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Original Article

The influence of CYP3A4 and CYP3A5 gene polymorphism on individualized medication of FK506 and hepatorenal function after liver transplantation

Kai Chen[1*], Yu Wu[4*], Rong-Sheng Tong[2,3,4], Zheng-Yao Hou[4], Xing-Xing Li[4], Yuan Zhang[2,3], Lei Zhong[2,3], Jun-Lan Chuan[2,3], Hong-Ji Yang[1], Xia He[2,3]

[1]OrganTransplant Center, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu 610072, Sichuan, China; [2]Department of Pharmacy, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu 610072, Sichuan, China; [3]Personalized Drug Therapy Key Laboratory of Sichuan Province, School of Medicine, University of Electronic Science and Technology of China, Chengdu 610072, Sichuan, China; [4]School of Medicine, University of Electronic Science and Technology of China, Chengdu 610054, Sichuan, China. [*]Equal contributors.

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Abstract: Objective: To investigate the role of CYP3A4*18B (rs2242480) and CYP3A5*3 (rs776746) genetic polymorphism in predicting the efficacy of tacrolimus (FK506) and the recovery of hepatorenal function after liver transplantation. Methods: Thirty-eight patients who received liver transplantation and treated with FK506 were enrolled. The genetic polymorphism of CYP3A4/5 was determined by DNA microarray and the blood trough concentration of FK506 was measured by enzyme multiplied immunoassay technique (EMIT). The adjusted concentration/dosage (C/D) ratio of FK506 and indicators of hepatorenal function were measured one, two and four weeks after transplantation. Results: Among 38 patients, there were 14 patients carrying CYP3A4 C/C (37.8%), 19 carrying CYP3A4 C/T (51.4%), 4 carrying CYP3A4 T/T (10.8%), and 1 undetectable genotype. The corrected C/D ratio was highest for CYP3A4 C/C group one week after operation ($P<0.05$). The recovery of ALT, Cr and INR of the CYP3A4 C/C group was slower than that of the CYP3A4 C/T group and CYP3A4 T/T group. Among 38 patients, we found 5 carriers of CYP3A5 A/A (13.1%), 15 carriers of CYP3A5 A/G (39.5%) and 18 carriers of CYP3A5 G/G (47.4%). CYP3A5 G/G group had higher corrected C/D ratio and slower recovery of Cr, ALT and INR than CYP3A5 A/G group and CYP3A5 A/A group. Conclusion: The gene polymorphism of CYP3A4/5 was an important factor for the significant individual pharmacokinetics differences of FK506. Slow metabolism genotypes (CYP3A4 C/C and CYP3A5 G/G) required a lower dose of FK506 to reach the proper blood concentration than fast metabolizers (CYP3A4 C/T, T/T and CYP3A5 A/A, A/G).

Keywords: Liver transplantation, genetic polymorphisms, FK506, pharmacokinetics, individualized immunosuppressive therapy

Introduction

With the advancement of surgical techniques, immunosuppressants and liver preservation techniques, liver transplantation has become a standard treatment for end-stage liver disease, which significantly improves the patients' quality of life [1]. Calcineurin inhibitors (CNIs), cyclosporine A (CsA) and tacrolimus (FK506) are the most commonly used immunosuppressants after liver transplantation. FK506, with a macrocyclic lactone structure, inhibits interleukin-2 (IL-2) synthesis and reduces the cytotoxic T lymphocytes infiltrated to the transplanted organ, resulting in the prevention of immune rejection after organ transplantation.

FK506 is well known for its narrow therapeutic index and great variations in pharmacokinetic characteristics among individuals. The current clinical practice is to adjust the dosage so that the blood trough concentration is among the safe range. However, acute and chronic rejection, FK506 poisoning and graft loss of function are inevitable. It is evidenced that FK506 is mainly metabolized through CYP3A4 and

CYP3A5 in liver and intestine, whose expression and activity are associated with their gene polymorphisms. Studies have shown that CYP3A4*18B and CYP3A5*3 are correlated to FK506 pharmacokinetics. Previous studies indicated that CYP3A5*3 created a cryptic consensus splice site which resulted in the production of improperly spliced mRNA, thus the protein it encoded was tremendously reduced [2]. CYP3A4*18B genetic mutation was suggested to increase CYP3A4 activity, affecting the plasma concentration of FK506 [3, 4]. In this study, we detected the CYP3A4/5 gene polymorphism and the blood concentration of FK506 in post-liver-transplantation patients. The recovery of hepatorenal function was also analyzed.

