)	0.846
Bodyweight (kg, mean ± SD)			62.7 ± 11.6	61.5 ± 11.6	0.633
Δ C0/Dose (%, median, range)			-3.5 (-29–1067)	-39.3 (-100 - -30)	0.001
Switching time (Months, median, range)			37.0 (4–163)	25.0 (1–161)	0.025
Recipient	CYP3A5		*1/*1: 14 (36.8%) *1/*3, *3/*3: 23 (60.5%) Missing: 1	*1/*1: 29 (59.2%) *1/*3, *3/*3: 16 (32.7%) Missing: 4	0.016
	MDR1	1236C > T	TT: 11 (28.9%) CC, CT: 26 (68.4%) Missing: 1	TT: 13 (26.5%) CC, CT: 36 (73.5%)	0.743
		2677G > T/A	AA, AT, TT: 14 (36.8%) CC, AC, CT: 23 (60.5%) Missing: 1	AA, AT, TT: 14 (28.6%) CC, AC, CT: 32 (65.3%) Missing: 3	0.478
		3435C > T	CT, TT: 21 (55.3%) CC: 16 (42.1%) Missing: 1	CT, TT: 22 (44.9%) CC: 27 (55.1%) Missing: 1	0.276
	ABCC2	-24C > T	CT, TT: 17 (44.7%) CC: 21 (55.3%)	CT, TT: 21 (42.9%) CC: 25 (51.0%) Missing: 3	0.933

Group 1: C0/dose reduction rate of < 30%; group 2: C0/dose reduction rate of ≥ 30%

* Haplotypes were predictably determined and analyzed based on the findings of previous studies.[12, 14, 25]

			Group 1 (n = 38)	Group 2 (n = 49)	p-value
		1249G > A	AA, AG: 5 (13.2%) GG: 33 (86.8%)	AA, AG: 10 (20.4%) GG: 38 (77.6%) Missing: 1	0.352
		3972C > T	CT, TT: 18 (47.4%) CC: 20 (52.6%)	CT, TT: 20 (40.8%) CC: 25 (51.0%) Missing: 4	0.790
		Haplotype*	High: 4 (10.5%) Wild / average: 17 (44.7%) Low: 17 (44.7%)	High: 5 (10.2%) Wild / average: 23 (46.9%) Low: 16 (32.7%) Missing: 5	0.739
	POR*28		CC: 11 (28.9%) CT, TT: 27 (71.1%)	CC: 15 (30.6%) CT, TT: 33 (67.3%) Missing: 1	0.817
Donor	CYP3A5		*1/*1: 12 (31.6%) *1/*3, *3/*3: 14 (36.8%) Missing: 12	*1/*1: 21 (42.9%) *1/*3, *3/*3: 14 (28.6%) Missing: 14	0.283
	MDR1	1236C > T	TT: 14 (36.8%) CC, CT: 22 (57.9%) Missing: 2	TT: 16 (32.7%) CC, CT: 27 (55.1%) Missing: 6	0.878
		2677G > T/A	AA, AT, TT: 11 (28.9%) CC, AC, CT: 17 (44.7%) Missing: 10	AA, AT, TT: 15 (30.6%) CC, AC, CT: 22 (44.9%) Missing: 12	0.919

Group 1: C0/dose reduction rate of < 30%; group 2: C0/dose reduction rate of ≥ 30%

* Haplotypes were predictably determined and analyzed based on the findings of previous studies.[12, 14, 25]

		Group 1 (n = 38)	Group 2 (n = 49)	p-value
	3435C > T	CT, TT: 17 (44.7%) CC: 13 (34.2%) Missing: 8	CT, TT: 18 (55.3%) CC: 22 (44.9%) Missing: 9	0.334
ABCC2	-24C > T	CT, TT: 14 (36.8%) CC: 19 (50.0%) Missing: 5	CT, TT: 16 (32.7%) CC: 27 (55.1%) Missing: 6	0.645
	1249G > A	AA, AG: 2 (5.3%) GG: 30 (78.9%) Missing: 6	AA, AG: 10 (20.4%) GG: 32 (65.3%) Missing: 7	0.042
	3972C > T	CT, TT: 14 (36.8%) CC: 21 (55.3%) Missing: 3	CT, TT: 11 (22.4%) CC: 27 (55.1%) Missing: 11	0.320
	Haplotype*	High: 0 (0%) Wild / average: 18 (47.4%) Low: 14 (36.8%) Missing: 6	High: 7 (14.3%) Wild / average: 20 (40.8%) Low: 10 (20.4%) Missing: 12	0.013
POR*28		CC: 10 (26.3%) CT, TT: 24 (63.2%) Missing: 4	CC: 16 (32.7%) CT, TT: 26 (53.1%) Missing: 7	0.428

Group 1: C0/dose reduction rate of < 30%; group 2: C0/dose reduction rate of ≥ 30%

