Original Article

Effects of voriconazole on population pharmacokinetics and optimization of the initial dose of tacrolimus in children with chronic granulomatous disease undergoing hematopoietic stem cell transplantation

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Background: This study aimed to explore the effects of voriconazole on population pharmacokinetics and optimization of the initial dose of tacrolimus in children with chronic granulomatous disease (CGD) undergoing hematopoietic stem cell transplantation (HSCT).

Methods: Thirty-four children with CGD undergoing HSCT were assessed to establish a population pharmacokinetic model (PPM) using the non-linear mixed effect. Tacrolimus concentrations were simulated by the Monte Carlo method in children weighing <25 kg at different doses.

Results: In the final model, weight and concomitant use of voriconazole were included as covariates. With the same weight, the relative value of tacrolimus clearance was 1:0.388 in children not taking voriconazole: children taking voriconazole. Compared with children not taking voriconazole, the measured tacrolimus concentrations were all higher in children taking voriconazole (P<0.01); however, these were not corrected by dose or body weight for concentration differences. Thus, we simulated the tacrolimus concentrations using different body weights (5–25 kg) and different dose regimens (0.1–0.8 mg/kg/day) for the same body weight and dose. Tacrolimus concentrations in children taking voriconazole were higher than those in children not taking voriconazole (P<0.01). Also, in children with CGD undergoing HSCT who were not taking voriconazole, the initial dose regimen of 0.5 mg/kg/day was recommended for body weights of 5–10 kg, and 0.4 mg/kg/day was recommended for body weights of 10–25 kg. In children with CGD undergoing HSCT who were taking voriconazole, an initial dose regimen of 0.3 mg/kg/day was recommended for body weights of 5–25 kg.

Conclusions: We established, for the first time, a PPM of tacrolimus in children with CGD undergoing HSCT in which voriconazole significantly increased tacrolimus concentrations. In addition, the initial dose of tacrolimus in children with CGD undergoing HSCT was recommended.

Keywords: Voriconazole; tacrolimus; chronic granulomatous disease; hematopoietic stem cell transplantation

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Introduction

Chronic granulomatous disease (CGD), a rare primary immunodeficiency, affects 1 in 200,000–250,000 individuals (1). It is characterized by susceptibility to typical pathogens and is accompanied by recurrent infections as well as inflammatory and autoimmune complications (2-4). The diagnosis median age is 2.7–3.0 years (4-7), which can result in severe and life-threatening infections in affected children (8).

CGD involves a defect in the phagocytic system. The nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex generates reactive oxygen species (ROS), which are essential for killing pathogenic microorganisms (especially catalase-positive bacteria and fungi) (9). In CGD, the NADPH oxidase complex is dysfunctional, and CGD patients are more likely to suffer from autoimmune disorders, such as liver-function abnormalities, hollow-viscera obstruction, and inflammatory bowel disease, which exhibit multiple-system involvement (2,10,11).

Hematopoietic stem cell transplantation (HSCT) is the first-line treatment for CGD (12-14). HSCT may adjust superoxide generation, making neutrophil function within normal range and improvement in inflammatory progression (14). However, HSCT patients must take tacrolimus, a potent immunosuppressant, for a prolonged period to prevent transplant rejection (15-18). In addition, voriconazole, a second-generation triazole with potent broad-spectrum antifungal activity, is used for prophylaxis against invasive fungal disease (IFD), which is a major cause of morbidity and mortality in pediatric patients after HSCT (19,20). It has been reported that the concomitant use of voriconazole has effects on tacrolimus (21,22). However, the effects of voriconazole on population pharmacokinetics and optimization of the initial dose of tacrolimus in patients with CGD patients undergoing HSCT (especially children) remain unknown. Population pharmacokinetics mainly describes the dispersion degree and distribution of pharmacokinetic parameters from the patient population, explores the influencing factors of pharmacokinetics, and provides strong help for individual drug administration of patients.

In this study, we explored the effects of voriconazole on population pharmacokinetics and optimization of the initial dose of tacrolimus in children with CGD undergoing HSCT. We present the following article in accordance with the MDAR reporting checklist (available at https://dx.doi.org/10.21037/atm-21-4124).