Materials and methods

Subjects

Thirty-eight patients undergoing orthotopic liver transplantation were enrolled from January, 2009 to January, 2013 in Organ Transplant Center, Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital. There were 31 males and 7 females, aged 34 to 62 years old (mean ± standard deviation: 44.89±7.67), weighted 37 to 76 kg (mean ± standard deviation: 59.01±9.10), heighted 150 to 176 cm (mean ± standard deviation: 166.10± 7.67), the body surface area was from 1.25 to 1.93 m^2 (mean ± standard deviation: 1.64± 7.67).

Ethics

The study was performed in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of Sichuan Academy of Medical Sciences & Sichuan Provincial People's Hospital, and a written informed consent was obtained from all participants.

Immunosuppressive regimen after liver transplantation

All participants were treated with FK506 (Astellas Pharma China, Inc., Shenyang, China), mycophenolate mofetil capsules (MMF, Shanghai Roche Pharmaceuticals Ltd., Shanghai, China), and corticosteroids (Xianju Pharma Ltd., Zhejiang, China). Methylprednisolone (500 mg, Pfizer Manufacturing) was intravenously injected at the start of surgery and unclamping portal vein. One day after surgery, 0.05 mg/(kg•d) FK506 and 1 g/d MMF were administered through a gastric tube twice, following oral administration after removing the tube. Then the medication dose was adjusted according to the blood trough concentration and clinical indicators; the target trough concentration of FK506 was 10-15 μg/L. Methylprednisolone (240 mg) was administered at the first day after surgery, then reduced to 40 mg daily until the 7^{th} day, and maintained at 20 mg until one month.

Measurement of FK506 blood trough concentrations

Twelve hours after taking FK506, 2 ml peripheral blood with EDTA anticoagulant were collected and analyzed with SYVA automatic analytical instrument (Siemens China, Beijing, China). The blood trough concentration of FK506 was detected by enzyme multiplied immunoassay technique (EMIT, Viva-E System, Siemens China, Beijing, China) at 1, 2 and 4 weeks.

Genotype detection

DNA was extracted from peripheral blood using Shanghai BaiO blood kit. Gene chips and primers were designed and manufactured in BaiO to access CYP3A5*3 and CYP3A4*18B polymorphism. PCR amplification conditions were 5 min of initial denaturation at 50°C and 5 min denaturation at 94°C, followed by 35 cycles of melting at 94°C for 25 sec, annealing at 53°C for 25 sec, and elongation at 72°C for 25 sec, followed by a final elongation for 5 min at 72°C. BaiO BE-2.0 gene chip scanner and ArrayDoctor software were used to analyze the results. Fifty SNPs from all 38 samples were randomly selected for sequencing to validate the results from gene chips, and the results were consistent.

Statistical analysis

All data were expressed as mean ± standard deviation ($\bar{X}$ ± SD) and analyzed with SPSS for Windows software (version 20.0; Chicago, IL, USA). The allele frequency (AF) = allele number/2 × sample number. Since the cases of our study were less than 40, one-way ANOVA analysis was used in comparisons among multiple groups via homogeneity of variance. Mann-Whitney U test was used in comparisons between two groups. $P<0.05$ was considered statistically significant.

