Original Article

Population pharmacokinetics and pharmacogenomics of tacrolimus in Chinese children receiving a liver transplant: initial dose recommendation

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Background: In order to improve the precision of treatment with tacrolimus in Chinese patients undergoing pediatric liver transplantation, the optimum initial dose of tacrolimus was determined based on population pharmacokinetics and pharmacogenomics.

Methods: Demographic data, clinical parameters, drug combinations and pharmacogenomics were integrated to build a population pharmacokinetic model using NONMEM. Additionally, Monte Carlo simulations were used to optimize the recommended initial dose.

Results: Weight, patient cytochrome 450 3A *(CYP3A)5* genotype, and co-administration with wuzhi-capsule (WZ) were incorporated into the final model. For children with a *CYP3A5*3/*3* genotype not co-administered WZ, 0.10 mg/kg/day split into two doses was recommended for patients weighing 5–17 kg, and 0.05 mg/kg/day split into two doses was recommended for patients weighing 17–60 kg. For children with a *CYP3A5*1* allele not co-administered WZ, 0.25 mg/kg/day for patients weighing 5–10 kg, 0.20 mg/kg/day for patients weighing 10–17 kg, 0.15 mg/kg/day for patients weighing 17–36 kg, and 0.10 mg/kg/day for patients weighing 36–60 kg; all split into two doses was recommended. For children with a *CYP3A5*3/*3* genotype co-administered WZ, 0.10 mg/kg/day for patients weighing 5–11 kg, and 0.05 mg/kg/day for patients weighing 11–60 kg; both split into two doses was recommended. For children with a *CYP3A5*1* allele who were co-administered WZ, 0.20 mg/kg/day for patients weighing 5–10 kg, 0.15 mg/kg/day for patients weighing 10–22 kg, and 0.10 mg/kg/day for patients weighing 22–60 kg all split into two doses was recommended.

Conclusions: The optimal initial dose of tacrolimus was determined based on population pharmacokinetics and pharmacogenomics in Chinese patients undergoing pediatric liver transplantation.

Keywords: Initial dose recommendation; pediatric liver transplantation; pharmacogenomics; population pharmacokinetics; tacrolimus

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Introduction

Tacrolimus is a macrolide produced by *Streptomyces tsukubaensis*, and is a powerful immunosuppressant that was first discovered in 1984 when seeking novel anti-cancer and immunosuppressive drugs (1). Since 1994, tacrolimus has been approved as a prophylactic for organ rejection following a liver transplant in the United States (1). At present, in addition to preventing graft rejection during renal transplant (2), heart transplant (3), lung transplant (4), hematopoietic stem cell transplant (5) and other types of transplants, tacrolimus has also been used to treat a variety of diseases, which include systemic onset juvenile idiopathic arthritis (6), nephrotic syndrome (7), myasthenia gravis (8), ulcerative colitis (9), systemic lupus erythematosus (10), lupus nephritis (11) and autoimmune hepatitis (12). However, with a narrow treatment window and considerable pharmacokinetic variability between individuals, it is difficult to determine the optimal tacrolimus concentration within the window of treatment (13). Furthermore, low concentrations of tacrolimus can increase the risk of rejection, whereas high concentration can lead to adverse reactions, including nephrotoxicity, neurotoxicity, infection, nausea, tumors, diabetes and gastrointestinal reactions (1,14). Therefore, in clinical practice, subsequent doses are usually adjusted according to the range of the treatment window combined with therapeutic drug monitoring (TDM). However, determining the optimal initial dose remains difficult as there is no previous TDM concentration for comparison. In clinical practice, the initial dose is based on the drug instructions and the experience of physicians and pharmacists; however, this frequently results in a sub-optimal initial dose.

Fortunately, population pharmacokinetic models and Monte Carlo simulation can be used to assist in optimizing the initial dosage (15,16). Since the initial clinical use of tacrolimus, several population pharmacokinetics models based on patients receiving a liver transplant have been built (17-22). However, the precise treatment of tacrolimus and a model for the recommended initial dose in Chinese patients undergoing pediatric liver transplants has not been determined. Thus, the present study built a model to determine the initial dose of tacrolimus for Chinese patients undergoing pediatric liver transplantation based on population pharmacokinetics and pharmacogenomics. We present the following article in accordance with the TRIPOD reporting checklist (available at http://dx.doi.org/10.21037/tp-20-84).

