Original Paper

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Impact of CYP3A5 genotype of recipients as well as donors on the tacrolimus pharmacokinetics and infectious complications after living-donor liver transplantation for Japanese adult recipients

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Yuichi Muraki[1ABCDEF], Masanobu Usui[2ADEF], Shuji Isaji[2DEF], Shugo Mizuno[2ADEF], Kaname Nakatani[3AB], Tomomi Yamada[4ACDE], Takuya Iwamoto[1ACE], Shinji Uemoto[5DE], Tsutomu Nobori[3AB], Masahiro Okuda[1ADEF]

[1] Department of Pharmacy, Mie University Hospital, Tsu, Mie, Japan
[2] Department of Transplantation and Hepatobiliary Pancreatic Surgery, Mie University Graduate School of Medicine, Tsu, Mie, Japan
[3] Department of Molecular and Laboratory Medicine, Mie University Graduate School of Medicine, Tsu, Mie, Japan
[4] Department of Translational Medical Science, Mie University Graduate School of Medicine, Tsu, Mie, Japan
[5] Department of Transplantation and Hepatobiliary Pancreatic Surgery, Kyoto University Graduate School of Medicine, Sakyo-ku, Kyoto, Japan

Summary

Background: The impact of cytochrome P450 3A5 (CYP3A5) genotype of recipients (intestine) as well as donors (graft liver) on the tacrolimus pharmacokinetics and the incidence of infectious complications was assessed in Japanese living-donor liver transplant (LDLT) adult recipients.

Material/Methods: Fifty-six patients were divided into 4 groups based on the CYP3A5 genotype (expression of *1 allele: expressor (EX) and non-expressor (NEX)) in each recipients (R) and donors (D), EX-R/EX-D (n=9), EX-R/NEX-D (n=7), NEX-R/EX-D (n=12) and NEX-R/NEX-D (n=28). Tacrolimus blood concentration and concentration/dosage ratio (C/D) were evaluated every week until 4 weeks and every month until 12 months after LDLT. The incidences of postoperative infectious complication, acute cellular rejection and tacrolimus adverse effect were compared.

Results: The tacrolimus blood concentrations among 4 groups did not significantly differ at each follow-up time period. The C/Ds were significantly lower in EX-R/EX-D (median: 122.3 at 2 weeks) than in NEX-R/NEX-D (389.6 at 2 weeks) until 12 months. The C/Ds in EX-R/NEX-D (163.2 at 2 weeks) have been significantly lower than those in NEX-R/NEX-D until 6 months. Over 6 months, however, those in NEX-R/EX-D showed lower levels (84.1 at 8 months) than those in NEX-R/NEX-D (189.3 at 8 months). Additionally, logistic regression analysis showed that EX-R/EX-D had significantly higher risk for the development of infectious complications than NEX-R/NEX-D (odds ratio 8.67, p=0.03).

Conclusions: Preoperative assessment of CYP3A5 genotypes in both recipients and donors would be useful not only for predicting tacrolimus pharmacokinetics but also defining high-risk group of infectious complications after LDLT.

Key words: **CYP3A5 • single nucleotide polymorphism • tacrolimus • pharmacokinetics • liver transplantation**

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Author's address: Masahiro Okuda, Department of Pharmacy, Mie University Hospital, Faculty of Medicine, Mie University, 2-174 Edobashi, Tsu, Mie 514-8507, Japan, e-mail: okudam@clin.medic.mie-u.ac.jp

Background

Tacrolimus, an immunosuppressing drug used worldwide in organ transplantation, is characterized by a narrow therapeutic index and high inter-individual variations in its pharmacokinetics, which makes it difficult to establish an empirical dosage regimen of the drug [1]. Underdosing of tacrolimus leads to rejection, whereas overdosing also increases the risk of infection and serious drug-specific adverse effects [2]. As for the poor quantitative correlation between drug dosage and blood concentration, the tacrolimus dose is adjusted frequently according to its blood concentration in order to achieve a balance between efficacy and toxicity. Achieving therapeutic target levels is of critical importance during the initial period post-transplantation therapy, when the risk of rejection is the greatest [3,4].

Tacrolimus is mainly metabolized by cytochrome P450 isozymes, CYP3A4 and CYP3A5, expressed in the intestine as well as in the liver. Recent advances in pharmacogenomics have uncovered several single nucleotide polymorphisms (SNPs) in intron 3 of CYP3A5 which are correlated with gene expression and enzyme activity because it creates a cryptic splice site and results in either the presence (expressor, *1/*1 and *1/*3) or absence (non-expressor, *3/*3) of CYP3A5 [5].