Table 1. Mutation frequency and genotypic frequency of CYP3A4 and CYP3A5 genotypes

Genotype	Control (n=101)	Transplantation (n=38)	*P* value (χ^2 test)
CYP3A5 AA*1/*1	6 (5.9%)	5 (13.1%)	
GG*3/*3	54 (53.5%)	18 (47.4%)	
AG*1/*3	41 (40.6%)	15 (39.5%)	0.615
A	26.20%	32.9%	
G	73.8%	67.1%	
CYP3A4 CC*1/*1	62 (61.4%)	14 (37.8%)	
TT*18B/*18B	9 (8.9%)	4 (10.8%)	
CT*1/*18B	30 (29.7%)	19 (51.4%)	0.958
C	76.25%	63.5%	
T	23.75%	36.5%	

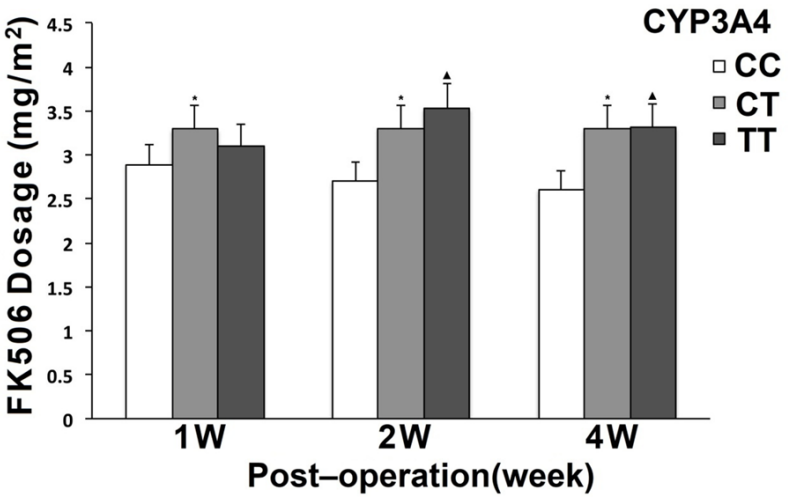

Figure 1. The surface dosage of FK506 in liver transplantation patients with different CYP3A4 genotypes. *C/C vs C/T; ▲C/C vs T/T; *P*<0.05.

Results

The distribution of CYP3A4 and CYP3A5 gene polymorphism in Han population

The distribution of CYP3A4 and CYP3A5 polymorphisms was shown in **Table 1**. Through chi-square χ^2 test, there was no significant difference in allele frequency distribution between the participants and healthy subjects, which was coincident with Hardy-Weinberg genetic equilibrium (*P*>0.05). The frequency of the genetic polymorphisms of the two sites was not correlated with age or gender.

Among the 38 patients with liver transplantation, we found 14 with wide-type (37.8%) CYP3A4 C/C (*1/*1), 19 with heterozygous mutation (51.4%) CYP3A4 C/T (*1/*18B) and 4 with homozygous mutation (10.8%) CYP3A4 T/T (*18B/*18B). For CYP3A5 polymorphisms, we found 5 with CYP3A5 A/A (*1/*1) (wild-type, 13.1%), 15 with CYP3A5 A/G (*1/*3) (heterozygous mutation, 39.5%) and 18 with CYP3A5 G/G (*3/*3) (homozygous mutation, 47.4%).

The correlation between CYP3A4 polymorphism and the C/D ratio of FK506

One week after surgery, the dosage of FK506 of CYP3A4 C/C group was lower than that of CYP3A4 C/T group (*P*<0.05) and CYP3A4 T/T group. Two weeks after surgery, the dosage of CYP3A4 C/C group was further reduced, while the dosage of CYP3A4 C/T and CYP3A4 T/T groups was increased. We observed significant differences of FK506's dosage between these three groups (*P*<0.05). Four weeks after surgery, the dosage of CYP3A4 C/C group continued declining, and the dosage of CYP3A4 C/T and CYP3A4 T/T groups also decreased, but significant difference in the dosages still exists (*P*<0.05). However, there were no differences between CYP3A4 C/T and CYP3A4 T/T (**Figure 1**). The corrected C/D ratio of CYP3A4 C/C group was significantly higher than that of CYP3A4 C/T and CYP3A4 T/T groups one week after operation (*P*<0.05), while there was significant difference only between CYP3A4 C/C group and CYP3A4 C/T group 2 weeks after surgery (*P*<0.05). There was no statistical difference among the three groups 4 weeks after surgery (**Figure 2** and **Table 2**).