Methods

Patients

Data on Chinese children who underwent a liver transplant and were treated with tacrolimus between September 2014 and October 2019 at the Children's Hospital of Fudan University were collected retrospectively. Partial basic clinical data of children were gathered from previous studies (23,24). The present study was conducted in accordance with the Declaration of Helsinki (2013 revision) and was approved by the Ethics Committee of the Children's Hospital of Fudan University (Ethical code: [2019] 020). Demographic data of patients and drug combinations were collected. The present study was performed retrospectively, and only used leftover or discarded specimens. Therefore, the need for written informed consent was waived by the Ethics Committee of Children's Hospital of Fudan University.

TDM and pharmacogenomic analysis

Tacrolimus concentration was tested using the Emit® 2000 Tacrolimus Assay (Siemens Healthcare Diagnostics Inc., Newark, NJ, USA) with a range of 2.0–30 ng/mL. Pharmacogenomic analysis was performed using TDM residual blood samples, which was measured by Admera Health using a PGxOne®160 via the Illumina X10 Sequencing System. Hardy-Weinberg Equilibrium was determined using STATA version 12.0 (Stata Corp., LP., USA). $P<0.05$ was considered to indicate a statistically significant difference.

Population pharmacokinetic model

The non-linear mixed-effects modeling software, NONMEM (Edition 7; ICON Development Solutions, Ellicott City, MD, USA) and a first-order conditional estimation method with interaction (FOCE-I method) were used to build the model. The pharmacokinetic parameters covered CL/F, V/F, and Ka. The value of Ka was fixed to 4.48/h (23,25).

Random effects model

Inter-individual variabilities were estimated using Eq. [1]:

$$C_i = TV(C) \times \exp(\eta_i) \quad [1]$$

C_i represents individual parameters and $TV(C)$ represents

typical individual parameters. η_i was the symmetrical distribution, which was a random term with zero mean and variance ω^2.

Random residual variabilities were estimated using Eq. [2]:

$$C_i = C_{prei} \times (1+ \varepsilon_1) + \varepsilon_2 \quad [2]$$

C_i were the observed concentrations, C_{prei} were the individual predicted concentrations and ε_1 and ε_2 were symmetrical distributions, which was a random term with zero mean and variance σ_2.

Covariate model

Pharmacokinetic parameters and weight were evaluated using Eq. [3]:

$$C_i = C_{std} \times (W_i / W_{std})^{\text{POWER}} \quad [3]$$

C_i represents the ith individual parameters, W_i represents the ith individual weight. W_{std} represents the standard weight of 70 kg. C_{std} was the typical individual parameter. POWER was the allometric coefficient: 0.75 for the CL/F and 1 for the V/F (26).

Pharmacokinetic parameters and genotypes were evaluated using Eq. [4].

$$C_i = TV(C) \times \theta^{\text{genotype}} \quad [4]$$

Pharmacokinetic parameters and the other continuous covariates or categorical covariates were described with Eqs. [5] and [6], respectively.

$$C_i = TV(C) \times (Cov_i / Cov_{median})\theta \quad [5]$$

$$C_i = TV(C) \times (1+\theta \times Cov_i) \quad [6]$$

where C_i represents individual parameters, $TV(C)$ represents typical individual parameters. θ represents the parameter which was assessed and Cov_i represents the covariate of the ith individual. Cov_{median} represents the populations median value.

Statistical analysis

Changes of objective function value (OFV) were calculated via covariate inclusions. An OFV decrease of >3.84 (χ^2, α=0.05, d.f. =1) was used as a standard for inclusion. When a full regression model was built, the model was tested by excluding these covariates from each parameter individually. An OFV increase >6.63 (χ^2, α=0.01, d.f. =1) was used as a standard for retention.

