Population pharmacokinetics of tacrolimus in pediatric refractory nephrotic syndrome and a summary of other pediatric disease models

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Abstract. Different tacrolimus (TAC) population pharmacokinetic (PPK) models have been established in various pediatric disease populations. However, a TAC PPK model for pediatric refractory nephrotic syndrome (PRNS) has not been well characterized. The current study aimed to establish a TAC PPK model in Chinese PRNS and provide a summary of previous literature concerning TAC PPK models in different pediatric diseases. A total of 147 TAC conventional therapeutic drug monitoring (TDM) data from multiple blood samples obtained from 65 Chinese patients with PRNS were characterized using nonlinear mixed-effects modeling. The impacts of demographic features, biological characteristics and drug combination were evaluated. Model validation was assessed using the bootstrap method. A one-compartment model with first-order absorption and elimination was determined to be the most suitable model for TDM data in PRNS. The absorption rate constant (Ka) was set at 4.48 h^{-1}. The typical values of apparent oral clearance (CL/F) and apparent volume of distribution (V/F) in the final model were 5.46 l/h and 57.1 l, respectively. The inter-individual variability of CL/F and V/F were 22.2 and 0.2%, respectively. The PPK equation for TAC was: CL/F = 5.46 x exponential function (EXP)(0.0323 x age) x EXP(-0.359 x cystatin-C) x EXP(0.148 x daily dose of TAC). No significant effects of covariates on V/F were observed. In conclusion, the current study developed and validated the first TAC PPK model for patients with PRNS. The study also provided a summary of previous literature concerning other TAC PPK models in different pediatric diseases.

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Introduction

The incidence of nephrotic syndrome (NS) in children is 0.16‰, and is a primary concern in pediatric nephrology. NS may cause damage to the kidneys by enhancing glomerular basement membrane permeability (1,2). The majority of diagnosed children have steroid-sensitive nephrotic syndrome (SSNS), and ~20% of children do not achieve complete remission and ultimately develop steroid-resistant nephrotic syndrome (SRNS) (3). In addition, 80-90% of children with SSNS undergo relapse, and in those that relapse, 50% experience frequent relapses and develop steroid-dependent nephrotic syndrome (SDNS) (4-6). Therefore, the treatment of pediatric refractory nephrotic syndrome (PRNS), which includes SDNS and SRNS, is challenging. Patients with PRNS are administered repeated, long-term steroid therapy, which increases the risk of obesity, cushingoid appearance, hypertension, growth retardation, osteoporosis, infections and psychological problems (7).

Encouragingly, several investigations have used tacrolimus (TAC), a steroid-sparing agent, to treat patients with PRNS, which has improved responses and reduced adverse reactions to steroid therapy (8-15). However, as a potent immunosuppressive agent, the therapeutic window of TAC is narrow (16). Although adequate and continuous immunosuppression is necessary, excessive immunosuppression may give rise to severe adverse reactions, including infections and toxicity. TAC pharmacokinetics (PK) have exhibited considerable inter- and intra-individual variability, making it difficult to define an optimal dosing schedule (16,17).

Using population PK (PPK), PK data may be acquired by analyzing sparse data pooled from a group of people. Furthermore, the PPK method is able to differentiate between inter- and intra-individual variability. Thus, compared with traditional PK, PPK has the power to verify the effect of multiple factors on PK and may make it possible to determine an optimal dose schedule (18). Currently, different TAC PPK models have been set up in multiple populations, including patients undergoing renal transplant (19-24), liver transplant (25-30), hematopoietic stem cell transplant (31) and lung transplant (32). However, the TAC PPK model for PRNS is still unclear. The objective of the current study was to produce a TAC PPK model in Chinese patients with PRNS and to analyze factors involved in pharmacokinetic variability. The current study also summarizes previous literature regarding TAC PPK models in different pediatric diseases, including liver transplant (27,28,33-39), kidney transplant (23) and hematopoietic stem cell transplant (31).