The correlation between CYP3A5 polymorphism and the corrected ratio of C/D

One, two and four weeks after surgery, the dosage of FK506 of CYP3A5 G/G group was significantly lower than that of CYP3A5 A/G

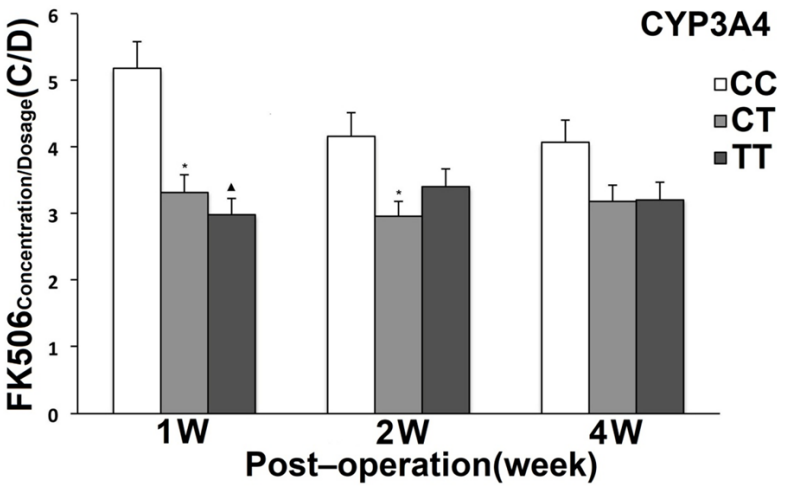

Figure 2. The C/D ratio in liver transplantation patients with different CYP3A4 genotypes. *C/C vs C/T; ▲C/C vs T/T; $P<0.05$.

Table 2. The surface dosage of FK506 and C/D ratio in liver transplantation patients with different CYP3A4 genotypes

CYP3A4		Time		
Genotypes (n)		1 W	2 W	4 W
C/C (14)	(D)	2.8922±0.3392	2.7035±0.4813	2.6065±0.5178
	(C/D)	5.1783±1.0460	4.1762±1.5372	4.0734±0.8632
C/T (19)	(D)	3.2935±0.4612[a]	3.3018±0.8847[a]	3.2985±1.1060[a]
	(C/D)	3.3292±1.2929[a]	2.9567±1.1249[a]	3.1853±1.4815
T/T (4)	(D)	3.1005±0.4644	3.5283±0.4098[b]	3.3160±0.5210[b]
	(C/D)	2.9843±0.9470[b]	3.4034±0.8513	3.2173±0.9465

[a]C/C vs C/T; [b]C/C vs T/T; $P<0.05$

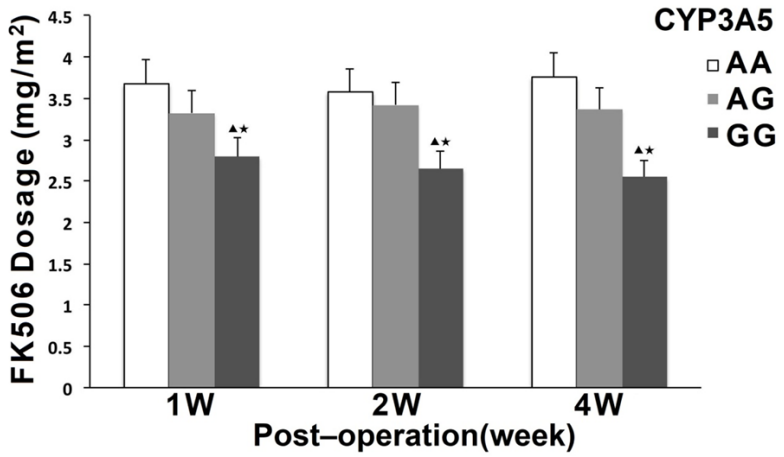

Figure 3. The surface dosage of FK506 in liver transplantation patients with different CYP3A5 genotypes. ▲A/A vs G/G; ★A/G vs G/G; $P<0.05$.

and CYP3A5 A/A groups ($P<0.05$). However, difference between CYP3A5 A/G and CYP3A5 A/A groups was not of significance (**Figure 3**). Similarly, the corrected C/D ratio of CYP3A5 G/G group was significantly higher than that of CYP3A5 A/G and CYP3A5 A/A groups 1, 2 and 4 weeks after operation ($P<0.05$). There was no statistical difference between CYP3A5 A/G group and CYP3A5 A/A group (**Figure 4** and **Table 3**).