Several studies have shown that the CYP3A5 expressors are associated with significantly lower dose-corrected tacrolimus exposure and increased tacrolimus dose requirements in order to achieve target blood concentrations compared with CYP3A5 non-expressors [6–11]. In the liver transplantation, therefore, the impact of CYP3A5 genotype of recipients (intestine) as well as donors (graft liver) should be considered on the tacrolimus pharmacokinetics.

The information is little known about whether the CYP3A5 genotype affected to transplantation performance, though CYP3A5 genotype has been gradually shown to affect the tacrolimus pharmacokinetics in transplantation. In renal transplantation, several studies have shown that these different gene polymorphisms impact on adverse effects or graft survival [12,13]. However, there has been a lack of studies examining the impact of these different gene polymorphisms considering the incidence of infectious complications, acute cellular rejection and tacrolimus adverse effects in Japanese LDLT recipients. Recently, we reported that the Japanese adult recipients with CYP3A5 expressor had low immune response of peripheral blood CD4+ adenosine triphosphate (ATP) activity in spite of constant tacrolimus concentrations, and therefore suffered from infectious complications [14].

In the present study, we examined the CYP3A5 genotype of recipients (intestine) as well as donors (liver) to clarify their impact on the pharmacokinetics of tacrolimus every week until 4 weeks and every month until 12 months after LDLT. Furthermore, the correlation between CYP3A5 genotype and incidence of infectious complications, acute cellular rejection and tacrolimus adverse effects in LDLT recipients were analyzed.

Material and Methods

Patients

Between March 2002 and October 2006, 56 recipients and 56 donors were enrolled in this study, having first provided their written informed consent. Follow-up period was until March 2008. Recipients with end-stage liver disease underwent living-donor liver transplantation at Mie University Hospital and were immunosuppressed with a combination of tacrolimus and corticosteroids.

For all patients, the mean initial dosage of tacrolimus was 1 mg twice a day. The dose was then adjusted according to blood trough concentrations measured 12 hr after the previous dose (termed C_0). During the first month, the target C_0 was controlled between 10–15 ng/mL. After the first month, the target C_0 was decreased gradually to achieve about 5 ng/mL depending on the patient condition. Methylprednisolone (10 mg/kg) was intravenously administered at the time of graft reperfusion, and then the dosage was gradually reduced, and the patients were switched to oral prednisolone 1 week after transplantation. The dosage of prednisolone was progressively tapered off and was discontinued between 3 and 6 months after transplantation as long as the liver function was stable. Patients taking any other medications known to interact with calcineurin inhibitors were excluded from this study. This study was conducted in accordance with the Declaration of Helsinki and its amendments and was approved by the Mie University Graduate School and Faculty of Medicine, Ethics Committee.

Tacrolimus C_0 monitoring and C/D ratio evaluation

One mL of blood treated with EDTA for anticoagulation was collected 12 hr after the previous dose and tacrolimus blood C_0 was then measured by a semiautomated microparticle enzyme immunoassay (IMx, Abbott Co., Ltd, Tokyo, Japan). The daily dose of tacrolimus was recorded and its weight-adjusted dosage (mg/kg/day) was calculated after transplantation. Then the blood tacrolimus concentration measured was normalized by the corresponding dose per body weight 24-hour before blood sampling to obtain the concentration/dose (C/D) ratio, which was then used for the estimation of tacrolimus dose needed to achieve the target trough concentration. However, when the blood tacrolimus concentration was not measured at a given time point, the data were excluded.

Genotyping of cytochrome P450 3A5

The single nucleotide polymorphism of CYP3A5 at position 6986, i.e. A6986G, was analyzed for detection of the *3 allele, because previous reports suggested that CYP3A5*3 is the major defective allele and that other functional exonic SNPs are rare in Japanese subjects [15–17].