Methods

Ethical approval of the study protocol

This was a retrospective study. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the ethics committee of the Children's Hospital of Fudan University (Shanghai, China) ([2019] 020). Individual consent for this retrospective analysis was waived.

Data collection

The data of children with CGD undergoing HSCT treated with tacrolimus from May 2016 to January 2021 at the Children's Hospital of Fudan University were retrospectively collected.

Tacrolimus concentrations were tested using the Emit® 2000 Tacrolimus Assay (Siemens Healthcare Diagnostics, Newark, NJ, USA) with a range of 2.0–30 ng/mL. In addition, we collected the demographic data (sex, age, body weight), clinical and biochemistry results (albumin, alanine transaminase, aspartate transaminase, creatinine, urea, total protein, total bile acid, direct bilirubin, total bilirubin, hematocrit, hemoglobin, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration), and concurrent use of other medications (caspofungin, ethambutol, glucocorticoids, isoniazid, micafungin, mycophenolic acid, omeprazole, vancomycin, and voriconazole). A partial basic clinical dataset of some children were collected from a previous study (23).

Population pharmacokinetic model (PPM)

PPM mainly describes the dispersion degree and distribution of pharmacokinetic parameters from the patient population, explores the influencing factors of pharmacokinetics, and provides strong help for individual drug administration of patients. The non-linear, mixed-effects modeling software NONMEM v7 (Icon Development Solutions, Ellicott City, MD, USA) and a first-order conditional estimation method with interaction (FOCE-I) approach were used to establish the PPM of tacrolimus in children with CGD undergoing HSCT. The pharmacokinetic parameters included the apparent oral clearance (CL/F), volume of distribution (V/F), and absorption rate constant (K_a), which was fixed at 4.48/h (24,25).

Random-effect model

The inter-individual variability was estimated using Eq. [1]

$$S_i = TV(S) \times \exp(\eta_i) \quad [1]$$

where S_i is the individual parameter value, TV(S) is a typical individual parameter value, and η_i is the symmetrical distribution, which was a random term with a zero mean and variance of ω^2.

The random residual variability was estimated using Eq. [2]:

$$Q_i = IPC_i \times (1+\varepsilon_1) + \varepsilon_2 \quad [2]$$

where O_i is the observed concentration, IPC_i is the individual predicted concentration, and ε_1 and ε_2 are the symmetrical distribution, which were random terms with a zero mean and variance of σ^2.

Covariate model

The pharmacokinetic parameters and body weight were estimated using Eq. [3]

$$C_i = C_{std} \times (X_i / X_{std})^{power} \quad [3]$$

where C_i is the i-th individual parameter, C_{std} is a typical parameter, X_i is the i-th individual body weight, X_{std} is the standard body weight of 70 kg, and power was the allometric coefficient: 0.75 for CL/F and 1 for V/F (26).

The pharmacokinetic parameters and continuous covariates or categorical covariates were estimated using Eqs. [4] and [5]:

$$S_i = TV(S) \times (Cov_i / Cov_{median})^{\theta} \quad [4]$$

$$S_i = TV(S) \times (1+\theta \times Cov_i) \quad [5]$$

where S_i is the individual parameter value, TV(S) is a typical individual parameter value, θ is the parameter to be estimated, Cov_i is the covariate of the i-th individual, and Cov_{median} is the population median for the covariate.

Statistical analysis

Objective function value (OFV) changes were used as the inclusion criteria for covariates; a decrease in the OFV >3.84 (P<0.05) was the inclusion standard, while an increase in the OFV >6.63 (P<0.01) was the exclusion standard.

Model evaluation

The model was evaluated using the following: observations *vs.* population predictions, observations *vs.* individual predictions, conditional weighted residuals (WRES) *vs.* population predictions, conditional WRES *vs.* time after the start of therapy, a visual predictive check (VPC) of the model, and individual plots. In addition, model stability was evaluated using 1,000 bootstraps with different random sampling.

Simulation

Two scenarios were simulated to acquire tacrolimus concentrations: concomitant use of voriconazole or no concomitant use of voriconazole. In each scenario, 1,000 "virtual" children with CGD undergoing HSCT were simulated in five body weight groups (5, 10, 15, 20, and 25 kg) for eight doses (0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, and 0.8 mg/kg/day), which were divided evenly into two doses. In addition, the effects of tacrolimus initial dosage on target concentration (5–20 ng/mL) were explored by Monte Carlo simulations on the basis of final model.