The correlation between CYP3A4 gene polymorphism and postoperative hepatorenal function

The serum creatinine (Cr), ALT, total bilirubin (TBIL) and INR were decreased after liver transplantation. However, one week after surgery, the recovery of Cr, ALT and INR of CYP3A4 C/C group were significantly slower than that of CYP3A4 C/T group ($P<0.05$). Though these parameters of CYP3A4 C/C group were slower than that of CYP3A4 T/T group, there was no significant difference ($P>0.05$). Two weeks after surgery, the recovery of Cr of CYP3A4 C/C group was significantly slower than that of CYP3A4 C/T group ($P<0.05$), and the recovery of coagulation function of CYP3A4 C/C group was significantly slower than that of CYP3A4 T/T group ($P<0.05$). However, there was no significant difference in ALT among the three groups. Four weeks after surgery, the recovery speed of ALT of CYP3A4 C/C group was significantly slower than that of CYP3A4 T/T group ($P<0.05$). There was no significant difference in serum Cr in the three groups (**Table 4**).

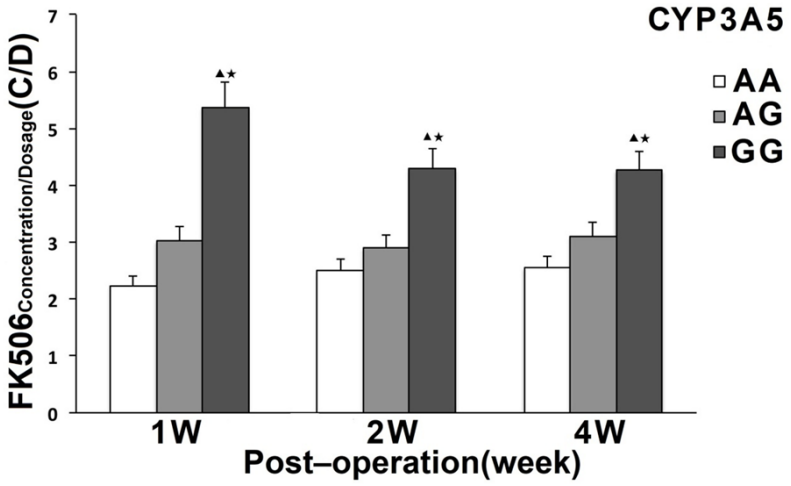

Figure 4. The C/D ratio in liver transplantation patients with different CYP3A5 genotypes. ▲A/A vs G/G; ★A/G vs G/G; $P<0.05$.

Table 3. The surface dosage of FK506 and C/D ratio in liver transplantation patients with different CYP3A5 genotypes

CYP3A5		Time		
Genotypes (n)		1 W	2 W	4 W
A/A (5)	(D)	3.6684±0.2177	3.5742±0.6904	3.7537±0.8365
	(C/D)	2.2318±0.5352	2.4948±0.6766	2.5511±0.5914
A/G (15)	(D)	3.3231±0.3723	3.4220±0.8901	3.3663±1.0838
	(C/D)	3.0210±0.8390	2.9010±1.020	3.0980±1.5102
G/G (18)	(D)	2.7951±0.2572[b,c]	2.6481±0.4154[b,c]	2.5444±0.4114[b,c]
	(C/D)	5.3736±0.61496[b,c]	4.2900±1.3670[b,c]	4.2622±0.8435[b,c]

[b]A/A vs G/G; [c]A/G vs G/G; $P<0.05$.