Patients and methods

Patients and data collection. Patients <18 years of age, who were diagnosed with PRNS and were receiving TAC therapy were recruited into the present study. Patients were excluded if they presented with other serious diseases, including kidney transplantation. A total of 65 Chinese patients (44 males and 21 females) with PRNS treated at the Children's Hospital of Fudan University (Shanghai, China) between January 2014 and October 2017 (2.4-16.4 years old; mean age, 7.6±3.9 years) were retrospectively analyzed. Drug concentrations were collected from therapeutic drug monitoring (TDM) records and relevant clinical information was acquired from medical records. The study was approved by the Research Ethics Committee of the Children's Hospital of Fudan University.

Information extracted from the medical records included age, weight, daily dose of TAC (TAMT), albumin (ALB), globulin (GLB), albumin/globulin (A/G), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine (CR), total protein (TP), cystatin-C (CYSC), gamma-glutamyl transpeptidase (GGT), urea (UR), uric acid (UA), hematocrit (HCT), hemoglobin (HGB), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and concomitant drugs (corticosteroids, clarithromycin, ceftriaxone, warfarin, simvastatin, cimetidine, ranitidine, omeprazole, nifedipine, diltiazem, felodipine, fosinopril, dihydrochlorothiazide, spirolactone, ciclosporin, mycophenolate mofetil, montelukast, loratadine, piperazine ferulate, vitamin B6 and shegan mixture). The information was verified for accuracy as comprehensively as possible.

Drug administration. All patients received oral TAC (capsule, 1 and 0.5 mg). The initial TAC dose was 0.5-2.0 mg twice daily and the dose range of TAC was 1.0-4.0 mg/day. The dose of TAC was adjusted based on efficacy, adverse effects and the trough concentration in TDM. All blood concentrations were collected prior to the subsequent administration. The TAC concentrations used in the current research were trough concentrations.

Analytical method. Whole blood concentrations of TAC were measured using the Emit® 2000 Tacrolimus assay (Siemens Healthineers, Erlangen, Germany), which was linear over the range of 2.0-30.0 ng/ml and blood samples exceeding the upper limit of the calibration range of 30.0 ng/ml were diluted according to the manufacturer's protocol.

Population pharmacokinetic modeling. Data were analyzed using a nonlinear mixed-effects model computer program (NONMEM, version 7; ICON Development Solutions, LLC, Ellicott City, MD, USA). The first-order conditional estimation method with interaction option was used to estimate PK parameters and their variability. A one-compartment model with first-order elimination was used for describing the absorption phase, since all the TAC concentrations in the current research were trough concentrations. The bioavailability (F) and absorption with a lag time could not be estimated because TAC was orally administered and TAC concentration data were insufficient. Thus, the PK parameters were comprised of apparent oral clearance (CL/F) and apparent volume of distribution (V/F). The absorption rate constant (Ka) of the model was set as 4.48 h^{-1}, according to what was previously set in the literature (28,40,41).

Random effect model. The inter-individual variability in PK parameters was explored with additive, proportional and exponential error models. The residual error variability was evaluated with additive, proportional, exponential and mixed error models.

Covariate model. To determine the variability of PK parameters, the associations were examined between covariates and all the PK parameters where inter-individual variability was tested. The possible covariates included age, weight, TAMT, ALB, GLB, A/G, AST, ALT, CR, TP, CYSC, GGT, UR, UA, HCT, HGB, MCH, MCHC and concomitant medication. The covariate model was established in a stepwise way. To compare hierarchical models, a likelihood ratio test was adopted. The change in objective function values (OFV) caused by the inclusion of a covariate is proportional to twice the negative log likelihood of the data and approximates a chi-square distribution (42). In the univariate analysis, a decrease in OFV >3.84 (P<0.05, degrees of freedom = 1) was selected as a standard for inclusion of the covariate in the base model. The significant covariates were reserved in the model. When a full regression model was built, the model was further validated by discarding the covariate of each parameter one by one to acquire the final model. An increase in OFV >6.64 (P<0.01, degrees of freedom = 1) was selected as a standard to retain significant covariates in the final model.

