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Original Article

Association between the CYP3A4 *18B polymorphism and pharmacokinetics of cyclosporine-A in recipients of kidney transplantation in Chinese patients: a meta-analysis of observational studies

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Abstract: Purpose: The mutation frequency of the CYP3A4 *18B genetic polymorphism is relatively high in Asian populations. The influence of this polymorphism on the pharmacokinetics of cyclosporine A (CsA) is controversial. We investigated the association between the CYP3A4 *18B polymorphism and CsA pharmacokinetics in Chinese renal-transplant recipients. Methods: A literature search was conducted in PubMed, the Cochrane Library, EMBASE and the Chinese Wanfang database. Three studies involving 232 recipients were studied. Results: Our results showed a significant difference in the mean CsA dose-adjusted peak concentration (C_2) between carriers of CYP3A4 *1/*1 and carriers of CYP3A4 *18B (standard mean difference (SMD), 0.26; 95% confidence interval (95% CI), 0.08-0.44; *P*=0.005). Compared with subjects with CYP3A4 *1/*18B (AG)-CYP3A5 *1/*3 (AG) or CYP3A4 *18B/*18B (AA)-CYP3A5 *1/*1 (AA), a significantly higher CsA dose-adjusted C_2 was required in recipients with CYP3A4 *1/*1 (GG)-CYP3A5 *3/*3 (GG) when pooled data were evaluated regardless of post-transplant time points (SMD, 0.22; 95% CI, 0.03-0.42; *P*=0.027). Conclusions: These findings suggest that, relative to carriers of CYP3A4 *18B, recipients with CYP3A4 *1/*1 (especially those carrying CYP3A4 *1/*1 and CYP3A5 *3/*3) require a lower maintenance dose to achieve target CsA concentrations in blood 1 month after transplantation.

Keywords: CYP3A4, Cyclosporine-A, kidney transplantation, polymorphism, meta-analysis

Introduction

The calcineurin inhibitor cyclosporine-A (CsA) is the most frequently used maintenance immunosuppressive agent for prevention of allograft rejection after solid-organ transplantation [1]. CsA is characterized by a narrow therapeutic index and high pharmacokinetic variations between individuals. Therefore, blood concentrations of CsA must be monitored to improve efficacy and minimize toxicity [2]. Multiple factors contribute to the difficulties in attaining a defined therapeutic range of CsA levels in blood, including genetic and non-genetic (e.g., environment, allograft function, diets, drug interactions) factors [3].

Single nucleotide polymorphisms (SNPs) located in genes responsible for the proteins/enzymes involved in the transport/metabolism of drugs have been suggested to have critical roles in CsA pharmacokinetics after kidney transplantation [4, 5]. Among these genes, *cytochrome P450 3A* (CYP3A), which is distributed mainly in liver microsomes, is believed to have a major role in CsA metabolism [6]. SNPs in CYP3A4 and CYP3A5 (the two main CYP3A isoforms in adults) are rare, especially in Chinese populations. Of these SNPs, only the mutation frequency of CYP3A4 *18B and CYP3A5 *1 are relatively high in Chinese populations, and could contribute to differences in CsA metabolism among recipients [7, 8]. The SNP CYP3A4 *18B (a novel SNP in intron 10 of CYP3A4) is characterized by a G→A substitution at position 82266 [9]. Several studies have shown that this SNP contributes to the variable pharmacokinetics of Cs in Chinese subjects, and the nucleotide mutant has been speculated to be associated with the increased activity of CYP3A4 [9-12]. However, the effect of the