In brief, blood samples obtained from the patients were utilized for the isolation of genomic DNA using a QIAamp Blood kit (Qiagen, Hilden, Germany). A fragment containing the A6986G polymorphism was amplified as follows. Ten-fold PCR buffer, 2 mM dNTP, 0.1 mM primers, and Taq polymerase (Applied Biosystems, Foster City, CA, USA), primers: forward 5'-tacccacgtatgtaccaccc-3' and reverse 5'-gcactgttctgatcacgtcg-3' at 95°C for 10 min, 40 cycles (94°C for 30 s, 58°C for 30 s, and 72°C for 30 s) and 72°C for 7 min. After purification using calf intestine alkaline phosphatase (CIP, Promega, Madison, WI, USA), 1.0 µL of cleaned PCR product was mixed with 2.5 µL of SNaPshot ready Reaction Mix (ABI) and 20 pmol/µL of SNaPshot primer (5'-aagagctcttttgtctttca-3'). The cycling program consisted of 25 cycles of 96°C for 10 s, 50°C for 5 s, and 60°C for 30 s. Post-extension products were purified with CIP and incubated at 37°C for 45 min and at 75°C for 10 min. One µL of the final product was diluted 1:30 with distilled water and denatured with 9.0 µL Hi-Di Formamide (ABI) at 95°C for 5 min. The fragments were run on an ABI Prism 310 Genetic Analyzer, in accordance with the manufacturer's recommendations and using the 310 Data Collection v2.1 program with a POP-6 polymer in conjunction with a GS STR POP-6 (1 mL) E5v2 module. To generate a Matrix File that corrects for the spectral overlap of fluorescent dyes, a matrix standard set at DS120LIZ was run. Following the run, samples were analyzed using GeneScan 3.1 software (ABI).

Influence of CYP3A5 genotype on the incidences of postoperative infectious complication, acute cellular rejection and tacrolimus adverse effect in LDLT recipients

Logistic regression analysis was used to assess the impact of multiple covariates (CYP3A5 genotype of recipients and donors) for infectious complication, acute cellular rejection and tacrolimus adverse effects during the first hospitalization, excepting the patients with early death case and incompatibility (n=9). The incidences of postoperative infectious complication, acute cellular rejection and tacrolimus adverse effect were made diagnoses by physician. Infectious complication was classified into bacteremia, intra-abdominal abscess, urinary-tract infection, pneumonia, surgical site infection and unknown, which contained overlap. Acute cellular rejection diagnosis was based on histologic criteria. Tacrolimus adverse effects examined renal dysfunction (serum creatinine >1.4 mg/dL), hyperkalemia (serum potassium level >5 mEq/L) and hyperuricemia (serum urate level >8 mg/dL), respectively.

Table 1. Demographics of recipients and the distribution of CYP3A5 genotypes in 56 living-donor liver transplant recipients and their corresponding donors.

		Recipient CYP3A5 genotype			
		*1/*1	*1/*3	*3/*3	Total (%)
Donor CYP3A5 genotype	*1/*1	1	0	0	1 (1.8)
	*1/*3	3	5	12	20 (35.7)
	*3/*3	0	7	28	35 (62.5)
Total (%)		4 (7.1)	12 (21.5)	40 (71.4)	56 (100.0)
Gender (male/female)		0/4	7/5	29/11	36/20
Age in years, (median, range)		63 (55–69)	51 (28–70)	53.5 (20–68)	53.5 (20–70)
Weight in kg (median, range)		56 (50–72)	60 (46–85)	64 (38–95)	62 (38–95)
Primary disease	HCV (HCC)	3 (3)	0	17 (11)	20 (14)
	HBV (HCC)	0	3 (3)	7 (3)	10 (6)
	PBC	0	1	3	4
	Others	1	8	13	22

HCV – hepatitis C virus; HCC – Hepatocellular carcinoma; HBV – hepatitis B virus; PBC – primary biliary cirrhosis.

Statistical analyses

Kruskal-Wallis tests with Bonferroni's multiple comparison were used for comparisons among several groups. These statistical analyses were performed with GraphPad InStat, version 3 (GraphPad Software, Inc., San Diego, CA, USA). The results of the logistic regression analysis are expressed as odds ratios with 95% confidence intervals and a p value. A value $p<0.05$ was considered statistically significant in all analyses, which were performed using SAS for Windows version 9 (SAS Institute Inc., Cary, NC, USA).