Model validation. An internal validation bootstrap method was used to evaluate the stability and reliability of parameter estimates in the final model (43). Goodness-of-fit plots applied to models were generated using R software (version 3.4.2; https://www.r-project.org/). Bootstrapping was produced using repeated random sampling with replacement of the original data (44,45). This procedure was performed using the software package Wings for NONMEM (version 7; ICON Development Solutions, LLC) and repeated 2,000 times with different random draws. Bootstrap outcomes with successful minimization and acceptable covariance were applied for further analysis. The medians and 2.5-97.5% percentiles in the bootstrap result set parameters were compared with the parameter estimates of final PK.

Summary of TAC PPK models in different pediatric diseases. To investigate the differences and similarities in TAC PPK models and factors that cause its variation among various pediatric diseases, the study also provided a summary of previous literature regarding TAC PPK models in pediatric patients with PRNS, liver transplant, kidney transplant and hematopoietic stem cell transplant. Studies between January 1995 and October 2017 were retrieved from PubMed (https://www.ncbi.nlm.nih.gov/pubmed) and Web of Science Knowledge

Table I. Demographic and clinical characteristics of patients (n=65).

Characteristic	Mean ± SD	Median	Range
Age (years)	7.61±3.92	6.8	2.4-16.4
Weight (kg)	30.85±17.12	25.0	13.5-86.5
TAMT (mg)	1.62±0.75	1.5	1.0-4.0
A/G	1.16±0.44	1.1	0.6-2.6
ALB (g/l)	25.41±8.87	24.1	12.3-45.3
ALT (IU/l)	9.91±6.48	8.0	2.0-35.0
AST (IU/l)	15.93±6.49	14.0	5.0-35.0
CR (μmol/l)	30.49±12.67	27.0	14.0-69.0
GLB (g/l)	22.16±3.32	22.6	15.2-31.2
TP (g/l)	47.51±10.22	46.9	29.5-69.1
CYSC (mg/l)	0.85±0.25	0.8	0.4-2.3
GGT (IU/l)	32.85±54.52	22.0	9.0-446.0
UR (mmol/l)	4.41±2.59	4.0	1.9-18.1
UA (μmol/l)	343.42±117.00	315.0	134.0-799.0
HCT (%)	42.62±4.94	42.6	27.4-55.3
HGB (g/l)	144.79±17.34	146.0	90.0-180.1
MCH (pg)	28.91±1.46	29.0	26.0-32.0
MCHC (g/l)	340.12±14.91	342.0	302.0-366.0

TAMT, daily dose of tacrolimus; A/G, albumin/globulin; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CR, creatinine; GLB, globulin; TP, total protein; CYSC, cystatin-C; GGT, gamma-glutamyl transpeptidase; UR, urea; UA, uric acid; HCT, hematocrit; HGB, hemoglobin; MCH, mean corpuscular hemoglobin; MCHC, MCH concentration; SD, standard deviation.

(https://login.webofknowledge.com/). Search terms included: Tacrolimus, population pharmacokinetics and relevant pediatric diseases. Primary research papers matching the criteria were identified and evaluated.

Results

Data collection. Whole blood concentration of TAC was evaluated in 147 samples from 65 Chinese patients with PRNS consisting of 44 males and 21 females, and data were made available for population modeling. Patient characteristics and drug combinations are summarized in Tables I and II, respectively.

Modeling and validation. A one-compartment model with first order absorption and elimination was best fitted to the data. Ka was set at 4.48 h^{-1} according to the literature (28,40,41). Furthermore, the Ka parameter was also tested using other values to evaluate the sensitivity. Ka was increased or reduced 5-fold, from 0.896 to 22.4 h^{-1}. However, the results of CL/F, V/F and the OFV exhibited minimal changes. Using this method, it was determined that the appropriate Ka value was 4.48 h^{-1}. The PK parameters of TAC, CL/F and V/F were estimated using NONMEM. Inter-individual variability and residual variability were best described by exponential and mixed error models, respectively. Of all the tested covariates, only three had a significant effect on PK parameters: Age, CYSC and TAMT on CL/F. No covariates notably influenced V/F. The changes in OFV are presented in Table III. The final

Table II. Drug combinations administered to patients.