Model evaluation

The final model was estimated using goodness-of-fit plots (observations *vs.* population predictions, observations *vs.* individual predictions, conditional weighted residuals *vs.* population predictions, and conditional weighted residuals *vs.* time after the start of therapy) and a bootstrap method (n=1,000).

Simulation

The effect of the initial dose on the probability of achieving the target concentrations (5–20 ng/mL) was studied using Monte Carlo simulations based on the final model. The simulation included four scenarios, (I) recipients with cytochrome 450 3A *(CYP3A)5*3/*3* and not co-administered WZ, (II) recipients with a *CYP3A5*1* allele (*CYP3A5*1/*1* and *CYP3A5*1/*3*) not co-administered WZ, (III) recipients with *CYP3A5*3/*3* co-administered WZ, and (IV) recipients with a *CYP3A5*1* allele co-administered WZ. In each case, 7 weight groups (5, 10, 20, 30, 40, 50 and 60 kg) and nine doses (0.01, 0.05, 0.10, 0.15, 0.20, 0.25, 0.30, 0.35 and 0.40 mg/kg/day) were simulated 1,000 times each.

Results

Patient information

Data on 12 Chinese patients who underwent pediatric liver transplantation, including 8 boys and 4 girls, age range from 0.47–7.96 years was used in the present study. Demographic data of patients and drug combinations are shown in *Table 1*. Partial basic clinical data of some children were gathered from previous studies (23,24). Pharmacogenetics data as well as the Hardy-Weinberg equilibrium test results are shown in *Table 2*. Pearson χ^2-test P>0.05, showing Hardy-Weinberg equilibrium of genotypes from the present study were representative of the general population.

Modeling

The final population pharmacokinetic models were as follows:

$$\text{CL/F} = 6.57 \times (\text{WT}/70)^{0.75} \times 1.61^{\text{CYP3A5}} \times (1-0.108 \times \text{WZ}) \quad [7]$$

$$\text{V/F} = 77.6 \times (\text{WT}/70) \quad [8]$$

Table 1 Demographic data of patients and drug combination (n=12)

Characteristic	Mean ± SD	Median (range)
Gender (boys/girls)	8/4	
Age (years)	3.11±2.28	2.42 (0.47–7.96)
Weight (kg)	13.79±5.12	13.00 (6.40–28.00)
Post-transplantation day (days)	253.00±340.00	121.00 (4.00–1,877.00)
Albumin (g/L)	38.69±5.17	39.80 (22.20–49.00)
Alanine transaminase (IU/L)	49.28±58.61	26.00 (9.00–417.00)
Aspartate transaminase (IU/L)	49.18±45.36	34.00 (13.00–288.00)
Creatinine (μmol/L)	25.72±11.78	22.00 (7.00–82.00)
Urea (mmol/L)	4.52±1.87	4.20 (0.70–12.60)
Total protein (g/L)	63.25±9.69	64.10 (40.30–86.60)
Total bile acid (μmol/L)	13.99±17.29	8.90 (1.20–167.50)
Direct bilirubin (μmol/L)	9.12±27.08	3.25 (1.00–226.70)
Total bilirubin (μmol/L)	19.22±39.60	11.10 (2.80–330.80)
Hematocrit (%)	32.83±4.95	33.71 (15.84–43.30)
Hemoglobin (g/L)	107.19±18.34	110.00 (49.00–149.00)
Mean corpuscular hemoglobin (pg)	27.33±23.40	25.80 (16.10–312.00)
Mean corpuscular hemoglobin concentration (g/L)	325.73±18.01	325.00 (258.00–371.00)
Number of co-medications		
Glucocorticoid	11	
Wuzhi-capsule	6	
Aspirin	9	
Fluconazole	2	

Where WT, *CYP3A5*, and WZ represents weight, recipient *CYP3A5* genotype, and co-administration of WZ, respectively. For patients who were *CYP3A5*3/*3*, the *CYP3A5* value =0; for patients with a *CYP3A5*1* allele, the *CYP3A5* value =1; and for patients co-administered WZ, the WZ value =1, otherwise WZ value =0.