* Haplotypes were predictably determined and analyzed based on the findings of previous studies.[12, 14, 25]

Polymorphisms affecting tacrolimus C0/dose

Recipient CYP3A5 *1/*3 and *3/*3 were more frequent in group 1 than in group 2, while CYP3A5 *1/*1 was more frequent in group 2 than in group 1 (p = 0.016) (Table 1). However, there were no significant differences in the frequency of donor CYP3A5 variants between the two groups. As concerns donor ABCC2 1249G > A, the proportions of genotypes AA and AG were higher in group 2 than in group 1 (p = 0.042). The donor high-activity ABCC2 group was significantly more frequent in group 2 than in group 1, while the low-activity group was more frequent in group 1 than in group 2 (0% vs. 14.3%; 36.8% vs. 20.4%;

p = 0.013). However, there were no significant differences in the proportion of *ABCC2* haplotypes between recipients. Shorter switching time, recipient CYP3A5 *1/*1, and donor ABCC2 1249G > A AA and AG genotypes were found to be factors favoring the decrease in tacrolimus C0/dose as determined through the logistic regression analysis following missing data exclusion to reduce bias (Table 2). After adjusting switching time due to significant differences between the two groups (Tables 1 and 2), no factors were found to be associated with the decrease in tacrolimus C0/dose. As shown in Table 2, a combination of recipient CYP3A5 expression and donor ABCC2 1249G > A genotypes AA and AG significantly induced a decrease in tacrolimus C0/dose as compared to a combination of recipient CYP3A5 non-expression and donor ABCC2 1249G > A genotype GG (p = 0.021) (Fig. 1).

Table 2
Analyses of risk factors for a decrease in tacrolimus C0/dose following the switch to once-daily dosing, with missing value cases (n = 70) excluded

		Group 1 (n = 31)	Group 2 (n = 39)	Multivariate analysis		
				OR	95% CI	p-value
Switching time (Months, median, range)		37.0 (4–163)	25.0 (9–161)	0.980	0.965–0.996	0.013
Recipient	CYP3A5	*1/*1: 13 (41.9%) *1/*3, *3/*3: 18 (58.1%)	*1/*1: 25 (64.1%) *1/*3, *3/*3: 14 (35.9%)	0.350	0.118–1.037	0.058
Donor	ABCC2 1249G > A	AA, AG: 2 (6.5%) GG: 29 (93.5%)	AA, AG: 10 (25.6%) GG: 29 (74.4%)	0.182	0.031–1.062	0.058
Group 1: C0/dose reduction rate of < 30%; group 2: C0/dose reduction rate of ≥ 30%						

Discussion

In this study, recipient *CYP3A5* polymorphism and donor ABCC2 1249G > A were found to play an important role in tacrolimus pharmacokinetics following the switch to once-daily dosing. To the best of our knowledge, ours is the first study to demonstrate the effects of donor and recipient *MDR1*, *ABCC2*, *POR*28*, *CYP3A5* polymorphisms on tacrolimus levels in the liver transplant patients following the switch to once-daily dosing.

In addition to recipient *CYP3A5* polymorphism, the presence of the CYP3A5*1 allele in donors was also been reported to affect tacrolimus levels following liver transplantation.[4, 5, 9, 10, 26, 27] Moreover, tacrolimus C0/dose was found to be significantly decreased in patients who had received donor livers with the CYP3A5*1 allele following the administration tacrolimus once daily.[24] In this study, recipient CYP3A5*1/*1 induced a decrease in tacrolimus C0/dose, as reported in previous studies. However, unlike

in previous studies, donor CYP3A5*1 was found not to affect tacrolimus C0/dose in this study, even through sub-analysis. Uesugi et al. reported that intestinal and hepatic CYP3A5 play an important role in tacrolimus pharmacokinetics following liver transplantation.[7] Based on the findings of this study and those of previous studies, recipient CYP3A5 can particularly be important as the first pharmacokinetic mediator in the intestines.

ABCC2 polymorphism has been reported to affect tacrolimus pharmacokinetics in kidney transplant patients.[12, 13] Genotypes AA and AG of ABCC2 1249G > A and genotype CC of ABCC2 3972C > T were found to be related to a decrease in tacrolimus C0/dose; in addition, the ABCC2 high activity group also induced a reduction in the dose-normalized concentration of tacrolimus.[12] The findings of this study were consistent with these previous findings, as ABCC2 1249G > A and its high activity group induced a significant decrease in tacrolimus C0/dose. In contrast, *ABCC2* polymorphism was found not to be associated with changes in tacrolimus levels in other studies.[14, 15] Vanhove et al. also reported that no relationship existed between *ABCC2* diplotypes and tacrolimus C0/dose; however, for CYP3A5 non-expressers, tacrolimus C0/dose was lower in the ABCC2 low activity group than in the average and high activity groups.[28] MRP2, an ATP-binding cassette transporter, is located in hepatocyte membranes, gallbladder epithelial cells, renal tubular cells, and enterocytes; it is mainly expressed in hepatocyte apical canalicular membranes, where it contributes to the detoxification and biliary excretion of xenobiotics.[29] It can be inferred that ABCC2 1249G > A was more active in hepatocytes, as in this study, tacrolimus levels decreased only in donors, but not in recipients. This study is the first to demonstrate the effects of *ABCC2* polymorphism on the pharmacokinetics of tacrolimus administered once daily in liver transplant patients.