Results

Genotype identification

Fifty-six patients were divided into 4 groups based on the CYP3A5 genotype (expression of *1 allele: expressor (EX) and non-expressor (NEX)) in each recipients (R) and donors (D), EX-R/EX-D (n=9), EX-R/NEX-D (n=7), NEX-R/EX-D (n=12) and NEX-R/NEX-D (n=28). Table 1 summarizes the demographics of the recipients and the CYP3A5 genotype distribution in the recipients and their corresponding donors. Of the recipients, 4 (7.1%) were *1/*1 genotype, whereas 12 (21.5%) were heterozygous and 40 (71.4%) were homozygous for the *3 allele. The genotype distribution of the donors was as 1 (1.8%), 20 (35.7%), and 35 (62.5%), respectively. The mean age of the recipients was 52.9±11.1 years, and the mean recipients body weight was 62.8±11.3 kg. Primary diseases most recipients had were hepatitis C (n=20) or hepatitis B (n=10).

The impact of CYP3A5 genotype of recipients (intestine) as well as donors (graft liver) on the tacrolimus pharmacokinetics after LDLT

The tacrolimus blood concentrations among 4 groups did not significantly differ at each follow-up time point (Tables 2, 3). Patients with no available tacrolimus levels at the time were excluded. In contrast, the C/D ratios were significantly lower in EX-R/EX-D group than in NEX-R/NEX-D group after 2 weeks. When compared between EX-R/NEX-D and NEX-R/NEX-D groups, the C/D ratios in EX-R/NEX-D group have been significantly lower than those in NEX-R/NEX-D group from 2 weeks through 6 months. On the other hand, the C/D ratios in NEX-R/EX-D group have been lower than those in NEX-R/NEX-D group over 6 months.

Influence of CYP3A5 genotype on the incidences of postoperative infectious complication, acute cellular rejection and tacrolimus adverse effect in LDLT recipients

Table 4 shows demographics of the infectious complication, acute cellular rejection and tacrolimus adverse effects in the patients divided by CYP3A5 genotypes during the first hospitalization,

Table 2. Tacrolimus blood concentration or concentration/dosage ratio for different combination of CYP3A5 genotypes for both recipients (intestine) and donors (liver) until 4 weeks post-transplantation.

Recipient/donor (Intestine/liver)	n	1 week	2 weeks	3 weeks	4 weeks
Blood concentration (ng/mL)					
EX-R/EX-D	9	8.3	6.6	8.5	6.9
		(7.5, 9.4)	(5.4, 8.5)	(4.5, 11.7)	(3.0, 9.4)
EX-R/NEX-D	6	7.3	10.0	9.8	9.0
		(6.4, 9.6)	(8.3, 10.4)	(6.3, 12.0)	(6.8, 11.3)
NEX-R/EX-D	12	9.6	10.2	8.3	7.8
		(8.2, 11.1)	(9.4, 11.7)	(7.7, 12.2)	(7.1, 9.2)
NEX-R/NEX-D	24	10.5	10.1	10.4	9.4
		(9.7, 12.4)	(8.1, 12.0)	(7.5, 14.2)	(7.8, 12.3)
Concentration/dosage ratio (ng/mL)/(mg/kg/day)					
EX-R/EX-D	9	159.5	122.3*	130.0*	167.3*
		(135.9, 208.4)	(97.8, 197.0)	(114.4, 141.3)	(113.3, 180.0)
EX-R/NEX-D	6	139.6	163.2*	153.6*	160.1*
		(105.8, 152.3)	(142.9, 177.3)	(108.1, 202.2)	(94.0, 207.0)
NEX-R/EX-D	12	243.3	242.3	230.9	302.3
		(120.4, 396.7)	(202.7, 459.4)	(162.0, 338.3)	(156.4, 515.6)
NEX-R/NEX-D	24	333.4	389.6	365.9	460.8
		(232.7, 522.2)	(280.3, 566.9)	(291.0, 478.6)	(256.9, 790.7)

Values presented are medians (25 percentile, 75 percentile) *: $p < 0.05$ with Bonferroni's correction (*vs.* NEX-R/NEX-D). EX – expressor (*1/*1 or *1/*3); NEX – non-expressor (*3/*3). Patients with no available tacrolimus levels at the time were excluded.

excepting the patients with early death case and incompatibility. The incidence rate of infectious complications in EX-R/EX-D groups was 85.7%, whereas tacrolimus adverse effects (renal dysfunction, hyperkalemia, and hyperuricemia) did not differ among 4 groups. Additionally, incidence of acute cellular rejection was also similar among 4 groups. Logistic regression analysis showed that EX-R/EX-D group showed significantly higher risk for the development of infectious complications than NEX-R/NEX-D group (odds ratio 8.67, p=0.03, Table 5).