The correlation between CYP3A5 gene polymorphism and postoperative hepatorenal function

In the 38 patients with liver transplantation, the Cr, ALT, TBIL and INR were significantly decreased after surgery. However, there was no significant difference one week after surgery. Two weeks after surgery, the recovery speeds of Cr and INR of CYP3A5 G/G group were significantly slower than that of CYP3A5 A/G group ($P<0.05$), and the recovery of ALT of CYP3A5 G/G group were significantly slower than that of CYP3A5 A/A group ($P<0.05$). Four weeks after surgery, the recovery speed of serum Cr of CYP3A5 G/G group were significantly slower than that of CYP3A5 A/G group ($P<0.05$), and the recovery speed of ALT of CYP3A5 G/G group were significantly slower than that of CYP3A5 A/A and CYP3A5 A/G groups ($P<0.05$). However, there was no significant difference in all indicators between CYP3A5 A/A group and CYP3A5 A/G group (**Table 5**, **Figure 5**).

Discussion

Liver transplantation is the most effective method for end-stage liver diseases, and the immunosuppression is the key factor of prognosis. FK506 is one of the most common immunosuppressants for prevention of rejection after transplantation. As FK506 has strong firstpass effect and low oral bioavailability with an average of 20%, the individual differences are significant, and the dosage needs to be adjusted based on the blood trough concentrations to reduce immune rejection or adverse events. Although the non-genetic factors could affect the blood concentration of FK506 [5-7], the genetic variance was still a key factor for the difference [8]. ALT is the most sensitive indicator for reflection of liver damage, which is increased after liver transplantation. The half-life of coagulation factors is within 72 h, so the INR ratio in the first week after transplantation could represent the recovery of synthesis of coagulation factors and clear of anticoagulation substances. TBIL has important function for reflecting bile secretion and excretion of transplanted liver. Cr is the most sensitive indicator for reflecting renal function. Therefore, we chose ALT, TBIL, INR and Cr as the indicators for evaluation of hepatorenal function recovery.

The influence of CYP3A4 gene polymorphisms on FK506 dosage and hepatorenal function recovery

CYP3A4 enzyme is rich in liver. There are about 34% important drugs in clinic which are CYP3A4 enzyme's substrates [9]. However, the activity of the enzyme had significant individual differ-

Table 4. Indicators of hepatorenalfunction recovery in liver transplantation patients with different CYP3A4 genotypes

CYP3A4	Time											
	1 W				2 W				4 W			
Genotypes (n)	Cr	ALT	TBIL	INR	Cr	ALT	TBIL	INR	Cr	ALT	TBIL	INR
C/C (14)	111.83±41.52	145.79±61.44	53.61±20.59	1.32±0.19	93.53±32.76	109.00±44.69	42.84±17.26	1.23±0.16	82.93±25.57	83.71±26.13	40.36±21.24	1.15±0.15
C/T (19)	97.18±33.51	102.74±55.58[a]	57.49±53.86	1.24±0.19	70.98±25.76[a]	80.89±44.45	44.04±39.54	1.13±0.12	71.66±15.17	66.68±38.73	33.28±28.44	1.08±0.09
T/T (4)	83.33±50.36	98.25±70.44	69.05±63.66	1.22±0.13	66.10±23.55	113.25±54.88	46.65±19.70	1.04±0.10[b]	83.78±24.70	46.50±26.41[b]	30.98±11.94	1.06±0.06

[a]C/C vs C/T; [b]C/C vs T/T; *P*<0.05.

Table 5. Indicators of hepatorenal function recovery in liver transplantation patients with different CYP3A5 genotypes

CYP3A5	Time											
	1 W				2 W				4 W			
Genotypes (n)	Cr	ALT	TBIL	INR	Cr	ALT	TBIL	INR	Cr	ALT	TBIL	INR
A/A (5)	108.12±30.78	141.80±78.25	67.38±56.30	1.24±0.10	70.82±30.04	51.40±34.33	40.20±17.60	1.09±0.15	70.14±30.12	55.40±45.74	29.80±10.20	1.08±0.08
A/G (15)	86.10±35.14	110.47±57.04	47.60±17.53	1.25±0.21	64.37±17.98	104.93±63.04	38.39±19.52	1.10±0.12	71.93±9.46	57.73±36.63	28.01±16.16	1.06±0.09
G/G (18)	112.24±39.49	124.28±64.96	61.58±55.14	1.28±0.19	94.10±31.40[c]	102.39±48.88[b]	49.05±38.88	1.22±0.15[c]	85.24±23.94[c]	90.94±26.43[b,c]	43.08±30.10	1.15±0.14

[b]A/A vs G/G; [c]A/G vs G/G; P<0.05.