Results

Patient information

Thirty-four children (age range, 2.29±1.89 years) with CGD undergoing HSCT were included in the analyses. The demographic data of patients and drug combinations are shown in *Table 1*. A partial basic clinical dataset of some children were collected from a previous study (23). A total of 293 tacrolimus concentrations were included in the present study, and the mean number of concentrations per patient was 8.6.

Modeling and evaluation

The final models were:

$$CL/F = 35.4 \times (WT/70)^{0.75} \times (1-0.612 \times VRC) \quad [6]$$

$$V/F = 5970 \times (WT/70) \quad [7]$$

where WT denotes body weight, and VRC refers to voriconazole. If a patient took voriconazole, then the VRC value was 1; otherwise the VRC value was 0.

Model evaluation is shown in *Figure 1*. *Figure 1A-1E* display the observations *vs.* population predictions, observations *vs.* individual predictions, conditional WRES *vs.* population predictions, conditional WRES *vs.* time after

Table 1 Demographic data of patients and drug combination (n=34)

Characteristic	Mean ± SD	Median (range)
Gender (boys/girls)	33/1	–
Age (years)	2.29±1.89	1.41 (0.38–9.28)
Weight (kg)	11.17±3.77	10.00 (6.30–24.80)
Albumin (g/L)	36.99±2.97	37.20 (27.70–43.10)
Alanine transaminase (IU/L)	25.36±15.38	21.40 (5.20–70.30)
Aspartate transaminase (IU/L)	41.70±37.39	31.00 (18.90–228.50)
Creatinine (μmol/L)	22.09±9.57	20.00 (14.00–69.00)
Urea (mmol/L)	3.27±1.43	3.15 (1.00–8.50)
Total protein (g/L)	60.91±5.68	61.15 (45.50–74.20)
Total bile acid (μmol/L)	7.34±6.54	5.10 (1.60–31.70)
Direct bilirubin (μmol/L)	2.60±0.97	2.50 (1.00–5.60)
Total bilirubin (μmol/L)	7.94±3.16	7.20 (2.70–17.60)
Hematocrit (%)	26.47±4.08	25.67 (16.60–38.10)
Hemoglobin (g/L)	88.74±13.80	85.50 (57.00–126.00)
Mean corpuscular hemoglobin (pg)	25.61±2.16	25.50 (21.20–31.30)
Mean corpuscular hemoglobin concentration (g/L)	335.24±12.67	333.00 (315.00–374.00)
Number of co-medications		
Caspofungin	21	
Ethambutol	26	
Glucocorticoids	23	
Isoniazid	31	
Micafungin	7	
Mycophenolic acid	10	
Omeprazole	34	
Vancomycin	14	
Voriconazole	32	

the start of therapy, and VPC of the model, respectively. The final model had good performance according to *Figure 1A-1D*. VPC revealed that most of the observed concentrations were within the 95% prediction intervals of the simulation data. Hence, the prediction-corrected concentrations were well served by the final model. *Figure 2* shows the individual plots, and demonstrated that the final model had acceptable predictability.

The final model's parameter estimates and bootstrap validation are shown in *Table 2*. The median values of the 1,000 bootstraps were close to the final model's respective parameter values, showing that the model was accurate and reliable.

Effects of voriconazole on tacrolimus in children with CGD undergoing HSCT

Tacrolimus CL/F in children with CGD undergoing HSCT is shown in *Figure 3*. Under the equal weight, tacrolimus CL/F was 1:0.388 in children not taking voriconazole: children taking voriconazole. Compared with children not taking voriconazole, the measured tacrolimus concentrations