Discussion

The present study clarified the temporal alteration on tacrolimus pharmacokinetics among the patients divided by the CYP3A5 genotypes of recipients as well as donors after LDLT. In addition, it was evaluated whether the CYP3A5 genotypes affected the incidence of infectious complications as well as adverse events.

Analyses for the combinations of CYP3A5 genotypes in both donors and recipients showed that the C/D ratios of EX-R/NEX-D group were significantly lower than those of NEX-R/NEX-D group from 2 weeks through 6 months after transplantation (Table 2). Uesugi et al. reported that the tacrolimus C/D ratio was lower in the recipients with CYP3A5 expressor than the recipients with the CYP3A5 non-expressor until 1 month. Additionally, the recipients with the intestinal CYP3A5 expressor tended to require a higher dose of tacrolimus compared to the other group with the same hepatic CYP3A5 genotype [7]. They also suggested that intestinal CYP3A5 as well as hepatic CYP3A5 plays an important role in the first-pass effect of orally administered tacrolimus until 35 days [7]. Notably, the present

Table 3. Tacrolimus blood concentration or concentration/dosage ratio for different combinations of CYP3A5 genotype in both recipients (intestine) and donors (liver) until 12 months post-transplantation.

Recipient/donor (Intestine/liver)	n	2 months	4 months	6 months	8 months	10 months	12 months
Blood concentration (ng/mL)							
EX-R/EX-D	9	6.8	4.9	4.5	3.5	2.8	3.4
		(4.8, 7.4)	(4.3, 5.0)	(3.9, 6.0)	(2.8, 4.0)	(1.8, 4.3)	(1.7, 3.7)
EX-R/NEX-D	6	6.9	6.1	4.0	8.8	7.7	8.1
		(4.9, 7.6)	(4.5, 7.1)	(2.1, 6.3)	(5.9, 9.0)	(4.6, 8.8)	(5.5, 10.0)
NEX-R/EX-D	12	6.3	5.5	5.7	4.5	4.9	3.9
		(3.8, 9.0)	(3.8, 8.3)	(4.1, 6.7)	(2.6, 5.1)	(4.7, 5.6)	(2.8, 4.8)
NEX-R/NEX-D	24	8.3	5.5	6.1	5.3	6.4	5.7
		(5.7, 10.2)	(3.8, 7.0)	(4.8, 7.7)	(4.6, 6.9)	(4.3, 7.8)	(4.4, 7.3)
Concentration/dosage ratio (ng/mL)/(mg/kg/day)							
EX-R/EX-D	9	134.0*	90.0*	93.3*	98.7	57.9*	93.2*
		(95.0, 171.6)	(43.7, 96.0)	(51.8, 119.6)	(55.6, 130.9)	(41.0, 63.3)	(51.2, 115.7)
EX-R/NEX-D	6	96.6*	86.4	103.8*	112.2	98.2	162.8
		(83.3, 204.8)	(78.3, 143.3)	(85.7, 109.3)	(109.7, 218.6)	(81.8, 187.9)	(152.9, 177.6)
NEX-R/EX-D	12	167.4	95.8	101.9	84.1*	110.1*	134.4*
		(117.6, 338.0)	(75.8, 147.6)	(92.3, 192.4)	(56.3, 89.3)	(86.0, 146.1)	(63.9, 189.7)
NEX-R/NEX-D	24	375.4	268.5	254.9	189.3	288.0	274.6
		(255.2, 644.0)	(154.6, 479.7)	(204.7, 349.3)	(164.3, 264.4)	(174.6, 456.8)	(199.3, 370.4)

Values presented are medians (25 percentile, 75 percentile) *: $p < 0.05$ with Bonferroni's correction (*vs.* NEX-R/NEX-D). EX – expressor (*1/*1 or *1/*3); NEX – non-expressor (*3/*3). Patients with no available tacrolimus levels at the time were excluded.

results that polymorphisms in the recipient (intestine) CYP3A5 gene seem to contribute more to such variation than in the donor (graft liver) until 6 months but not 1 month.

It was reported that pharmacogenomic factors are responsible for the inter-individual variations in the pharmacokinetics of tacrolimus in the recipients until 12 month after LDLT [18]. In the present study, it was also demonstrated that the tacrolimus C/D ratio in EX-R/EX-D group have been lower than those in NEX-R/NEX-D group until 12 months. Additionally, the C/D ratios of NEX-R/EX-D group were significantly lower than those for NEX-R/NEX-D group over 6 months (Table 3). Therefore, polymorphisms of the donor CYP3A5 gene as well as those of recipient seem to contribute increasingly to such variation. These results demonstrate that the metabolism of tacrolimus affected by the graft liver as well as the small intestine in the stable condition. On the other hand, this is a single-institution study. Thus, it is difficult to obtain a large number of patients, especially for the patients with EX-R/EX-D. Multicenter study would be prerequisite to obtain definitive conclusion.