Drug	Category	n	%
Corticosteroids	0	1	1.5
	1	64	98.5
Clarithromycin	0	64	98.5
	1	1	1.5
Ceftriaxone	0	63	96.9
	1	2	3.1
Warfarin	0	64	98.5
	1	1	1.5
Simvastatin	0	64	98.5
	1	1	1.5
Cimetidine	0	64	98.5
	1	1	1.5
Ranitidine	0	64	98.5
	1	1	1.5
Omeprazole	0	55	84.6
	1	10	15.4
Nifedipine	0	64	98.5
	1	1	1.5
Diltiazem	0	61	93.8
	1	4	6.2
Felodipine	0	63	96.9
	1	2	3.1
Fosinopril	0	52	80.0
	1	13	20.0
Dihydrochlorothiazide	0	42	64.6
	1	23	35.4
Spirolactone	0	43	66.2
	1	22	33.8
Ciclosporin	0	63	96.9
	1	2	3.1
Mycophenolate mofetil	0	63	96.9
	1	2	3.1
Montelukast	0	63	96.9
	1	2	3.1
Loratadine	0	63	96.9
	1	2	3.1
Piperazine ferulate	0	58	89.2
	1	7	10.8
Vitamin B6	0	64	98.5
	1	1	1.5
Shegan mixture	0	61	93.8
	1	4	6.2

0, not administered; 1, administered.

Table III. Change of OFV in covariate analysis.

Step	Model description	OFV	ΔOFV	P-value
Inclusion	Base model	455.868	N/A	N/A
	Influence of age on CL/F	438.708	-17.160	<0.05
	Influence of CYSC on CL/F	427.426	-11.282	<0.05
	Influence of TAMT on CL/F	420.171	-7.255	<0.05
Elimination	Full model	420.171	N/A	N/A
	Eliminate age on CL/F	428.159	7.988	<0.01
	Eliminate CYSC on CL/F	433.351	13.180	<0.01
	Eliminate TAMT on CL/F	427.426	7.255	<0.01

OFV, objective function values; CL/F, apparent oral clearance; CYSC, cystatin-C; TAMT, daily dose of tacrolimus.

Table IV. Parameter estimates of final model and bootstrap validation.

Parameter	Estimate	SE (%)	Bootstrap (n=2000) Median	Bootstrap (n=2000) 95% confidence interval	Bias (%)
CL/F (l/h)	5.4600	22.7	5.640	[0.160, 9.895]	3.297
V/F (l)	57.1000	46.8	59.500	[0.298, 496.750]	4.203
Ka (h^{-1})	4.4800 (fixed)	N/A	N/A	N/A	N/A
θ_{AGE}	0.0323	35.0	0.033	[0.007, 0.062]	2.477
θ_{CYSC}	-0.3590	26.1	-0.375	[-0.719, -0.087]	4.457
θ_{TAMT}	0.1480	47.9	0.140	[0.012, 0.350]	-5.405
$\omega_{CL/F}$	0.2220	18.5	0.216	[0.053, 0.342]	-2.703
$\omega_{V/F}$	0. 0020	48.5	0.001	[0.001, 0.009]	-50.000
σ_1	0.3590	8.2	0.345	[0.235, 0.417]	-3.900
σ_2	0.8040	31.5	0.806	[0.003, 1.594]	0.249

95% confidential interval was the 2.5th and 97.5th percentile of bootstrap estimates. CL/F, apparent oral clearance; V/F, apparent volume of distribution; Ka, absorption rate constant; θ_{AGE}, θ_{CYSC} and θ_{TAMT}, coefficients of age, CYSC and TAMT, respectively; $\omega_{CL/F}$, inter-individual variability of CL/F; $\omega_{V/F}$, 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 x 100; SE, standard error.

models were as follows: CL/F = $\theta_{CL/F}$ x EXP(θ_{AGE} x age) x EXP (θ_{CYSC} x CYSC) x EXP (θ_{TAMT} x TAMT); V/F = $\theta_{V/F}$; where $\theta_{CL/F}$ and $\theta_{V/}$F were the typical population values of CL/F and V/F, respectively, and θ_{AGE}, θ_{CYSC} and θ_{TAMT} were the coefficients of age, CYSC and TAMT, respectively.