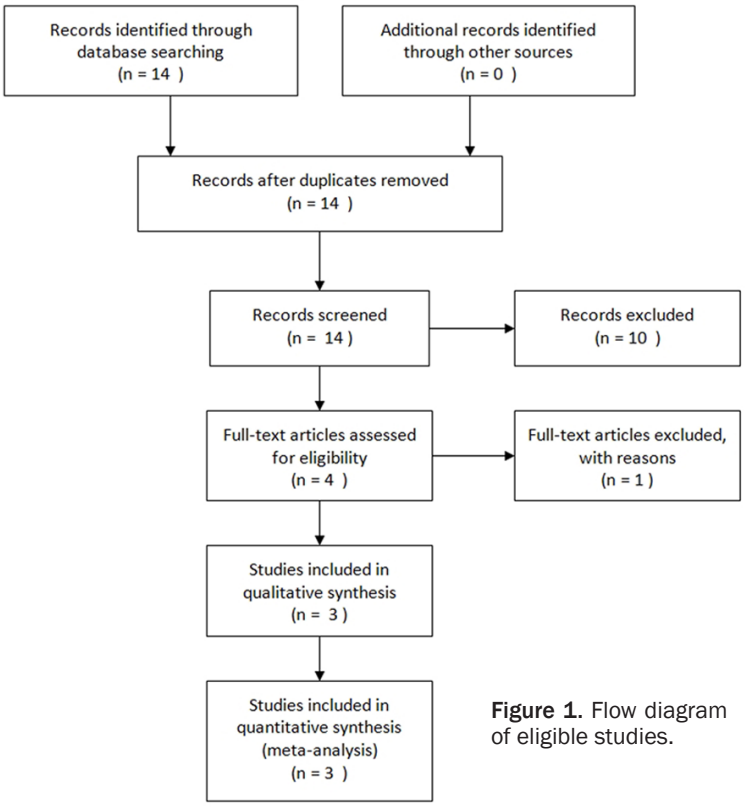


Figure 1. Flow diagram of eligible studies.

CYP3A4 *18B genetic polymorphism on trough and peak concentrations of CsA in the blood in patients who have received a renal transplant is still unclear.

The objective of our meta-analysis was to investigate the relationship between CYP3A4 *18B genetic polymorphisms and CsA pharmacokinetics in adult renal-transplant recipients (RTRs).

Methods and materials

Literature search

A comprehensive literature search was conducted in PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), Embase and the China CNKI database (updated on 1st Augest 2016) to identify all potential studies by two independent authors (LK and LXZ). The following search items were used: (mesh items, "kidney transplantation"), and ("genetic polymorphisms" or "single nucleotide polymorphism" or "SNP" or "gene mutation" or "genetic variants"), and ("cyclosporine" or "cyclosporine A" or "CsA" or "Nerol"), and ("CYP3A4"), and ("18B"). Moreover, the reference lists of all studies included in the meta-analysis, as well as the abstracts of annual meetings of the American Society of Nephrology, the International Transplant Society and the European Dialysis and Transplantation Association, were reviewed. If there were more than one articles published with the same content, we will choose the most complete one.

Inclusion and exclusion criteria

Two main criteria were used to include relevant studies: (i) a case-control or cohort study designed to investigate the influence of the specific gene polymorphism CYP3A4 *18B on CsA pharmacokinetics in *de novo* or secondary RTRs; (ii) trough or peak concentrations of CsA in blood were measured separately in subjects with three genotypes or separately in *1/*1 and *1/*18B + *18B/*18B genotypes. According to the criteria shown above, two authors (LK and LXZ) assessed and selected trials for the final analysis independently, with divergences resolved by consensus. Studies with insufficient data for pooling that with no frequencies of genotypes for each polymorphism and outcome were excluded.

Data extraction and quality assessment

Relevant data from all relevant studies were extracted independently by two reviewers (SG and LXZ), and discrepancies in data extraction were resolved through consensus. The following information was collected: first author; ethnicity; publication year; study design; demographic data; immunosuppression protocol; Hardy-Weinberg equilibrium of genotype distribution; CsA dose; trough/peak concentrations of CsA; method of genotype measurement; genotype frequency; dose-adjusted trough concentration (C_0) and peak (C_2) concentration in blood (C_0/dose and C_2/dose). For continuous data, information was collected as the mean ±

Table 1. Basic characteristics of eligible studies

Author	Year	Country	Case number	Age (mean ± SD, years)	Males (%)	Weight (mean ± SD, kg)	Genetic equilibrium	Genotype method	CsA measurement	ISD therapy
XY Qiu	2008	China	103	40±10	70.87	59±11	Yes	PCR-RFLP	FPIA	CsA + MMF + corticosteroids
YF Hu	2009	China	63	42.7±13.2	65.08	56.4±11.0	Yes	PCR-RFLP	FPIA	CsA + MMF + corticosteroids
DY Li	2013	China	66	37.2±8.1	84.33	NA	Yes	PCR-RFLP	EMIT	CsA + MMF + corticosteroids

CsA, cyclosporine-A; MMF, mycophenolate mofetil; ISD, immunosuppressive drugs; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; FPIA, fluorescence polarization immunoassay; EMIT, enzyme multiplied immunoassay technique; NA, not available.

Table 2. Quality assessment of eligible studies

Author	Ascertainment of cases	Ascertainment of control	Quality control of genotyping	Population stratification	Confounding bias	Selective ouctome report	HWE
XY Qiu	Yes	Yes	Yes	Yes	Yes	Yes	Yes
YF Hu	Yes	Yes	NA	Yes	Yes	Yes	Yes
DY Li	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Abbreviations: HWE, Hardy-Weinberg equilibrium; NA, not available.

SD. If data were expressed as subjects with three genotypes, statistical methods from the Cochrane Handbook [13] were used to estimate the mean ± SD.

The quality assessment for included studies was also performed independently by two authors (LK and LXZ). A modified method based on both traditional epidemiologic considerations and genetic issues which was developed by Thakkinstan et al. [14] was applied. Five domains including information bias, confounding bias, selective reporting of outcomes, population stratification and assessment of Hardy-Weinberg equilibrium (HWE) in the control group were assessed for all studies included in our analysis. Disagreement was resolved by third author (XZY).