In the present study, EX-R/EX-D group significantly affected the incidences of infectious complication for NEX-R/NEX-D group, as evidenced by the logistic regression analysis (Table 5). For all patients, the regimen as immunosuppression therapy was performed as well. However, the acute cellular rejection or tacrolimus adverse effect did not affect the CYP3A5 genotype in the first hospital or to death. There are reports investigating that CYP3A5 polymorphism is a risk factor for organ transplantation [13,18]. Kuypers et al. reported that higher accumulation of active metabolites of tacrolimus in the CYP3A5

Table 4. Demographics of the infectious complication, acute cellular rejection and tacrolimus adverse effects in the patient groups divided by CYP3A5 genotype.

Recipient/donor	EX-R/EX-D (n=7)	EX-R/NEX-D (n=6)	NEX-R/EX-D (n=11)	NEX-R/NEX-D (n=23)
Infectious complication (%)	6 (85.7)	3 (50.0)	5 (45.5)	9 (40.9)
Bacteremia	4	1	2	2
Intra-abdominal abscess	4	3	3	7
Urinary-tract infection	2	3	0	2
Pneumonia	2	1	0	2
Surgical Site Infection	0	0	0	1
Unknown	0	0	1	0
Acute cellular rejection (%)	1 (14.2)	1 (16.7)	1 (9.1)	5 (21.7)
Tacrolimus adverse effects				
Renal dysfunction (%)	3 (42.9)	2 (33.3)	6 (54.5)	11 (50.0)
Hyperkalemia (%)	4 (57.1)	4 (66.7)	6 (54.5)	18 (81.8)
Hyperuricemia (%)	1 (14.3)	2 (33.3)	3 (27.3)	7 (31.8)

EX – expressor (*1/*1 or *1/*3); NEX – non-expressor (*3/*3).

Table 5. The impact on CYP3A5 genotype on infectious complication using logistic regression analysis.

Parameters	Odds Ratio (95% Confidence interval)		p value
Infectious complication			
EX-R/EX-D (recipient/donor)	8.67	(1.20–178.90)	0.0309
EX-R/NEX-D (recipient/donor)	1.44	(0.22–9.46)	0.6911
NEX-R/EX-D (recipient/donor)	1.20	(0.22–9.46)	0.8036
NEX-R/NEX-D (recipient/donor)		–	

EX – expressor (*1/*1 or *1/*3); NEX – non-expressor (*3/*3). Four groups divided recipient or donor genotype as confounding factor were submitted to multivariate analysis using a logistic regression model.

expressor might contribute to the nephrotoxicity [13]. Fukudo et al. reported that the cumulative incidence of renal dysfunction within one year after transplantation was significantly associated with the recipient's but not the donor's CYP3A5 genotype [18]. We also reported that the CYP3A5 expressors showed low immune response as evidenced by peripheral blood CD4+ ATP activity in spite of keeping the tacrolimus concentration among the therapeutic window and thereby suffered from infectious complications [14]. Furthermore, Shimomura et al. reported that the appearance of the minor metabolite of tacrolimus (31-O-desmethyltacrolimus, M-II) in bile could be associated with the extensive metabolism of tacrolimus and/or the requirement for larger oral dosage [19]. Therefore, it is plausible that the increased accumulation of active metabolites in patients harboring CYP3A5 expressor may have caused excessive immunosuppression, resulting in lethal infectious diseases. However, analyses of pharmacodynamic parameters such as calcineurin activity or ATP activity in the patient harboring CYP3A5 expressor should be performed as a part of future studies.

Conclusions

In conclusion, CYP3A5 genotype in both recipients (intestine) and donors (graft liver) significantly affects tacrolimus pharmacokinetics after LDLT, which are mainly affected by the recipient's genotype during early postoperative period and by the recipient and donor's genotypes

during late postoperative period. Preoperative assessment of CYP3A5 genotypes in both recipients and donors would be important not only to predict tacrolimus pharmacokinetics but also to define high-risk group of infectious complications after LDLT.

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