The goodness-of-fit plots of the final model compared with the base model are presented in Figs. 1 and 2. From 2,000 bootstrap runs, 1,791 runs were successfully minimized by covariance steps, and finally they were added into the bootstrap analysis. The parameter estimates of the final model and bootstrap validation are presented in Table IV. The median values of the parameter estimated from bootstraps were near to the final model's respective values, indicating that the PK parameter estimates from the final model were precise and the model was reliable.

TAC PPK models in different pediatric diseases. Twelve pediatric TAC PPK models were identified in the literature, including the current PRNS model, nine liver transplant models, one kidney transplant model and one hematopoietic stem cell transplant model. Table V summarizes these PPK studies in different pediatric diseases. However, TAC PPK models vary in pediatric diseases, which indicates that disease state may lead to differences in CL/F and V/F in different pediatric disease populations.

Discussion

TAC has been used for the treatment of patients with PRNS to improve their responses and reduce adverse reactions to steroid therapy. Since TAC exhibits considerable inter- and intra-individual PK variability, PPK analysis of TAC is crucial (8-17). To the best of our knowledge, the current model may be the first pediatric study of TAC PPK in patients with refractory nephrotic syndrome. In the current study, TAC PPK was performed in Chinese patients with PRNS using a

Table V. Population pharmacokinetics of tacrolimus in different pediatric disease models.