Validation

Figure 1 shows goodness-of-fit plots from the final model and *Table 3* shows the final model parameter estimates and bootstrap validation. The bootstrap median values were similar to the final model estimated values. Therefore, we can see that the final model was dependable.

Initial dose recommendation

As shown in *Figure 2*, under the same weight, tacrolimus clearance was different in recipients with a *CYP3A5*3/*3* genotype not co-administered WZ, recipients with a *CYP3A5*1* allele not co-administered WZ, recipients with a *CYP3A5*3/*3* genotype co-administered WZ, and recipients with a *CYP3A5*1* allele co-administered WZ; their clearance ratios were 1:1.61:0.892:1.43612, respectively. Using Monte Carlo simulations, the initial dose recommendation of tacrolimus with different cases were simulated, the results of which are shown in *Figure 3* and *Table 4*. For children with a *CYP3A5*3/*3* genotype not co-administered WZ, 0.10 mg/kg/day split into two doses was recommended for

Table 2 Pharmacogenetics analysis and Hardy-Weinberg equilibrium

Gene	Variation	Genotype	Frequency	%	P value[a]
ABCB1	rs1045642	A/A	2	16.67	0.0543
		A/G	2	16.67	
		G/G	8	66.66	
ABCC4	rs1751034	C/C	1	8.33	0.9768
		C/T	5	41.67	
		T/T	6	50.00	
ABCC8	rs757110	A/A	5	41.67	0.7003
		A/C	5	41.67	
		C/C	2	16.66	
ABCG2	rs2231142	G/G	6	50.00	0.3865
		G/T	4	33.33	
		T/T	2	16.67	
CYP2C9		*1/*1	11	91.67	–
		*3/c.820-6326A>C	1	8.33	
CYP2C19		*1/*1	4	33.33	–
		*1/*2	6	50.00	
		*2/*2	2	16.67	
CYP3A4		*1A/*1A	5	41.67	–
		*1A/*1G	5	41.67	
		*1A/*18B	1	8.33	
		*1G/*1G	1	8.33	
CYP3A5		*1/*1	2	16.66	–
		*1/*3	5	41.67	
		*3/*3	5	41.67	
CYP4F2		*1/*1	7	58.33	–
		*1/*3	5	41.67	
UGT1A1		*1/*1	4	33.33	–
		*1/*6	5	41.67	
		*28/*80	3	25.00	
UGT1A8	rs1042597	C/C	2	16.67	0.9212
		C/G	6	50.00	
		G/G	4	33.33	
UGT2B15	rs1902023	A/A	4	33.33	0.2482
		A/C	4	33.33	
		C/C	4	33.33	

[a], Pearson chi-squared test.