Few studies have reported controversial findings on *MDR1* polymorphisms in liver transplant patients. MDR1 1236C > T and MDR1 2677G > T/A were found to affect tacrolimus pharmacokinetics, but MDR1 3435C > T was not in another study[8], MDR1 3435C > T was found to be significantly associated with tacrolimus pharmacokinetics.[9] However, Bruendía et al. reported that MDR1 1236C > T and 2677G > T/A did not affect the pharmacokinetics of tacrolimus administered once or twice daily in the liver transplant patients.[5] The findings of other studies have also shown that tacrolimus C0/dose is not affected by MDR1 2677G > T/A and 3435C > T.[10, 11] Furthermore, MDR1 3435C > T was shown not to affect tacrolimus levels, even with the once-daily extended-release regimen[24]; this is consistent with the findings of our study. In this study, none of the three donor or recipient *MDR1* SNPs was found to have any effects on tacrolimus C0/dose.

*POR*28* polymorphism has been reported to be related to reduced tacrolimus levels in renal transplant patients.[14, 16, 18] However, there was a discrepancy in the findings reported by these three studies. In one of the studies, the dose-normalized tacrolimus trough level was reported to decrease in CYP3A5 non-expressers but not in CYP3A5 expressers.[14] In the other studies, in CYP3A5 expressors, the tacrolimus trough level was significantly lower in patients with the POR*28 CT and TT genotypes than in those with the CC genotype, and dose adjustment was necessary; however, there were no differences between the two CYP3A5 non-expresser patient groups.[16, 18] These findings indicated that POR*28 did not exert any

effect on its own, but elicited its effect when combined with CYP3A5. However, in this study, *POR*28* polymorphism did not affect tacrolimus C0/dose. Although our study did not show any significant results, it is the first study to attempt elucidating the relationship between *POR*28* polymorphism and tacrolimus pharmacokinetics in liver transplant patients.

Tacrolimus dose and trough levels were higher in patients who were switched to once-daily dosing within 1 year of transplantation than in those who were switched more than 1 year after transplantation; in addition, dose adjustment was more necessary in the group that was switched early because of the need for higher therapeutic levels within the period following transplantation.[30] Suh et al. reported that the proportion of abnormal liver function test results was significantly lower in patients who were switched to once-daily tacrolimus dosing more than 5 years after transplantation.[22] In this study, switching time was found to be shorter in patients with a ≥ 30% decrease in tacrolimus C0/dose following the switch. Thus, the switching time should be as long as possible following transplantation.

This study has several limitations that must be considered. First, the sample size was small owing to missing data on the genotypes of each polymorphism. DNA sequencing was performed using the stored paraffin blocks of patients who had undergone transplantation long ago, with difficulty in blood sample collection; thus, the results obtained were not as accurate as they should have been due to the long storage period and possible damage, which resulted in a small sample number. To prevent specimen damage, blood sample collection should be performed during the hospitalization period immediately before and after transplantation. Second, the measurement period for tacrolimus levels following the switch to once-daily dosing was not the same for every patient. This period ranged from 5–102 days due to different outpatient visiting schedules. It is necessary to measure tacrolimus levels within a fixed period following the switch to once-daily dosing. Third, unlike most previous studies, the time period between transplantation and the switch to once-daily dosing in this study was different for each patient due to the retrospective nature of the study. In the future, the same switching period should be established for all patients.

In conclusion, recipient CYP3A5*1 allele and donor ABCC2 1249G > A AA and AG genotypes induced a reduction in tacrolimus C0/dose following the switch to once-daily extended-release tacrolimus administration. Dose adjustment to maintain tacrolimus therapeutic levels following the switch to once-daily dosing should be considered based on polymorphisms in both the recipient and donor.

Abbreviations

ABCB1: P-glycoprotein

C0/dose: dose-adjusted trough level

CYP: cytochrome P450

MDR1: multidrug resistance-1

MRP2: multidrug resistance-associated protein 2

PCR: polymerase chain reaction

POR: P450 oxidoreductase

SNP: single-nucleotide polymorphism

Statements & Declarations

Compliance with Ethical Requirements

Conflict of interest

There were no conflicts of interest to declare.