Model	Reference	n	Age in years, average (range)	Time post-transplantation	Pharmacokinetic parameters	BSV CL (%)	BSV V (%)	Refs.
Refractory nephrotic syndrome	Current study	65	6.8[a] (2.4-16.4)	NR	CL/F (l/h) = 5.46 x EXP(0.0323 x AGE) x EXP(-0.359 x CYSC) x EXP(0.148 x TAMT); V/F (l) = 57.1; Ka (h^{-1}) = 4.48 (fixed)	22.2	0.2	N/A
Liver transplant	Yang *et al*, 2015	52	1.78[b] (0.42-17.8)	From the day after transplantation	CL/F (l/h) = 5.72 x $POD^{0.152}$ x $(ALT/70)^{-0.111}$; V/F (l) = 131 x $POD^{0.31}$ x $(ALT/70)^{-0.317}$ x $(TP/54)^{-2.01}$; Ka (h^{-1}) = 4.48 (fixed)	13.5	78.1	28
	Kassir *et al*, 2014	30	7.3[a] (0.4-18.4)	≤28 days, 8 patients; >28 days, 22 patients	CL/F (l/h) =12.1 x $(WT/20)^{0.75}$; V_1/F (l) = 31.3 x $(WT/20)^{1}$; Q/F (l/h) = 30.7 x $(WT/20)^{0.75}$; V_2/F (l) = 290 x $(WT/20)^{1}$; Ka (h^{-1}) = 0.342 x $(WT/20)^{-0.25}$; t_{lag} (h) =0.433	55.6	126.1	37
	Jalil *et al*, 2014	43	5[b] (0.65-17.56)	First year post-transplantation	CL/F $(l/h)^{c}$ = 12.9 x $(WT/13.2)^{0.75}$ x $e^{(-0.00158xPOD)}$ x $e^{(0.428xhFLAG)}$	40	NR	36
	Guy-Viterbo *et al*, 2013	42	1.35[a] (0.53-10.93)	From the day after transplantation until the patient experienced a rejection episode or, alternatively, until the end of the first year	CL/F $(l/day)^{d}$ = 0.001 x [1 + (314xTIME) / (17.4 + TIME)] x $[(Size / WT) / median (Size / WT)]^{0.12}$ x $(Hct/29)^{-0.85}$; V_1/F (l) = 253 x $(WT/10.2)^{0.9}$; V_2/F (l) =100 (fixed); Q/F (l/day) = 115	54.8	77.5	35
	Wallin *et al*, 2011	73	3.5[a] (0.4-16.9)	First year post-transplantation	CL/F $(l/h/kg^{-0.75})$ = 0.148 + (1.37 x $POD^{3.78}$) / ($5.38^{3.78}$ + $POD^{3.78}$); V/F (l/kg) = 27.2	NR	90	27
	Fukudo *et al*, 2006	100	1.2[a] (0.1-15.0)	First 50 days post-transplantation	CL/F $(l/h/kg)^{e}$ = (0.134 x 1.8^{iFLAG} + 0.0181 x 2^{hFLAG} x XPOD) x 8.6 x $(WT/8.6)^{0.341}$ x $e^{(-0.0358xAST/53)}$; V/F (l) = 17.1 x 8.6 x $(WT/8.6)^{0.341}$	48.7	82.6	33
	Garcia Sanchez *et al*, 2001	18	9.1[a] (0.3-16.0)	From 1 day to 6.8 years	CL (l/h) = 10.4 x $(WT/70)^{0.75}$ x $e^{(-0.00032T)}$ x $e^{(-0.057BILI)}$ x (1 - 0.079 x ALT); F = 20% (fixed)	24.3	NR	34
	Sam *et al*, 2000	20	3.7[b] (1.1-13.9)	0-7 days	CL (l/h) = 1.46 x [1 + 0.339 x (AGE - 2.25)]; V (l) = 39.1 x [1 + 4.57 x (BSA-0.49)]; F (%) = 0.197 x (1 + 0.0887 x WT - 11.4), BILI <200 μmol/l; F (%) = 0.197 x (1 + 0.0887 x WT - 11.4) x 1.61, BILI ≥200 μmol/l	33.5	33	38
	Yasuhara *et al*, 1995	33	4.2[b] (0.3-15)	52 days	CL (l/h) = (0.0749 + 0.000457 x POD) x [15 x $(WT/15)^{0.29}$]; V (l) = 2.76 x [15 x $(WT/15)^{0.29}$]; F =19%	52.1	27.4	39

Table V. Continued.

Model	Reference	n	Age in years, average (range)	Time post-transplantation	Pharmacokinetic parameters	BSV CL (%)	BSV V (%)	Refs.
Kidney transplant	Zhao *et al*, 2009	50	10[b] (2-18)	During the initial post-transplantation period (<2 months)	Ka (h^{-1}) = 0.462; t_{lag} (h) =0.356; CL/F (l/h)[f] = 13.9 x $(WT/70)^{0.75}$ x (2.26^{FLAG1}) + 7.11 x (1.74^{FLAG2}); V_1/F (l) = 57.9 x (WT/70); V_2/F (l) = 966 x (WT/70); Q/F (l) = 79.7 x $(WT/70)^{0.75}$	41.9	132	23
Hematopoietic stem cell transplant	Wallin *et al*, 2009	22	6[b] (0.5-18)	Within the first year after stem cell transplantation	CL (ml/h/$kg^{-0.75}$) = 106 x [1 + 18.7 x (S-$Crea^{-1}$ - S-$Crea^{-1}_{median}$)]; V (l/kg) = 3.71; F (%) = 15.7 x [1 + (-0.002) x POD - 14]	50	122	31