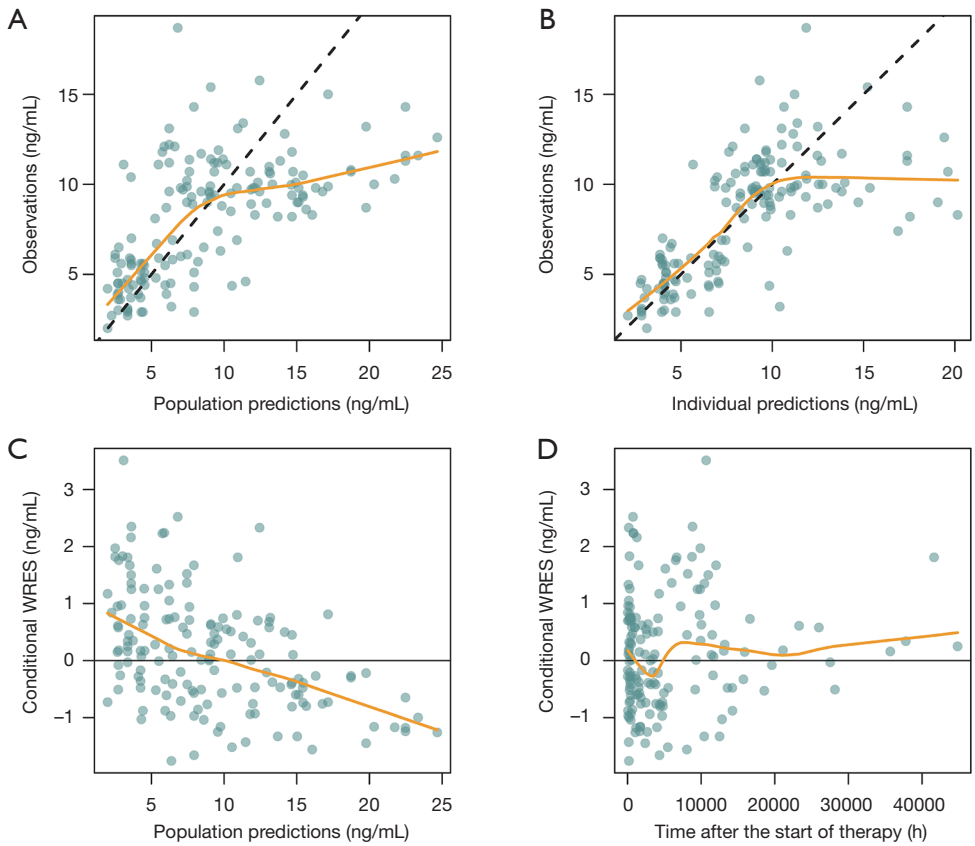

Figure 1 Goodness-of-fit plots from the final population model. (A) Observations *vs.* population predictions; (B) observations *vs.* individual predictions; (C) conditional WRES *vs.* population predictions; (D) conditional WRES *vs.* time after the start of therapy. Partial concentration values were collected in previous studies (23,24). WRES, weighted residuals.

Table 3 Parameter estimates of final model and bootstrap validation

Parameter	Estimate	SE	Bootstrap		Bias (%)
			Median	90% confidence interval	
CL/F (L/h)	6.57	0.414	6.57	(2.91, 9.10)	0
V/F (L)	77.6	1.198	71.4	(15.6, 501.9)	−7.99
Ka (h^{-1})	4.48 (fixed)	–	–	–	–
θ_{CYP3A5}	1.61	0.341	1.54	(1.17, 3.46)	−4.35
θ_{WZ}	−0.108	0.615	−0.095	(−0.210, −0.003)	−12.04
$\omega_{V/F}$	0.396	0.818	0.318	(0.088, 1.039)	−19.70
σ_1	0.288	0.137	0.274	(0.185, 0.318)	−4.86
σ_2	0.720	0.697	0.836	(0.241, 1.471)	16.11

90% confidential interval was displayed as the 5th, 95th percentile of bootstrap estimates. CL/F, apparent oral clearance (L/h); V/F, apparent volume of distribution (L); Ka, absorption rate constant (h^{-1}); θ_{CYP3A5} was the coefficient of CYP3A5 genotype; θ_{WZ} was the coefficient of the wuzhi-capsule; $\omega_{V/F}$, inter-individual variability of V/F; σ_1, residual variability, proportional error; σ_2, residual variability, additive error; Bias, prediction error, Bias = (Median − Estimate)/Estimate×100%.

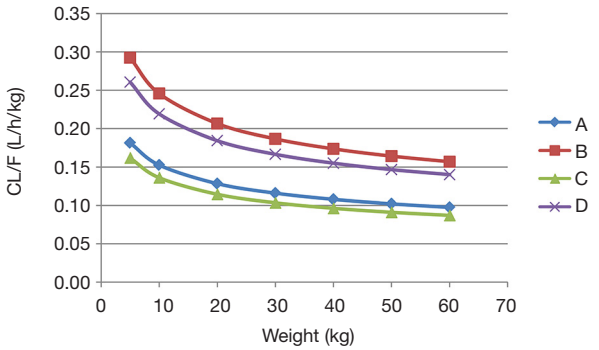

Figure 2 CL/F of tacrolimus in patients undergoing pediatric liver transplant. (A) *CYP3A5*3/*3* recipients who were not co-administered WZ; (B) recipients with a *CYP3A5*1* allele who were not co-administered WZ; (C) *CYP3A5*3/*3* co-administered WZ; (D) recipients with a *CYP3A5*1* allele co-administered WZ. WZ, wuzhi-capsule.