Informed Consent in Studies with Human Subjects

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients for being included in the study.

Animal Studies

This article does not contain any studies with animal subjects.

Acknowledgements

We would like to thank Hyunsook Hong, PhD, EunSung Kim, RN, Kieun Lee, RN, and Sukyoung Chang, RN for their contribution to this article.

Funding

This study was supported by grant no. 06-2020-0100 from the SNUH Research Fund.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Jangho Park, Kwang-Woong Lee, Seung Cheol Oh, Min Young Park, Jeong-Moo Lee, Su Young Hong, Suk Kyun Hong, YoungRok Choi, Nam-Joon Yi, and Kyung-Suk Suh. The first draft of the manuscript was written by Jangho Park and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript

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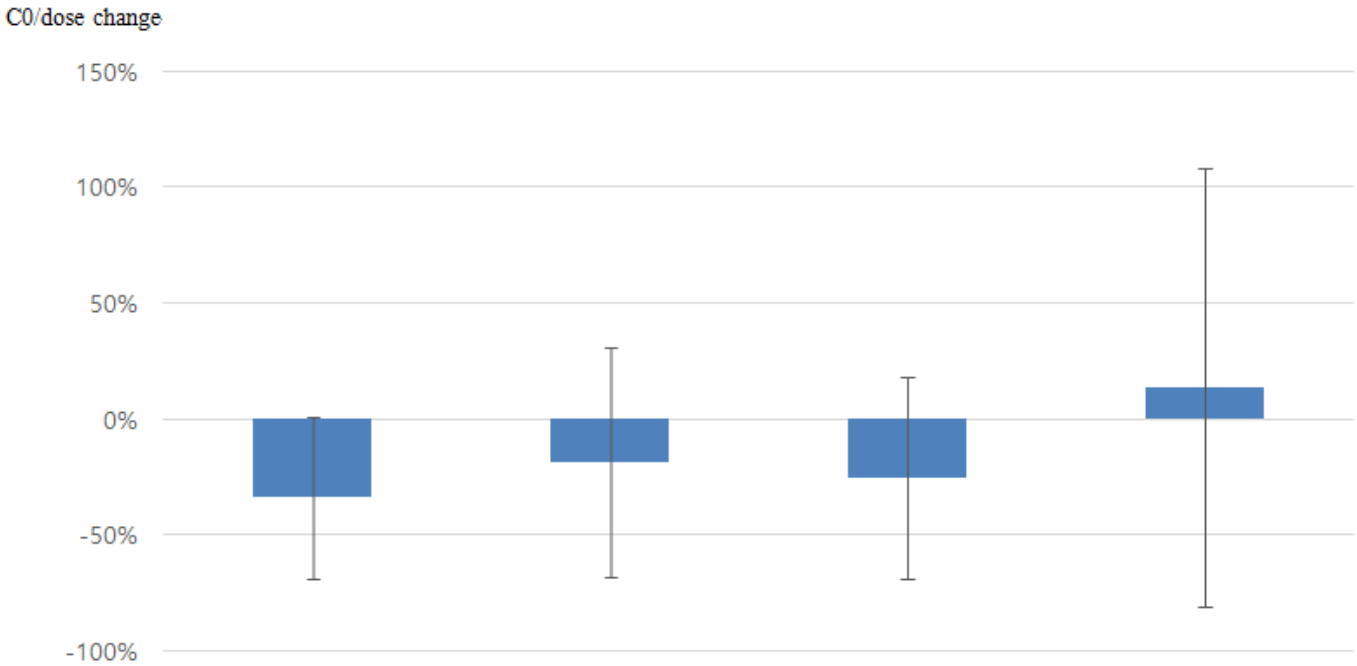
Figures



Recipient CYP3A5	*1/*1	*1/*1	*1/*3, *3/*3	*1/*3, *3/*3
Donor ABCC2 1249G>A	AA, AG	GG	AA, AG	GG
No. of patients	9 (12.9%)	29 (41.4%)	3 (4.3%)	29 (41.4%)
Mean ± SD	-33.8 ± 35.0	-18.5 ± 49.5	-25.4 ± 43.7	13.7 ± 94.8

└---p = 0.173*---┘ └---p = 0.538*---┘ └---p = 0.349*---┘
└----------p = 0.864*----------┘
└----------p = 0.084*----------┘
└----------p = 0.021*----------┘

* Mann-Whitney test

Figure 1

Combined effects of recipient CYP3A5 and donor ABCC2 1249G>A on tacrolimus C0/dose changes (%, mean ± SD), with missing value cases (n = 70) excluded

The combination of recipient CYP3A5 expression and donor ABCC2 1249G>A genotypes AA and AG induced a significant decrease in tacrolimus C0/dose as compared to the combination of recipient CYP3A5 non-expression and donor ABCC2 1249G>A genotype GG.