[a]Median value. [b]Mean value. [c]If the patient was a *CYP3A5*1* allele carrier, then hFLAG = 1; otherwise, 0. [d]Equation not fully provided by authors. [e]If POD was <21, then XPOD = POD; otherwise, XPOD = 21; if the donor was a *CYP3A5*1* allele carrier, then hFLAG = 1; otherwise, 0; and if the intestinal *MDR1* mRNA level was >0.22 amol (µg total RNA)$^{-1}$, then iFLAG = 1; otherwise, 0. [f]If *CYP3A5*3/*3*, FLAG1 = 0; if *CYP3A5*1/*3* or **1/*1*, FLAG1 = 1; if hematocrit ≥33%, FLAG2 = 1. AGE, age; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin concentration; BSA, body surface area; BSV, between-subject variability; CL, clearance; CL/F, apparent oral clearance; CYSC, cystatin-C; F, bioavailability; Hct, haematocrit; Ka, absorption rate constant; NR, not reported; POD, postoperative day; Q/F, intercompartmental clearance; S-Crea, serum creatinine; Size/WT, liver transplant size/body weight ratio; t_{lag}, lag time; T, time after initiation of treatment; TAMT, daily dose of tacrolimus; TIME, time after transplantation; TP, total protein; V, volume of distribution; V/F, apparent volume of distribution; V_1/F, apparent central volume of distribution; V_2/F, apparent peripheral volume of distribution; WT, body weight.

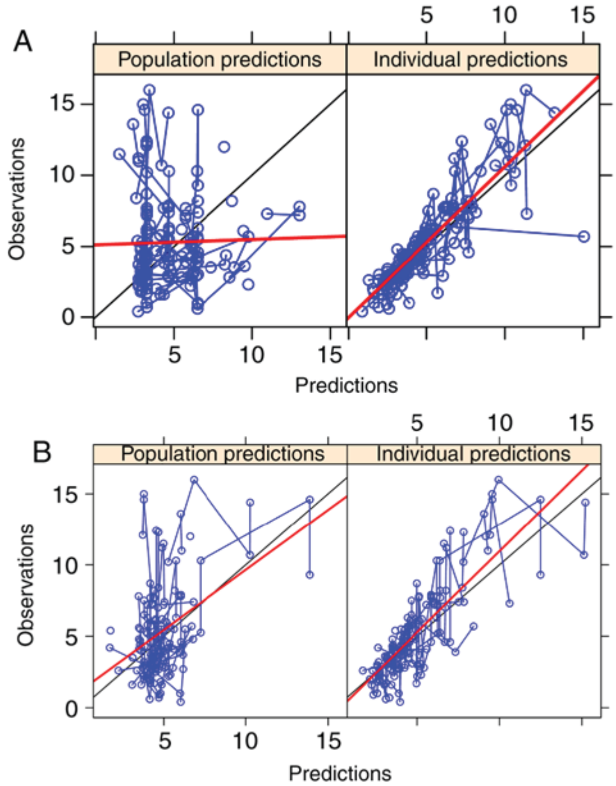

Figure 1. Population and individual predictions. (A) Observation vs. population predictions and individual predictions in the base model. (B) Observation vs. population predictions and individual predictions in the final model.

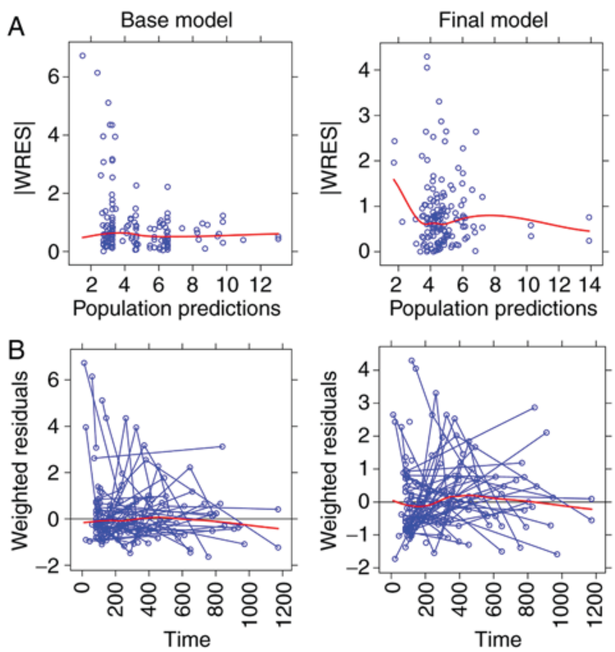

Figure 2. Weighted residuals. (A) Absolute value of weighted residuals vs. population predictions in the base and final model. (B) Weighted residuals vs. time in the base and final model. |WRES|, absolute value ofweighted residuals.