Statistical analyses

All statistical analyses were done using Stata v12.0 (Stata, College Station, TX, USA). Association between the CYP3A4 *18B polymorphism and CsA pharmacokinetics was evaluated using the standard mean difference (SMD) with 95% confidence intervals (95% CIs). $P<0.05$ was considered significant. Q and I^2 statistic tests were used to evaluate heterogeneity, which was defined as: 100% × (Q-df)/Q

Where Q is Cochran's heterogeneity statistic and df is the degrees of freedom, with a fixed-effect model set at low statistical inconsistency ($I^2<25\%$). Otherwise, we selected a random-effects model, which is better adapted to clinical and statistical variations [15]. Egger's regression test and the Begg's test were employed to analyze publication bias, which was considered to be present at $P<0.05$. Sensitivity analysis was also undertaken to evaluate the stability of the meta-analysis. Briefly, a new analysis was conducted by omitting one study at a time to test its influence on the overall estimate. In addition, subgroup analysis was performed for all the outcomes of the review based on the following variables: time course of CsA administration after kidney transplantation, C_0 and C_2 of CsA concentrations, methodological quality and participants under 15 years old. Interaction tests were made to evaluate the differences among subgroups.

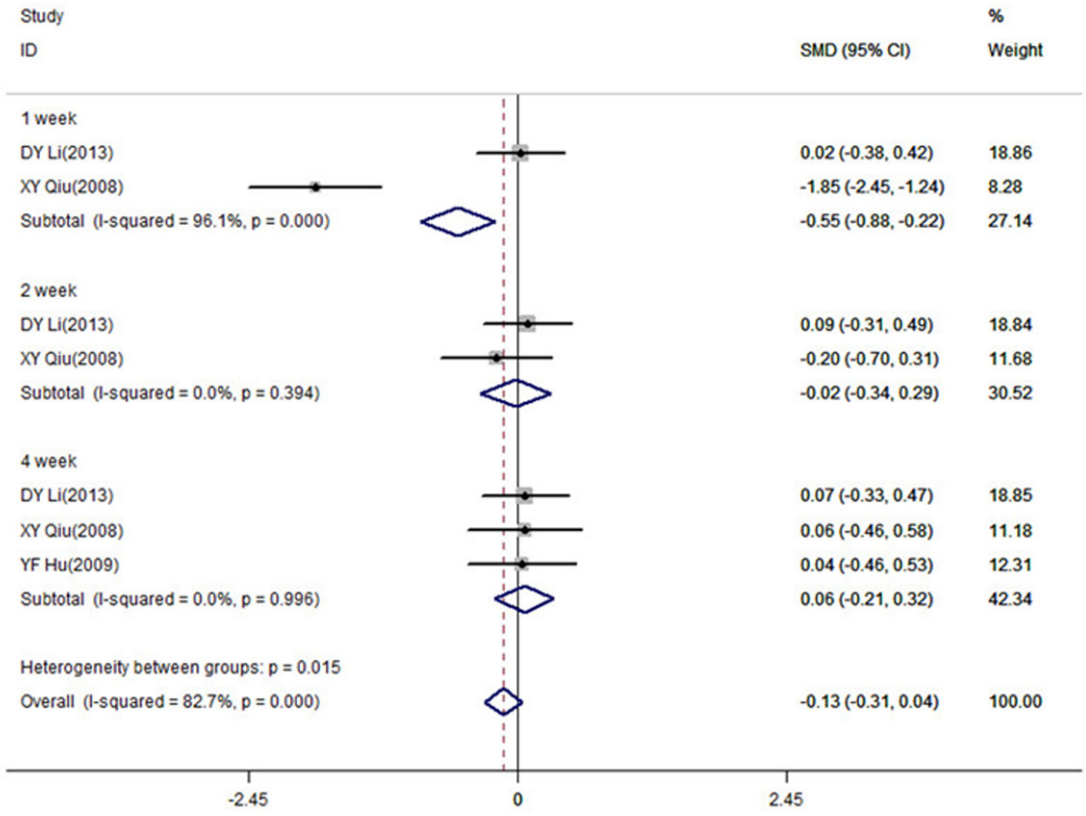
Results

Literature search and included studies

Our initial literature search identified 14 citations from electronic databases. Four remaining studies were considered to be "potentially eligible" after removal of duplicates and screening for titles and abstracts. Then, the full text of these studies was accessed, and study details evaluated. Only three studies [16-18] involving 232 RTRs were included in the further meta-analysis (**Figure 1**).