patients weighing 5–17 kg, and 0.05 mg/kg/day split into two doses was recommended for patients weighing 17–60 kg. For children with a *CYP3A5*1* allele not co-administered WZ, 0.25 mg/kg/day for patients weighing 5–10 kg, 0.20 mg/kg/day for patients weighing 10–17 kg, 0.15 mg/kg/day for patients weighing 17–36 kg, and 0.10 mg/kg/day for patients weighing 36–60 kg; all split into two doses was recommended. For children with a *CYP3A5*3/*3* genotype co-administered WZ, 0.10 mg/kg/day for patients weighing 5–11 kg, and 0.05 mg/kg/day for patients weighing 11–60 kg; both split into two doses was recommended. For children with a *CYP3A5*1* allele and co-administered WZ, 0.20 mg/kg/day for patients weighing 5–10 kg, 0.15 mg/kg/day for patients weighing 10–22 kg, and 0.10 mg/kg/day for patients weighing 22–60 kg all split into two doses was recommended.

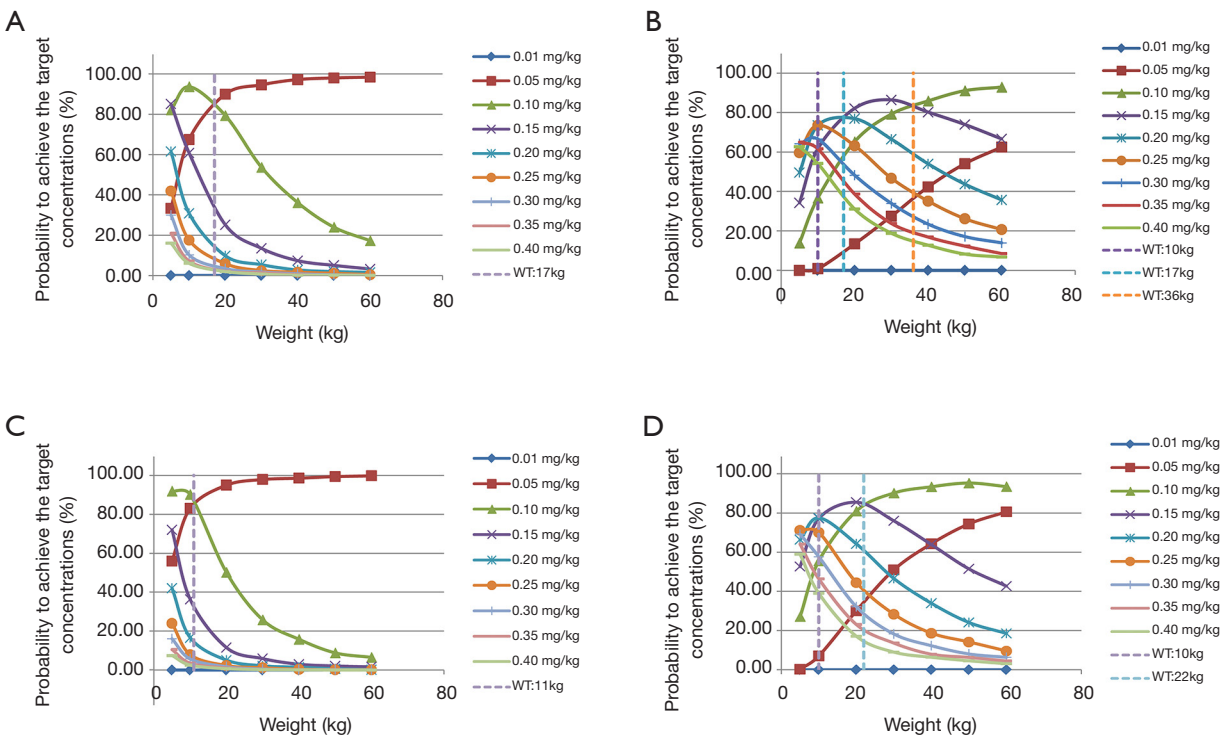

Figure 3 Probability of achieving the target concentrations. (A) *CYP3A5*3/*3* recipients who were not co-administered WZ; (B) recipients with a *CYP3A5*1* allele who were not co-administered WZ; (C) *CYP3A5*3/*3* recipients co-administered WZ; (D) recipients with a *CYP3A5*1* allele co-administered WZ. WZ, wuzhi-capsule.