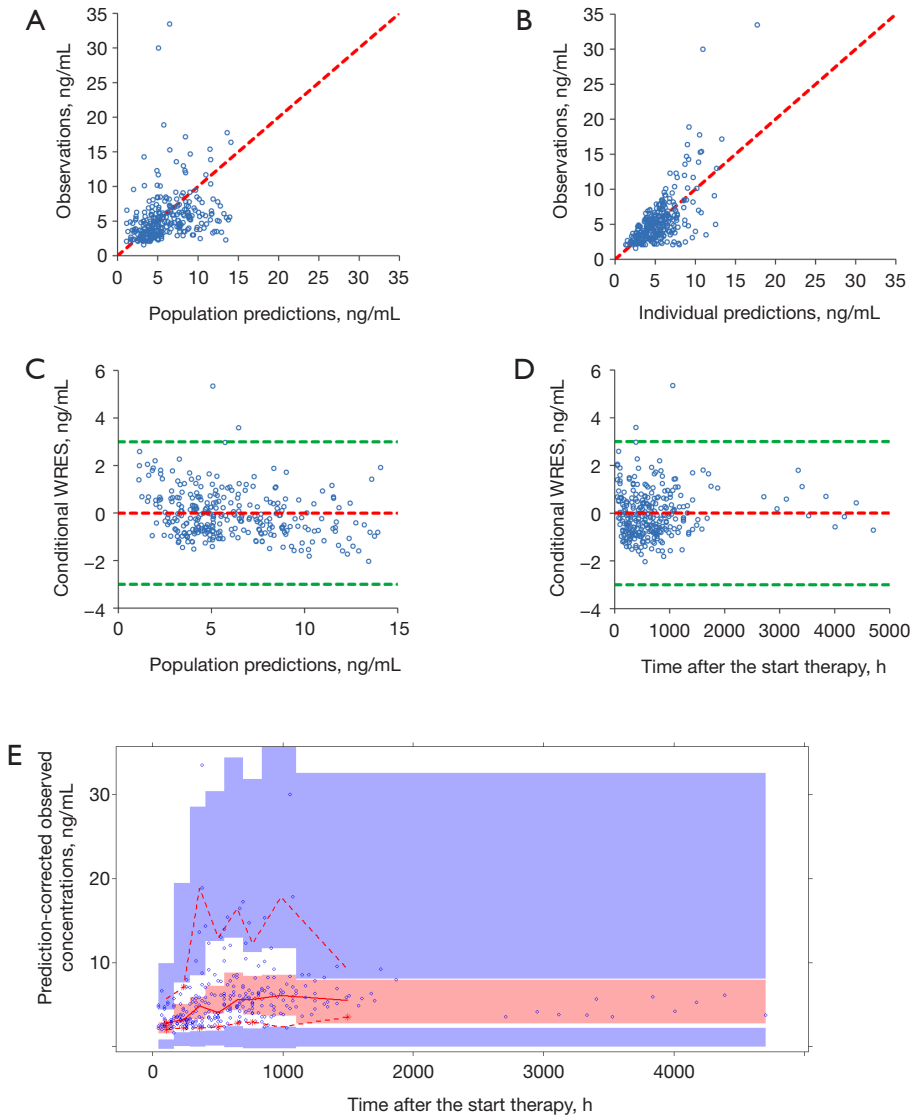

Figure 1 Model evaluation. (A) Observations *vs*. population predictions; (B) observations *vs*. individual predictions; (C) conditional WRES *vs*. population predictions; (D) conditional WRES *vs*. time after the start of therapy; (E) VPC of model. The middle solid line represents the median of the prediction-corrected concentrations. The lower and upper dashed lines are the 2.5th and 97.5th percentiles of the prediction-corrected concentrations. Partial concentration values were collected in previous study (23). WRES, weighted residuals; VPC, visual predictive check.

were all higher in children taking voriconazole (P<0.01); however, these were not corrected by dose or body weight for concentration differences.

Thus, we further simulated the tacrolimus concentrations for different body weights (5–25 kg) and dose regimens (0.1–0.8 mg/kg/day) (*Figure 4*). For an identical body weight and dose, tacrolimus concentrations in children taking voriconazole were higher than those in children not taking voriconazole (P<0.01). These results suggested that voriconazole significantly increased the tacrolimus concentrations in children with CGD undergoing HSCT. Hence, attention should be paid to adjustment of the drug dose to prevent toxicity if these two drugs are combined.