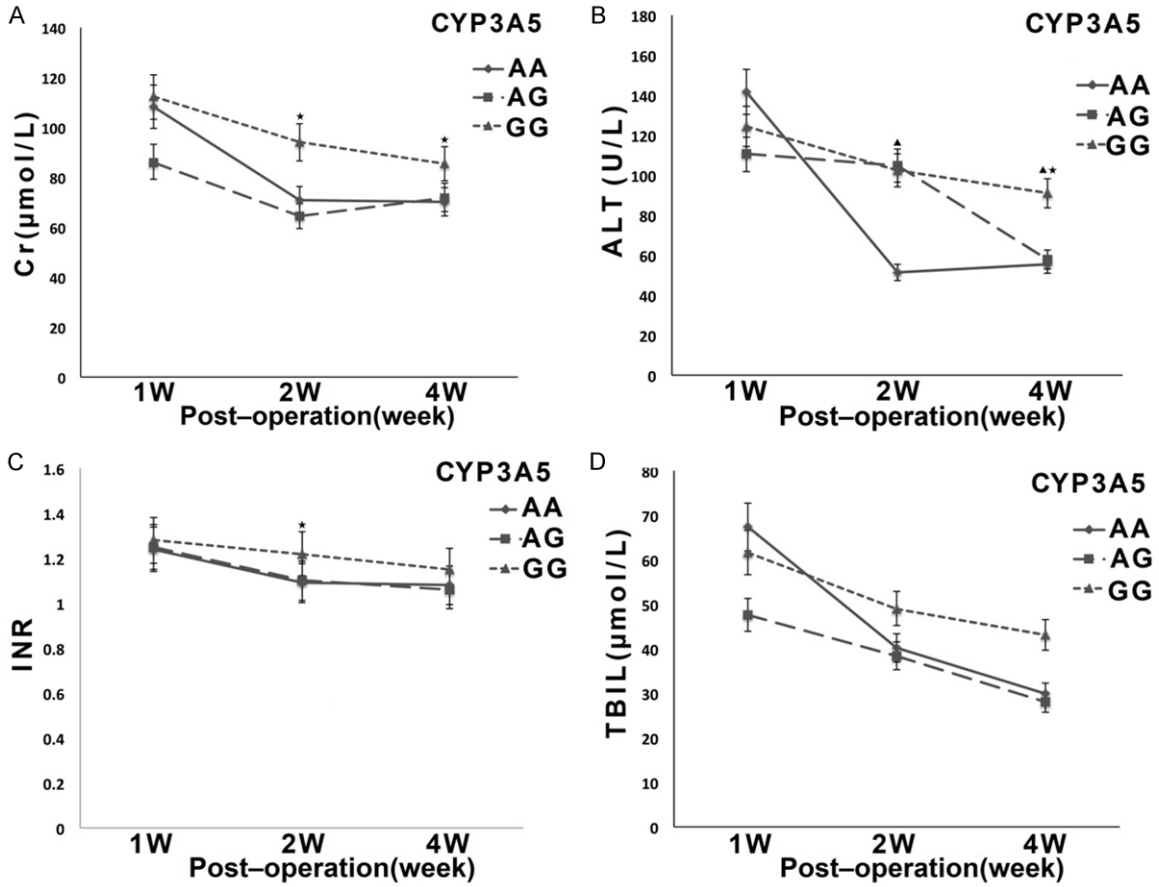

Figure 5. Indicators of hepatorenal function recovery in liver transplantation patients with different CYP3A5 genotypes. (A) Cr; (B) ALT; (C) INR; (D) TBIL. ▲A/A vs G/G; ★A/G vs G/G; $P<0.05$.

ences, which was mainly caused by genetic factors [10]. The CYP3A4*1B mutation, which is located in the promoter region, might affect the CYP3A4 enzyme activity, but the mutation hardly occurs in Chinese population [11, 12]. Previous research has found that the CYP3A4*1B mutation frequency was 30.8% in Chinese population [13], our study showed 37.8%. The frequency of CYP3A4 C/C (*1/*1), CYP3A4 C/T (*1/*18B) and CYP3A4 T/T (*18B/*18B) was 37.8%, 51.4% and 10.8%, respectively, which was consistent with the previous study [14].