population modeling method, which was particularly applicable since excessive blood sample collection is prohibited for pediatric patients compared with traditional PK studies (46). A

TAC PPK model that is able to determine the pharmacokinetic process in individual patients with PRNS may have important clinical applications.

In the current study, a one-compartment model with first-order elimination was used for describing the absorption phase, as all the TAC concentrations were trough concentrations, and the Ka of the model was fixed at 4.48 h^{-1} (28,40,41). The typical values of CL/F and V/F in the final TAC PPK model were 5.46 l/h and 57.1 l, respectively, and the CL/F value was similar to that in a PPK model of TAC in Chinese pediatric patients shortly after liver transplantation (28). The current model also tested various covariates on different parameters and the following covariates were determined to be significant: Age, CYSC and TAMT on CL/F. Przepiorka *et al* (47) also demonstrated that TAC clearance was age-dependent in pediatric patients undergoing hematopoietic stem cell transplant. Thus, CL/F of TAC was affected by age in PRNS and pediatric hematopoietic stem cell transplantation models; this may be associated with developmental maturity and how this influences the clearance of TAC.

Cystatin-C, generated by all nucleated cells and catabolized by proximal tubules, is a low molecular weight protein that is part of the cysteine protease family (48). Cystatin-C is superior to creatinine in estimating glomerular filtration rate (49) and is widely considered to be a predictive biomarker in kidney and cardiovascular diseases (50,51). Additionally, serum cystatin-C has been confirmed as a more sensitive biomarker than serum creatinine in predicting renal dysfunction in patients with primary NS (49,52). This also supports the previous claim that cystatin-C was a biomarker of NS and could predict the disease progress (49,52,53). The current study identified that CL/F was negatively associated with cystatin-C, which indicated the progression of disease had an impact on CL/F in a pediatric refractory nephrotic syndrome model.

In addition to age and CYSC, another key factor affecting TAC clearance was TAMT. It is established that TAC is primarily metabolized by the oxidative enzyme cytochrome P450 (CYP) 3A subfamily in the intestine and liver, with CYP3A4 and the highly polymorphic CYP3A5 as the major metabolizing enzymes (54). A previous study reported that individuals with the *CYP3A5**3/*3* genotype require less TAC to attain objective concentrations compared with patients with the *CYP3A5**1 allele (55-57). Additionally, genetically-induced *CYP3A5* hyperactivity increases the TAC daily dose (58). Therefore, the effect of TAMT on CL/F may be primarily derived from *CYP3A5* gene polymorphisms. Unfortunately, at present, *CYP3A5* genotyping is not routinely performed in Chinese patients with PRNS. Whether *CYP3A5* genotype could better assess the inter-individual variability in the current model of CL/F on TAC in PRNS should be determined in the future.

In addition, the current study provided a summary of previous literature concerning TAC PPK models in several pediatric diseases. Notably, TAC PPK models vary in different pediatric diseases. To a certain extent, this may indicate that disease situation may lead to differences in CL/F and V/F in different populations.

In conclusion, the first TAC PPK model in patients with PRNS was established using retrospective, routinely monitored data. Age, CYSC and TAMT were identified as significant covariates for CL/F. No covariates significantly influenced V/F. The current study also provided a summary of previous literature concerning TAC PPK models in different pediatric diseases.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

ZL conceived and designed the study. DW, JL and QL collected data and built the model. DW wrote the paper. JL and QL reviewed and edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Research Ethics Committee of Children's Hospital of Fudan University (Shanghai, China).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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