Optimization of the initial dose of tacrolimus in children with CGD undergoing HSCT

Figure 5 shows the probability of achieving the target

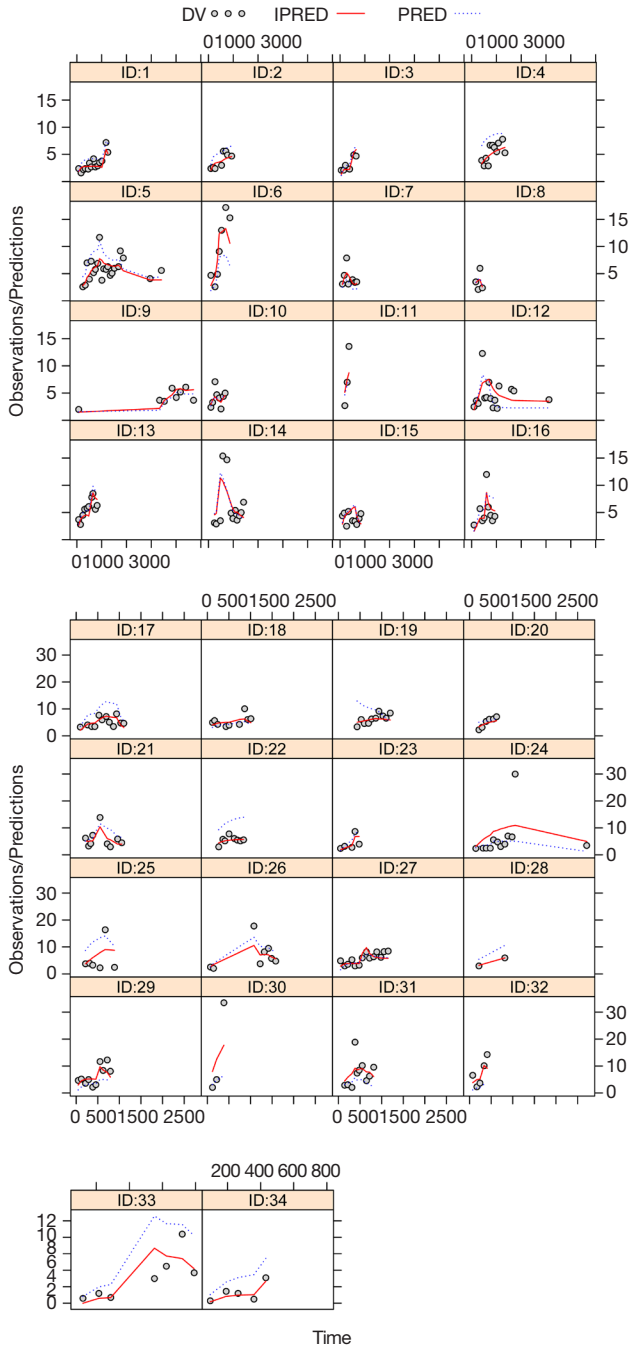

Figure 2 Individual plots. ID, patient ID number; DV, measured concentration value; IPRED, individual predictive value; PRED, population predictive value.

concentrations with different tacrolimus initial dosages. *Figure 5A* shows the data for children with CGD undergoing HSCT who were not taking voriconazole. *Figure 5B* shows the results for children with CGD undergoing HSCT who were administered voriconazole. In children with CGD undergoing HSCT who were not taking voriconazole, an initial dose of 0.5 mg/kg/day was recommended for body weights of 5–10 kg, and 0.4 mg/kg/day was recommended for body weights of 10–25 kg. In children with CGD undergoing HSCT who were taking voriconazole, an initial dose of 0.3 mg/kg/day was recommended for body weights of 5–25 kg.

Discussion

Conventional treatment for CGD is antifungal and antibacterial prophylaxis with azoles and cotrimoxazole, and immunosuppressive therapy (27,28). Prophylaxis leads to a significant reduction in death rates, but infections reportedly occur at a rate of 0.26–0.64 per patient-year (29,30), whose cumulative lifetime risk for aspergillosis of 20–40% being the leading cause of death (27). Martire *et al.* reported the median lifespan of CGD patients receiving conventional treatment to be 30–40 years (29), which was mainly relied on the NADPH oxidase's residual activity (5). Other treatment options, such as long-term use of corticosteroids (which are immunosuppressants), further increase the risk of infections and failure to thrive (27,28).