Characteristics of eligible studies are summarized in **Table 1**. Mean age of recipients was 37.2-42.7 years and 73.9% were male. All patients in our meta-analysis were Chinese. Polymerase chain reaction-restriction fragment length polymorphism was undertaken to determine the CYP3A4 *18B genotype and genotype

A


Study
ID
SMD (95% CI)
%
Weight
1 week
DY Li(2013)
0.02 (-0.38, 0.42)
18.86
XY Qiu(2008)
-1.85 (-2.45, -1.24)
8.28
Subtotal (I-squared = 96.1%, p = 0.000)
-0.55 (-0.88, -0.22)
27.14
2 week
DY Li(2013)
0.09 (-0.31, 0.49)
18.84
XY Qiu(2008)
-0.20 (-0.70, 0.31)
11.68
Subtotal (I-squared = 0.0%, p = 0.394)
-0.02 (-0.34, 0.29)
30.52
4 week
DY Li(2013)
0.07 (-0.33, 0.47)
18.85
XY Qiu(2008)
0.06 (-0.46, 0.58)
11.18
YF Hu(2009)
0.04 (-0.46, 0.53)
12.31
Subtotal (I-squared = 0.0%, p = 0.996)
0.06 (-0.21, 0.32)
42.34
Heterogeneity between groups: p = 0.015
Overall (I-squared = 82.7%, p = 0.000)
-0.13 (-0.31, 0.04)
100.00
-2.45
0
2.45

B

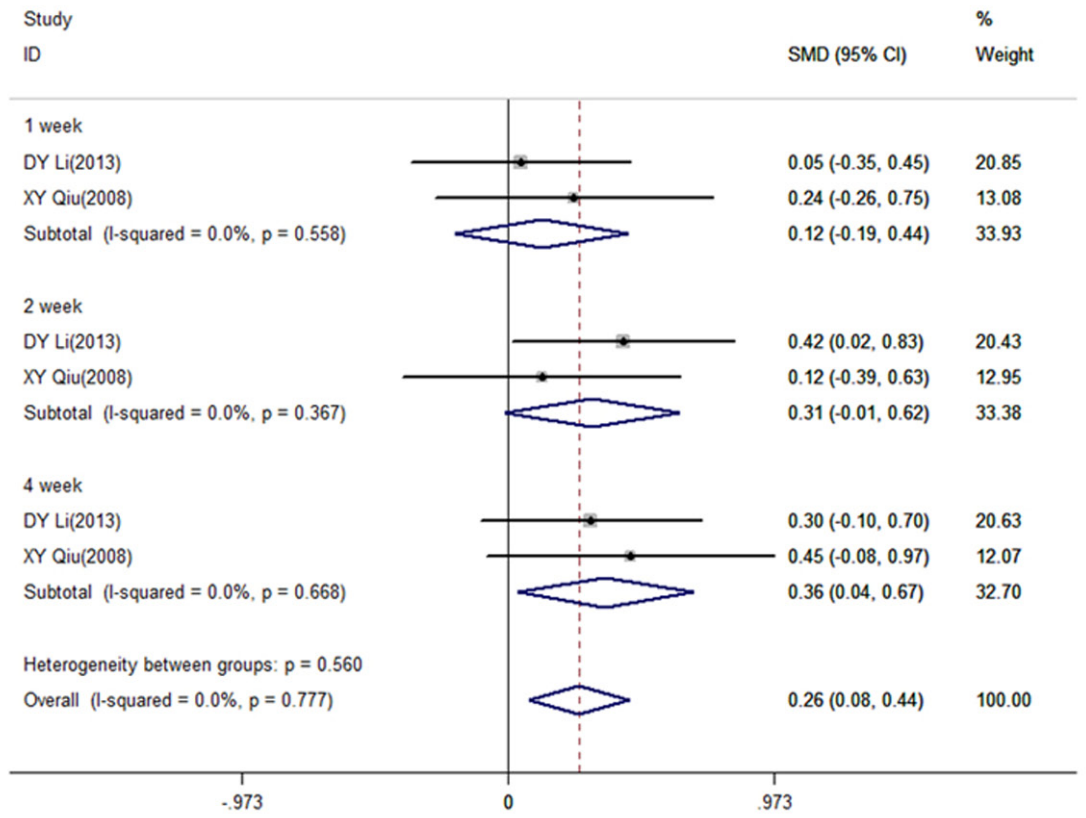

Study
ID
SMD (95% CI)
%
Weight
1 week
DY Li(2013)
0.05 (-0.35, 0.45)
20.85
XY Qiu(2008)
0.24 (-0.26, 0.75)
13.08
Subtotal (I-squared = 0.0%, p = 0.558)
0.12 (-0.19, 0.44)
33.93
2 week
DY Li(2013)
0.42 (0.02, 0.83)
20.43
XY Qiu(2008)
0.12 (-0.39, 0.63)
12.95
Subtotal (I-squared = 0.0%, p = 0.367)
0.31 (-0.01, 0.62)
33.38
4 week
DY Li(2013)
0.30 (-0.10, 0.70)
20.63
XY Qiu(2008)
0.45 (-0.08, 0.97)
12.07
Subtotal (I-squared = 0.0%, p = 0.668)
0.36 (0.04, 0.67)
32.70
Heterogeneity between groups: p = 0.560
Overall (I-squared = 0.0%, p = 0.777)
0.26 (0.08, 0.44)
100.00
-.973
0
.973