Table 4 Initial dosage recommendation of tacrolimus in paediatric liver transplant

Body weight (kg)	Dosage recommendation[b]	Genotype[a]		Drug combination	
		CYP3A5*1	CYP3A5*3/*3	Without WZ	With WZ
5–17	0.10 mg/kg/day		Yes	Yes	
17–60	0.05 mg/kg/day				
5–10	0.25 mg/kg/day	Yes		Yes	
10–17	0.20 mg/kg/day				
17–36	0.15 mg/kg/day				
36–60	0.10 mg/kg/day				
5–11	0.10 mg/kg/day		Yes		Yes
11–60	0.05 mg/kg/day				
5–10	0.20 mg/kg/day	Yes			Yes
10–22	0.15 mg/kg/day				
22–60	0.10 mg/kg/day				

[a], recipient; [b], splited into two doses; *CYP3A5*1*, *CYP3A5*1/*1* and *CYP3A5*1/*3*; WZ, wuzhi-capsule.

Discussion

Tacrolimus exhibits low oral bioavailability (10–20%), but this varies notably between individuals, due to intestinal P-glycoprotein efflux and intestinal and hepatic CYP3A-mediated metabolism (27). Human CYP3A is present in at least two heterogeneous expression isoforms, CYP3A4 and CYP3A5, of which, CYP3A5 is the most important metabolic enzyme with regard to tacrolimus (28).

At present, several tacrolimus population pharmacokinetic models based on Chinese patients undergoing pediatric liver transplant have been established (23,25). For example, in Yang *et al*., a tacrolimus population pharmacokinetic model was developed in Chinese children with early after liver transplantation (25). In this previous study, their goal was to model external predictiveness and set up a novel population pharmacokinetic model which was applicable to a traditional TDM datasets (23). The model from a previous publication was deemed inadequate when used with real-world datasets, and thus a new population pharmacokinetic model, which was applicable to real-world datasets was produced (23). However, neither of the above tacrolimus population pharmacokinetics studies in Chinese patients undergoing pediatric liver transplants considered the effect of genotype, which may result in considerable uncertainty and introduce deviations to the initial dosage optimization model. Thus, in the present study, population pharmacokinetics and pharmacogenomics were combined to achieve accurate initial dose recommendation in for Chinese patients undergoing pediatric liver transplants.

In our study, weight, *CYP3A5* genotype, and coadministration with WZ were incorporated into the final model. It has been shown that a Chinese medicine, WZ, which includes schisantherin A, schisandrol B and schisandrin (29), has a notable effect on tacrolimus and can increase the effective tacrolimus concentration (30-32) by inhibiting *CYP3A* which metabolizes tacrolimus (32,33). Thus, WZ can be used to reduce the tacrolimus dose and save money on health care, especially for children who need tacrolimus long term (34), such as children with liver transplants.

In addition, the present study found that under the same weight, tacrolimus clearance differed between *CYP3A5*3/*3* patients not co-administered WZ, patients with a *CYP3A5*1* allele not co-administered WZ, *CYP3A5*3/*3* patients co-administered WZ and patients with a *CYP3A5*1* allele co-administered WZ; the clearance ratios were 1:1.61:0.892:1.43612, respectively. Furthermore, based on simulations using the established model; for *CYP3A5*3/*3* patients not co-administered WZ, 0.10 mg/kg/day split into two doses was recommended for patients weighing 5–17 kg, and 0.05 mg/kg/day split into two doses was recommended for patients weighing 17–60 kg. For children with a *CYP3A5*1* allele not co-administered WZ, 0.25 mg/kg/day