Fortunately, HSCT can cure CGD with resolution of infections and inflammatory complications (31-35). Additionally, compared with those treated conservatively, the growth and quality of life of transplanted patients are improved (30,36). For example, Arnold *et al.* reported on HSCT in adolescent patients with CGD (37). Tang *et al.* demonstrated that HSCT using unrelated cord blood or unmanipulated haploidentical donors was efficacious against pediatric CGD with inflammatory complications and severe infection (38). Rocha *et al.* showed successful immune reconstitution by means of HSCT in a Colombian patient with CGD (39).

Nevertheless, HSCT has limitations. High-risk patients with ongoing infectious or active inflammatory complications at HSCT initiation have considerable transplant-related mortality (≤38%) (31,32). In addition, Dedieu *et al.* reported that CGD patients undergoing HSCT until 8 years of age showed excellent survival, but young children needed more intense conditioning to avoid graft rejection (27). Therefore, reducing infection while resisting graft-versus-host disease (GVHD) is particularly important (31,40,41).

Tacrolimus is a first-line agent for GVHD prevention

Table 2 Parameter estimates of final model and bootstrap validation

Parameter	Estimate	SE (%)	Bootstrap		Bias (%)
			Median	95% confidence interval	
CL/F (L/h)	35.4	12.2	36.0	[24.2, 45.0]	1.695
V/F (10^2 L)	59.7	25.1	59.2	[29.4, 152.1]	–0.838
Ka (h^{-1})	4.48 (fixed)	–	–	–	–
θ_{VRC}	–0.612	12.9	–0.631	[–0.876, –0.487]	3.105
$\omega_{CL/F}$	0.525	15.2	0.501	[0.003, 0.954]	–4.571
$\omega_{V/F}$	0.825	14.9	0.839	[0.003, 1.149]	1.697
σ_1	0.386	10.1	0.366	[0.003, 0.455]	–5.181
σ_2	0.354	116.4	0.511	[0.010, 3.479]	44.350

95% confidential interval was displayed as the 2.5th and 97.5th percentiles of bootstrap estimates. CL/F, apparent oral clearance (L/h); V/F, apparent volume of distribution (L); Ka, absorption rate constant (h^{-1}); θ_{VRC} was the coefficient of the voriconazole; $\omega_{CL/F}$, 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 ×100%.

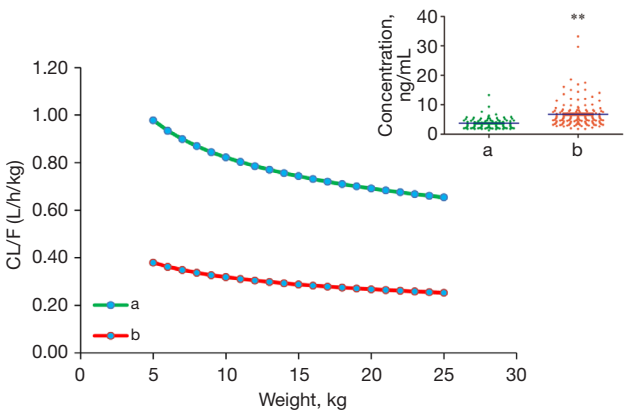

Figure 3 Tacrolimus CL/F in children with CGD undergoing HSCT. a: without voriconazole; b: with voriconazole. **, P<0.01 *vs.* children without voriconazole (measured tacrolimus concentrations). CGD, chronic granulomatous disease; HSCT, hematopoietic stem cell transplantation.

and has been routinely employed to stop rejection of HSCT (15-18). However, tacrolimus has a narrow therapeutic range; the use of high concentrations seems to be related to toxicity, while lower concentrations are related to an acute rejection's increased risk (23). More importantly, some combinations of clinical drugs have been shown to affect the population pharmacokinetic process of tacrolimus *in vivo* (42,43), thereby influencing its efficacy or producing toxicity. Therefore, it is particularly important to study the population pharmacokinetic process of tacrolimus in children with CGD as well as its influencing factors.

In the present study, 34 patients were enrolled, which were enough for population pharmacokinetics. For example, in Yonwises *et al.*'s study, population pharmacokinetics of meropenem in critically ill infant patients, 35 patients were enrolled (44). In Nassar-Sheikh Rashid *et al.*'s study, population pharmacokinetics of infliximab in children with juvenile idiopathic arthritis, 27 patients were enrolled (45). In Hao *et al.*'s study, population pharmacokinetics of tacrolimus in children with nephrotic syndrome, 28 patients were enrolled (46). In Zhao *et al.*'s study, population pharmacokinetics and bayesian estimator of mycophenolic acid in children with idiopathic nephrotic syndrome, 23 patients were enrolled (47).