Figure 2. Forest plot of the association between CsA metabolism and the CYP3A4 *18B genetic polymorphism. A. Forest plot of pooled data showed that no significant difference was found in the pooled mean CsA dose-adjusted C_0 concentration between CYP3A4 carriers of *1/*1 and carriers of CYP3A4 *18B. B. Forest plot of pooled results when all studies were combined in our initial analysis regardless of the post-transplant time-courses showed that there was a significant difference in the mean CsA dose-adjusted C_2 concentration between carriers of CYP3A4 *1/*1 and carriers of CYP3A4 *18B.

Table 3. Statistical results of the meta-analysis

	Time point	C_0/D			C_2/D		
		SMD	95% CI	*P*	SMD	95% CI	*P*
CYP3A4 *1/*1 vs. CYP3A4 *1/*18B + CYP3A4 *18B/*18B	(Weeks)						
	1	-0.55	(-0.88 to -0.22)	0.001	0.12	(-0.19 to 0.44)	0.45
	2	-0.022	(-0.34 to 0.29)	0.89	0.31	(-0.011 to 0.62)	0.059
	4	0.057	(-0.21 to 0.32)	0.68	0.36	(0.036 to 0.68)	0.029
	Total	-0.13	(-0.31 to 0.042)	0.14	0.26	(0.077 to 0.44)	0.005
CYP3A4 *1/*1-CYP3A5 *3/*3 vs. CYP3A4 *1/*18B-CYP3A5 *1/*3 + CYP3A4 *18B/*18B-CYP3A5 *3/*3							
	1	0.031	(-0.31 to 0.37)	0.86	0.19	(-0.15 to 0.53)	0.27
	2	0.15	(-0.19 to 0.49)	0.39	0.14	(-0.20 to 0.48)	0.42
	4	0.066	(-0.23 to 0.36)	0.66	0.34	(-0.007 to 0.68)	0.055
	total	0.080	(-0.11 to 0.27)	0.40	0.22	(0.025 to 0.42)	0.027

C_0/D, dose-adjusted trough concentration of cyclosporine-A; C_2/D, dose-adjusted peak concentration of cyclosporine-A; SMD, standard mean difference; 95% CI, 95% confidence interval.

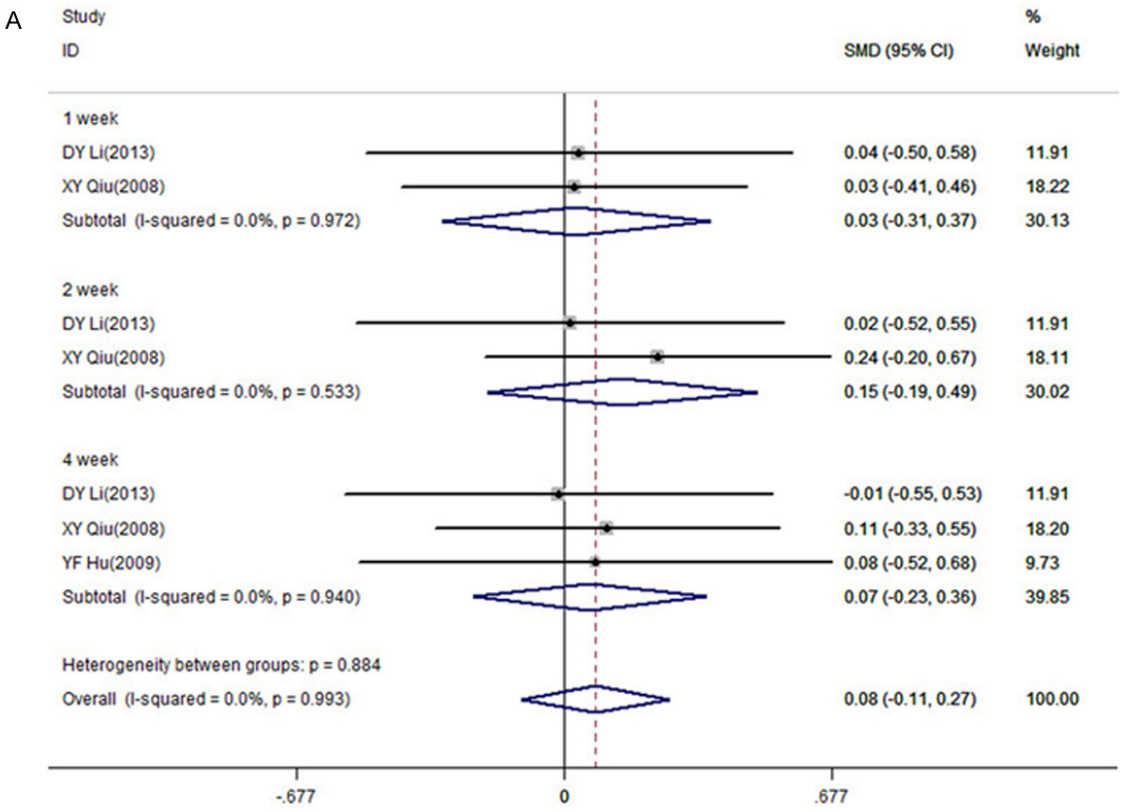
distribution in accordance with the Hardy-Weinberg equilibrium in all three eligible studies. CsA was administered twice daily. C_0 measurements were made before the morning dose and C_2 assessed 2 h after administration of the morning dose. Principal CsA-based immunosuppressive therapies contained mycophenolate mofetil and corticosteroids. Besides, results of quality assessments for all eligible studies are presented in **Table 2**.