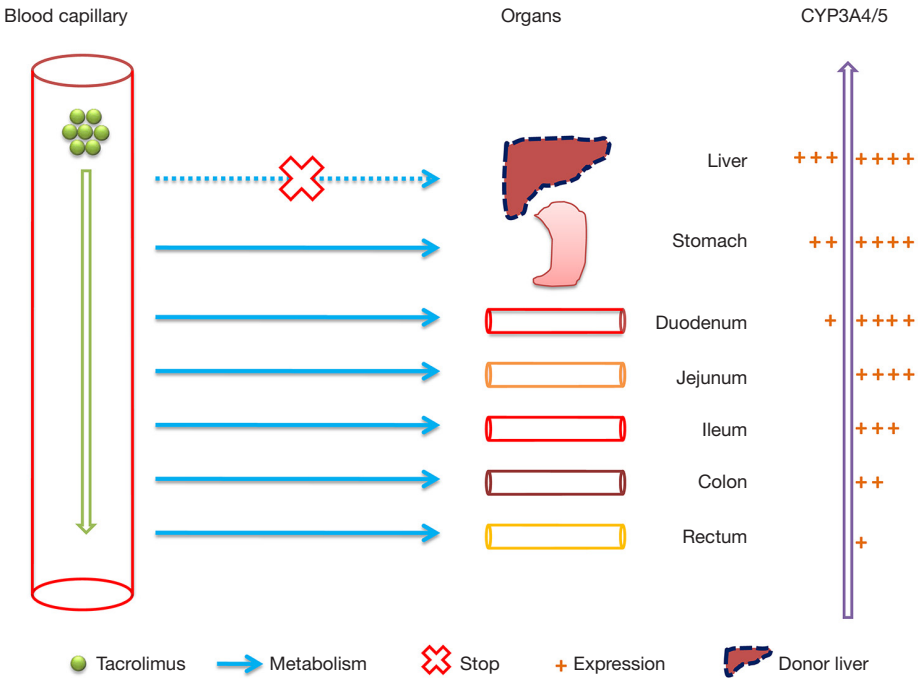

Figure 4 Metabolism of the initial dose of tacrolimus. Expression of CYP3A4/5 from the rectum, colon, ileum, jejunum, duodenum, to the stomach gradually increases (1).

for patients weighing 5-10 kg, 0.20 mg/kg/day for patients weighing 10–17 kg, 0.15 mg/kg/day for patients weighing 17–36 kg, and 0.10 mg/kg/day for patients weighing 36–60 kg; all split into two doses was recommended. For children with a *CYP3A5*3/*3* genotype co-administered WZ, 0.10 mg/kg/day for patients weighing 5–11 kg, and 0.05 mg/kg/day for patients weighing 11–60 kg; both split into two doses was recommended. For children with a CYP3A5*1 allele co-administered WZ, 0.20 mg/kg/day for patients weighing 5–10 kg, 0.15 mg/kg/day for patients weighing 10–22 kg, and 0.10 mg/kg/day for patients weighing 22–60 kg all split into two doses was recommended.

A novel discovery of the present study was that compared with tacrolimus clearance previously reported in Chinese patients with pediatric refractory nephritic syndrome patients (not receiving a liver transplant) (34), the clearance of tacrolimus was markedly reduced in the early stage of the liver transplant in Chinese children. This was primarily due to the limited function of the transplanted liver in the short period of time whilst still in the setting up stage, particularly in the early stage of administration of the initial dose, thus the metabolism of tacrolimus in the transplanted liver was insufficient. We hypothesize that the initial dose after transplantation is primarily metabolized by the intestine, which also explains why donor liver genotypes can be ignored when determining the initial dose, as shown in *Figure 4*. This also confirmed that although we did not consider donor liver genotypes, the recommended initial dose was still suitable.

However, there were limitations in the present study. This study is a single-center study and the number of patients was limited. Thus additional data from other sources are needed to verify the validity of our model.

Conclusions

The optimal initial dose of tacrolimus for Chinese patients undergoing pediatric liver transplantation was determined based on population pharmacokinetics and pharmacogenomics, for the first time.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tp-20-84). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was performed in accordance with the Declaration of Helsinki (2013 revision) and was approved by the Research Ethics Committee of the Children's Hospital of Fudan University (Ethical code: [2019] 020). Individual consent for this retrospective analysis was waived.

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