In addition, body weight and concomitant use of voriconazole were included as covariates. Voriconazole is used for prophylaxis against IFD, which is a major cause of morbidity and mortality in pediatric patients after HSCT (19,20). With the same body weight, we observed that the relative value of CL/F for tacrolimus was 1:0.388 in children not taking voriconazole: children taking voriconazole. Also, compared with children not taking voriconazole, the measured tacrolimus concentrations were all higher in children who were taking voriconazole; however, these were not corrected by dose or body weight for concentration differences. Thus, we further simulated the tacrolimus concentrations for different body weights and doses. Under an identical body weight and dose, tacrolimus concentrations in children taking voriconazole were higher

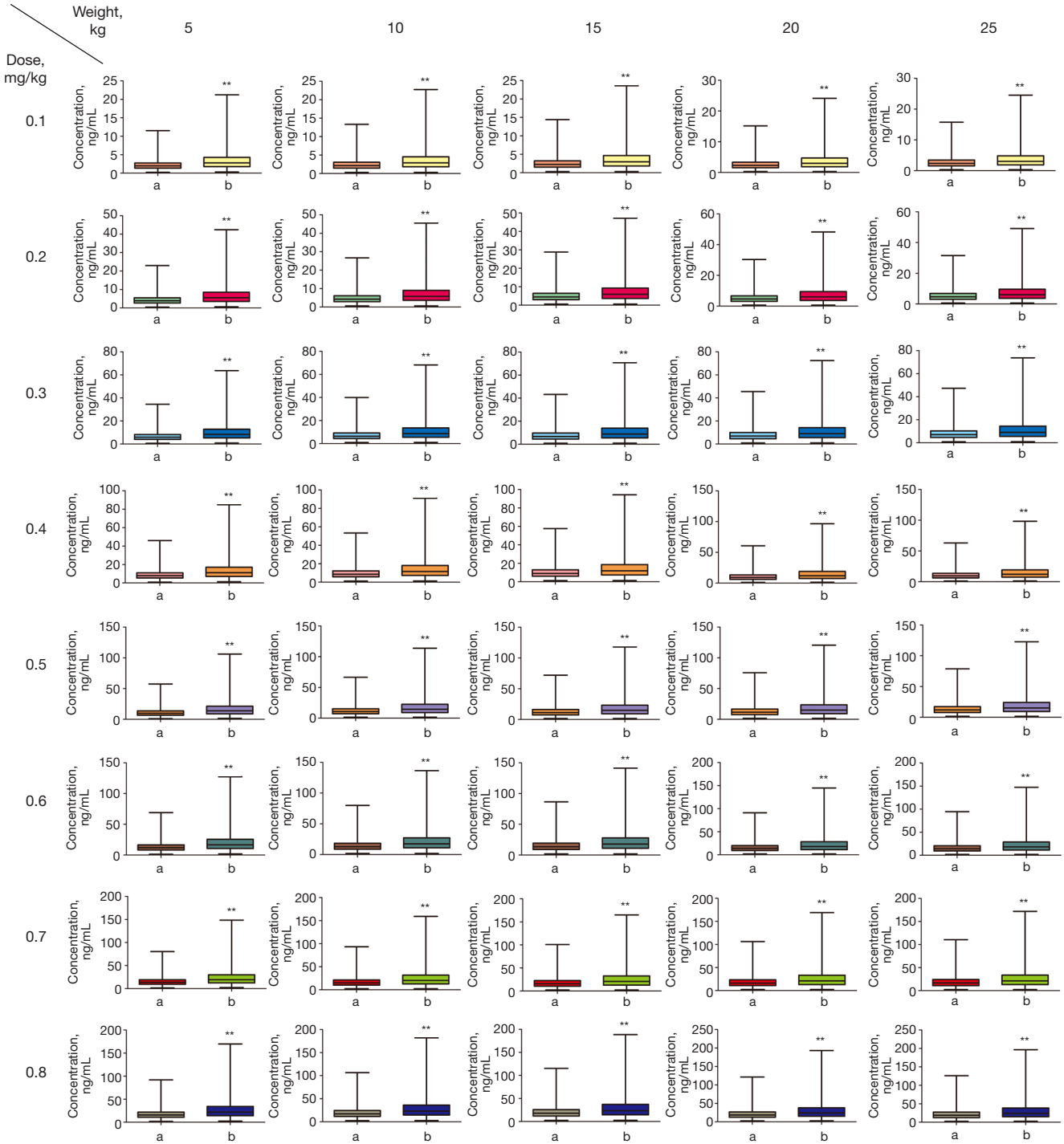

Figure 4 Effects of voriconazole on tacrolimus concentrations. a: without voriconazole; b: with voriconazole. **, P<0.01 *vs.* children without voriconazole.

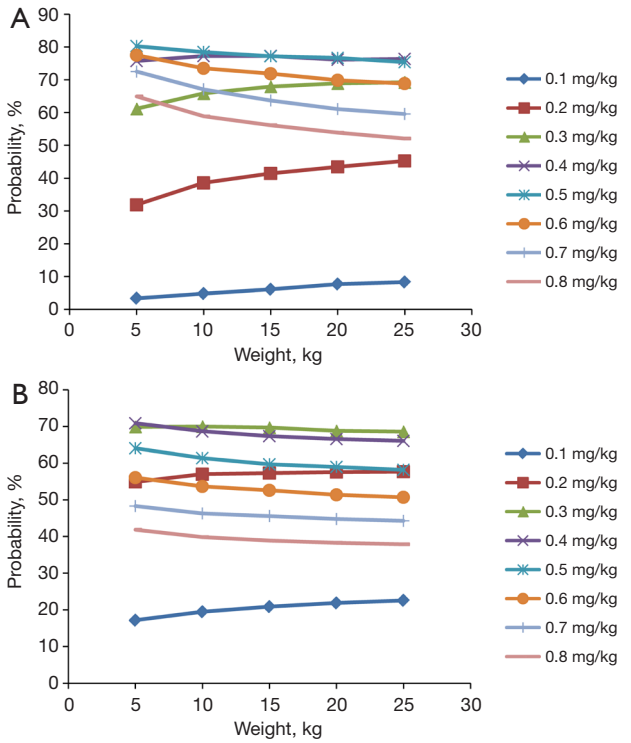

Figure 5 Probability of reaching tacrolimus concentrations. (A) CGD children undergoing HSCT without voriconazole; (B) CGD children undergoing HSCT with voriconazole. CGD, chronic granulomatous disease; HSCT, hematopoietic stem cell transplantation.

than those in children not taking voriconazole. In addition, in children with CGD undergoing HSCT who were not taking voriconazole, an initial dose of 0.5 mg/kg/day was recommended for body weights of 5–10 kg, and 0.4 mg/kg/day was recommended for children of body weight 10–25 kg. In children with CGD undergoing HSCT who were taking voriconazole, an initial dose of 0.3 mg/kg/day was recommended for body weights of 5–25 kg. Hence, the tacrolimus dose should be reduced if it is combined with voriconazole in children with CGD undergoing HSCT.

Our study had limitations: on the one hand, almost all of the children in the study cohort were boys. However, according to population pharmacokinetic studies of tacrolimus in pediatric patients, sex does not have a significant influence on the CL/F of tacrolimus (46,48). Therefore, the sex distribution in our study cohort had little influence on our conclusions. On the other hand, this was a retrospective study and some data were not available. For example, ROS is essential for killing pathogenic microorganisms in the treatment but without the concentration of ROS in serum in the retrospective analysis. These need be refined in future prospective studies.

Conclusions

We established, for the first time, a PPM of tacrolimus in children with CGD undergoing HSCT in which voriconazole use significantly increased tacrolimus concentrations. In addition, the initial dose of tacrolimus in children with CGD undergoing HSCT was recommended.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://dx.doi.org/10.21037/atm-21-4124

Data Sharing Statement: Available at https://dx.doi.org/10.21037/atm-21-4124

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-4124). 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. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the ethics committee of the Children's Hospital of Fudan University (Shanghai, China) ([2019] 020). Individual consent for this retrospective analysis was waived.

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