*Meta-analysis of CYP3A4 *18B polymorphism on CsA pharmacokinetics*

Results derived from the meta-analysis of CsA dose-adjusted C_0 and C_2 as well as the CYP3A4 *18B genotype are shown in **Figure 2** and **Table 3**, respectively. When all studies were combined in our initial analysis, regardless of the post-transplant time-courses, there was a significant difference in the mean CsA dose-adjusted C_2 concentration between carriers of CYP3A4 *1/*1 and carriers of CYP3A4 *18B (standard mean difference (SMD), 0.26; 95% CI, 0.08 to 0.44, *P*=0.005) (**Figure 2B**). Subgroup analysis for different time points after kidney transplantation revealed a significant difference in the mean CsA dose-adjusted C_2 concentration during 4 weeks between carriers of CYP3A4 *1/*1 and carriers of CYP3A4 *18B (SMD, 0.36; 95% CI, 0.04 to 0.67; *P*=0.029), but not in the mean CsA dose-adjusted C_2 concentration during 1 week or 2 weeks (1 week: 0.12, -0.19 to 0.44, 0.45; 2 weeks: 0.31, -0.01 to 0.62, *P*=0.059). However, no significant difference was found in the pooled mean CsA dose-adjusted C_0 concentration between CYP3A4 carriers of *1/*1 and carriers of CYP3A4 *18B (SMD, -0.13, 95% CI, -0.31 to 0.04; *P*=0.14) (**Figure 2A**). In the subgroup analysis for post-transplant time-courses, despite a significant difference at 1 week (SMD, -0.55; 95% CI, -0.88 to -0.22; *P*=0.001), there was no significant difference in mean CsA dose-adjusted C_0 concentration between carriers of CYP3A4 *1/*1 and carriers of CYP3A4 *18B at 2 weeks or 4 weeks (2 weeks: -0.02, -0.34 to 0.29, 0.89; 2 weeks: 0.06, -0.21 to 0.32, 0.68).

*Synergistic effect of CYP3A5 *3 and CYP3A4 *18B polymorphisms on CsA pharmacokinetics*

Next, we evaluated the combined effect of polymorphisms of CYP3A4 18B and CYP3A5 *3 on CsA dose-adjusted trough and peak concentra-


A
Study
ID
SMD (95% CI)
%
Weight
1 week
DY Li(2013)
0.04 (-0.50, 0.58)
11.91
XY Qiu(2008)
0.03 (-0.41, 0.46)
18.22
Subtotal (I-squared = 0.0%, p = 0.972)
0.03 (-0.31, 0.37)
30.13
2 week
DY Li(2013)
0.02 (-0.52, 0.55)
11.91
XY Qiu(2008)
0.24 (-0.20, 0.67)
18.11
Subtotal (I-squared = 0.0%, p = 0.533)
0.15 (-0.19, 0.49)
30.02
4 week
DY Li(2013)
-0.01 (-0.55, 0.53)
11.91
XY Qiu(2008)
0.11 (-0.33, 0.55)
18.20
YF Hu(2009)
0.08 (-0.52, 0.68)
9.73
Subtotal (I-squared = 0.0%, p = 0.940)
0.07 (-0.23, 0.36)
39.85
Heterogeneity between groups: p = 0.884
Overall (I-squared = 0.0%, p = 0.993)
0.08 (-0.11, 0.27)
100.00
-.677
0
.677