It has been reported [2, 13] that the C/D ratio of FK506 was significantly different among CYP3A4 genotypes: the C/D ratio of CYP3A4 C/T (*1/*18B) and CYP3A4 T/T (*18B/*18B) was significantly lower than that of CYP3A4 C/C (*1/*1) ($P<0.01$). In this study, the dosage of FK506 had statistical difference only between CYP3A4 C/C (*1/*1) group and CYP3A4 C/T (*1/*18B) group one week after surgery, which might be related to unstable internal environment and poor liver function. Two and four weeks after surgery, the dosage of FK506 showed significant individual differences. Similarly, the adjusted C/D ratio, ALT, Cr, TBIL and INR presented individual differences. Therefore, CYP3A4*1B mutation could increase the activity of CYP3A4 enzyme, accelerate the metabolism and excretion of FK506, and promote the recovery of liver and kidney function. We believe that detection of CYP3A4*18B single nucleotide polymorphisms can provide the reference value for the usage of FK506 after liver transplantation.

The influence of CYP3A4 gene polymorphisms on FK506 dosage and hepatorenal function recovery

CYP3A5 is another important metabolic enzyme of CYP enzymes, which is located in liver

and small intestine. CYP3A5 gene has multiple single nucleotide polymorphisms (SNPs), and the CYP3A5*3 plays a major role [15]. The homozygous mutation of CYP3A5 is named CYP3A5 (*3/*3), which is termed as slow metabolizer; the wild-type CYP3A5 (*1/*1) and the heterozygous mutation CYP3A5 (*1/*3) are termed as extensive metabolizers. It has been found that CYP3A5 (*1/*1) and CYP3A5 (*1/*3) accounts for 50%-61% in liver and intestine, while CYP3A5 (*3/*3) is only 2.7%-4.2% CYP3A5 [16]. Our study has been shown that the frequency of fast metabolizers is 52.6%, which is consistent with the literature.

Since CYP3A5 is expressed in liver and intestine, the enzyme activity and genotypes in liver and intestine would affect the metabolism of FK506 [17, 18]. Fukudo *et al.* found that CYP3A5 (*1/*1) and CYP3A5 (*1/*3) genotypes were important factors for clearance rate of individual differences [19, 20]. Uesugi *et al.* found that CYP3A5 could affect the metabolism of FK506, which was correlated with CYP3A5 genotypes, and patients with CYP3A5 (*1/*1) and CYP3A5 (*1/*3) genotypes needed greater dosage of FK506 [21]. Our results have shown that the dosage of FK506 of CYP3A5 A/A (*1/*1) and CYP3A5 A/G (*1/*3) groups is higher than that of CYP3A5 G/G (*3/*3) group. CYP3A5 genotypes are closely correlated with the blood concentration of FK506 [22-24], which has important guiding significance for determination of the immunosuppressive dose and reduction of side effects. The fast metabolizers of CYP3A5 gene polymorphism could increase the metabolism of FK506, accelerate its excretion, reduce the toxic effects, and promote the recovery of liver and kidney function. Therefore, we believe that CYP3A5 gene polymorphisms may be one of the factors which affect liver and kidney function recovery.

Conclusion

The C/D ratio of FK506 has large individual variations in patients undergoing liver transplantation. CYP3A4 and CYP3A5 gene polymorphism might be the important factors of significant individual differences of FK506 pharmacokinetics and recovery of hepatorenal function, which could help individualized medicine. CYP3A4 slow metabolizer (C/C) requires lower dosage of FK506 to reach target blood concentration than fast metabolizers (C/T and T/T). CYP3A5 slow metabolizer (G/G) requires lower dosage of FK506 to reach target blood concentration than fast metabolizers (A/A and A/G).

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Disclosure of conflict of interest

None.

Address correspondence to: Xia He, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, No. 32 West Second Section, First Ring Road, Chengdu, Sichuan, China. Tel: +86 28 87393405; Fax: +86 28 87393405; E-mail: yaan_hbx@163.com

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