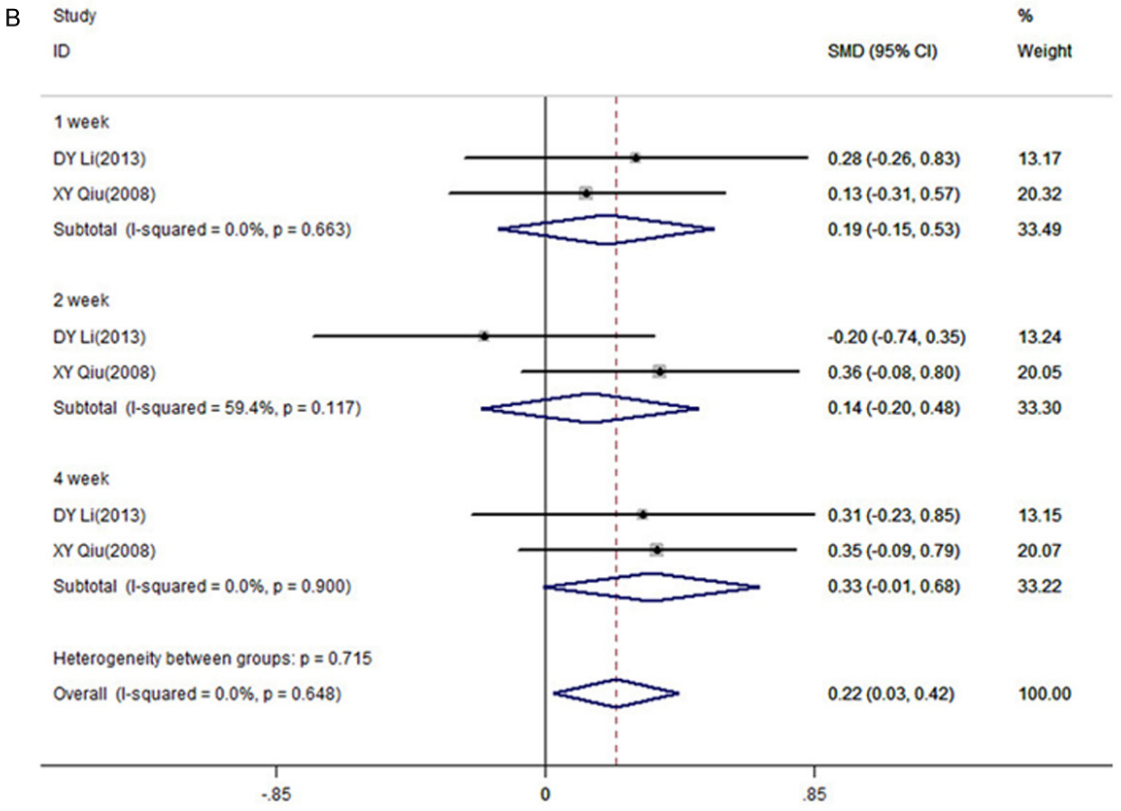

B
Study
ID
SMD (95% CI)
%
Weight
1 week
DY Li(2013)
0.28 (-0.26, 0.83)
13.17
XY Qiu(2008)
0.13 (-0.31, 0.57)
20.32
Subtotal (I-squared = 0.0%, p = 0.663)
0.19 (-0.15, 0.53)
33.49
2 week
DY Li(2013)
-0.20 (-0.74, 0.35)
13.24
XY Qiu(2008)
0.36 (-0.08, 0.80)
20.05
Subtotal (I-squared = 59.4%, p = 0.117)
0.14 (-0.20, 0.48)
33.30
4 week
DY Li(2013)
0.31 (-0.23, 0.85)
13.15
XY Qiu(2008)
0.35 (-0.09, 0.79)
20.07
Subtotal (I-squared = 0.0%, p = 0.900)
0.33 (-0.01, 0.68)
33.22
Heterogeneity between groups: p = 0.715
Overall (I-squared = 0.0%, p = 0.648)
0.22 (0.03, 0.42)
100.00
-.85
0
.85

Figure 3. Forest plot of the combined effect of CYP3A4 *18B and CYP3A5 *3 on CsA pharmacokinetics. A. Forest plot of pooled results showed that no significant difference was found in the subgroup analysis of the dose-adjusted C_2 concentration among various time points or meta-analysis of the CsA dose-adjusted C_0 concentration. B. Forest plot of pooled data showed that when compared with subjects with CYP3A4 *1/*18B (AG)-CYP3A5 *1/*3 (AG) or CYP3A4 *18B/*18B (AA) -CYP3A5 *1/*1 (AA), a significantly higher CsA dose-adjusted C_2 was required in a recipient with CYP3A4 *1/*1 (GG)-CYP3A5 *3/*3 (GG) when pooled data were evaluated regardless of post-transplant time points.

tions in Chinese RTRs (**Figure 3** and **Table 3**). Compared with subjects with CYP3A4 *1/*18B (AG)-CYP3A5 *1/*3 (AG) or CYP3A4 *18B/*18B (AA)-CYP3A5 *1/*1 (AA), a significantly higher CsA dose-adjusted C_2 was required in a recipient with CYP3A4 *1/*1 (GG)-CYP3A5 *3/*3 (GG) when pooled data were evaluated regardless of post-transplant time points (SMD, 0.22; 95% CI, 0.03 to 0.42; P=0.027) (**Figure 3B**). No significant difference was found in the subgroup analysis of the dose-adjusted C_2 concentration among various time points or meta-analysis of the CsA dose-adjusted C_0 concentration (SMD, 0.08; 95% CI, -0.11-0.27; P=0.40) (**Figure 3A**).

Discussion

The findings in our meta-analysis suggested that CYP3A4 *18B polymorphisms significantly influenced the pharmacokinetics of CsA in Chinese RTRs. Also, we identified a significant synergistic effect of polymorphisms of CYP3A4 *18B and CYP3A5 *1 on CsA pharmacokinetics in Chinese RTRs.

In all included studies, subjects carrying CYP3A4 *1/*1 (especially if combined with the mutant genotype of CYP3A5 *3/*3) had a higher dose-adjusted CsA peak concentration in total pooled data and subgroups at 4 weeks. Therefore, such patients may require a relatively lower daily dose of CsA within the first month after transplantation. These findings suggest that, relative to carriers of CYP3A4 *18B, CYP3A4 *1/*1 recipients (especially those carrying CYP3A4 *1/*1 and CYP3A5 *3/*3) required a lower maintenance dose to achieve target CsA concentrations in blood 1 month after transplanation.

CsA is a substrate of CYP3A and P-glycoprotein, which restricts CsA absorption by active extrusion from the interior of enterocytes back into the lumen of the small intestine [16, 19, 20]. In addition, CYP3A is involved in reducing the oral bioavailability of CsA by intestinal and hepatic metabolism, and then accelerating CsA secretion into bile (which is mainly responsible for the systemic clearance of CsA [21, 22]. SNPs in CYP3A4 and CYP3A5 (the two main isoforms in adults) have varying effects on CsA metabolism. Thus, adjustment of initial and maintenance doses based on CYP3A4 and CYP3A5 genotypes could help to achieve target levels of CsA in blood and avoid CsA-related toxicity. CYP3A4 *18B is considered to be the highest mutation in all the CYP3A4 identified in Chinese populations. Hence, studying the influence of CYP3A4 *18B on CsA pharmacokinetics in Chinese RTRs is very important.

In many centers, monitoring of C_0 is used to evaluate CsA metabolism *in vivo*. However, several studies have demonstrated C_2 to be superior to C_0 as a sensitive biomarker for CsA exposure and evaluation of rejection risk [23-25]. In our study, C_2/D (rather than C_0/D) displayed a significant difference between carriers of CYP3A4 *18B and subjects with CYP3A4 *1/*1. This phenomenon could be explained by the fact that mutations in CYP3A4 *1 to CYP3A4 *18B may increase the activity of the CYP3A4 enzyme and then accelerate the metabolism and secretion of CsA. Hu *et al.* [10] reported that, except for no significant difference between carriers of CYP3A4 *1/*1 and carriers of CYP3A4 *1/*18B, carriers of CYP3A4 *18B/*18B showed lower oral exposure to Cs than carriers of CYP3A4 *1 in healthy Chinese subjects. Those observations are in accordance with the findings reported by Tao *et al.* [26] and our findings.

Influence of CYP3A5 *3 on CsA pharmacokinetics in RTRs has been determined by Zhu *et al.* [27]. However, the combined effect of CYP3A5 *3 and CYP3A4 *18B on CsA metabolism in Chinese RTRs is not known. Here, we discovered that recipients with CYP3A4 *1/*1 and CYP3A5 *3/*3 displayed significantly lower C_2 levels than carriers of CYP3A4 *18B or carriers of CYP3A5 *1. These data suggest that, in the presence of CYP3A4 *18B, the effect of CYP3A5 becomes negligible and CYP3A4 *18B may have a more dominant role than CYP3A5

*3 in modulation of CsA pharmacokinetics in Chinese RTRs.

Our meta-analysis had two main limitations. First, we failed to carry out sensitivity analyses and to assess publication bias. Second, due to a lack of original information for each study and a small number of trials, subgroup analyses (e.g., immunosuppressive protocol and ethnicity), rather than different post-transplant time points, could not be undertaken.

Conclusion

Our meta-analysis involving 232 Chinese RTRs suggested that subjects with CYP3A4 *1/*1 (especially those with the CYP3A5 *3/*3 genotype) are associated with higher peak concentrations of CsA in blood and require a lower daily dose of CsA in the first month after transplantation.

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Disclosure of conflict of interest

None.

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