Initial dose recommendation for sirolimus in paediatric kaposiform haemangioendothelioma patients based on population pharmacokinetics and pharmacogenomics

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Abstract

Objective: Sirolimus has been used to treat paediatric kaposiform haemangioendothelioma patients. However, there is considerable pharmacokinetic variability among individuals, and it is difficult to develop an initial dosing regimen. The goal of the present study is to recommend an initial sirolimus dose in paediatric kaposiform haemangioendothelioma patients based on population pharmacokinetics and pharmacogenomics.

Methods: This was a retrospective clinical study. A population pharmacokinetics model was established and population characteristics, laboratory test results, drug combinations, and pharmacogenomics were considered as potential covariates. The Monte Carlo method was used to simulate the optimal initial dosage.

Results: The final covariates that affect sirolimus clearance include weight and the CYP3A5 genotype. The initial dosage of sirolimus for individuals with CYP3A5*3/*3 was 0.20 mg/kg split into two doses for 5 to 60 kg body weight. For individuals with CYP3A5*1, the initial dose was 0.23 mg/kg split into two doses for 5 to 30 kg body weight and 0.20 mg/kg split into two doses for 30 to 60 kg body weight.

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Conclusion: The recommendation for the initial sirolimus dose in paediatric kaposiform haemangioendothelioma patients was based on population pharmacokinetics and pharmacogenomics. This study may provide practical value for sirolimus clinical use in paediatric kaposiform haemangioendothelioma patients.

Keywords
Initial dose recommendation, sirolimus, paediatric kaposiform haemangioendothelioma, population pharmacokinetics, pharmacogenomics, CYP3A5 genotype

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Introduction
Sirolimus is a macrolide compound that is produced by Streptomyces hygroscopicus, and it was has mainly been used as an anti-rejection medication after solid organ transplantation.1–5 Recently, sirolimus has been used to treat paediatric kaposiform hemangioendothelioma.6–10 However, with considerable pharmacokinetic variability in different individuals, it is difficult to develop an initial dosing regimen.11,12 We previously built a sirolimus population pharmacokinetic model without pharmacogenomics and, unfortunately, this model could not accurately recommend the initial sirolimus dose in paediatric kaposiform haemangioendothelioma patients.13 That is mainly because sirolimus is metabolised by cytochrome P450 3A enzymes (CYP3A), which are located in the liver and gut mucosa.14–16 Additionally, sirolimus is also the substrate of P-glycoprotein,17 which is encoded by the multidrug resistance 1 (MDR1 or ABCB1) gene.18 Therefore, it is particularly important to explore the effect of these gene polymorphisms on the sirolimus clearance rate for dose recommendation. The goal of the present study was to recommend the initial sirolimus dose in paediatric kaposiform haemangioendothelioma patients based on population pharmacokinetics and pharmacogenomics.

Methods
Study design
This is a retrospective clinical study. Chinese paediatric kaposiform haemangioendothelioma patients who were treated with sirolimus from March 2016 to July 2019 at the Children’s Hospital of Fudan University (Shanghai, China) were enrolled. Population characteristics, laboratory test results, and drug combinations were collected from medical reports and therapeutic drug monitoring. Partial basic clinical information data from some patients were collected in a previous study.13 The rest of the discarded blood samples from therapeutic drug monitoring were stored and used for the pharmacogenomics analysis. The study was retrospective, and blood samples for the pharmacogenomics analysis were leftover or discarded specimens from therapeutic drug monitoring. The analysis was approved by the ethics committee at our hospital without the need for written informed consent. The present study was approved by the Research Ethics Committee at the Children’s Hospital of Fudan University (Ethical code: [2019] 019; Shanghai, China; 27 February 2019).

Sirolimus administration
Sirolimus was orally administered and the dose range was 0.16 to 1.5 mg/day.
Sirolimus dose adjustment was based on efficacy, adverse effects, and the therapeutic drug monitoring concentration. All blood concentrations were collected before the subsequent administration and, therefore, these concentrations used in the present study were trough concentrations. Sirolimus concentrations were tested using the Emit 2000 Sirolimus Assay (Siemens Healthcare Diagnostics Inc., Newark, NJ, USA) with a linear response range of 3.5 to 30 ng/ml.

**Pharmacogenomics detection**

Pharmacogenomics analysis was performed by Admera Health (Suzhou, China) using PGxOne® 160 with the Illumina X10 Sequencing System (Illumina Inc., San Diego, CA, USA). STATA computer software (version 12.0, StataCorp LP, College Station, TX, USA) was used to test the Hardy–Weinberg equilibrium, and $P<0.05$ was considered to be statistically significant.

**Population pharmacokinetics model**

The non-linear mixed-effects modelling software (NONMEM, edition 7, ICON Development Solutions, Ellicott, MD, USA) was used to develop population pharmacokinetic model. The pharmacokinetic parameters included apparent oral clearance ($CL/F$, where $CL$ is clearance and $F$ is bioavailability), volume of distribution ($V/F$, where $V$ is the volume of distribution and $F$ is bioavailability), and the absorption rate constant ($Ka$), which was fixed at 0.485/hour.$^{13}$

Equation (i) shows the inter-individual variability, as follows:

$$C = T(C) \times \exp(\eta)$$

where $C$ and $T(C)$ represent the individual parameter value and the typical individual parameter value, respectively, and $\eta$ represents symmetrical distribution, which was a random term with a mean of zero and a variance of $\omega^2$.

Equation (ii) shows the random residual variability, as follows:

$$C_{ij} = (1 + \varepsilon_i) \times Y_{ij}$$

where $C_{ij}$ and $Y_{ij}$ are the observed i-th concentration in the j-th individual and the individual predicted i-th concentration in the j-th individual, respectively, and $\varepsilon_i$ represents symmetrical distribution, which was a random term with a mean of zero and a variance of $\sigma^2$.

**Covariate model**

Equation (iii) shows the relationship between weight and pharmacokinetic parameters, as follows:

$$C_i = C_{std} \times \left(\frac{WT_i}{WT_{std}}\right)^{\text{index}}$$

where $C_i$ and $WT_i$ are the i-th individual pharmacokinetic parameter and the i-th individual weight, $C_{std}$ is the typical individual parameter of $WT_{std}$ (the standard weight of 70 kg), and the index is the allometric coefficient 0.75 for the CL/F and 1 for the V/F.$^{19,20}$

Equations (iv) and (v) showed continuous covariates and categorical covariates, respectively, as follows:

$$C_i = T(C) \times \left(\frac{\text{Cov}_i}{\text{Cov}_{\text{median}}}\right)^\theta$$

$$C_i = T(C) \times (1 - \theta \times \text{Cov}_i)$$

where $C_i$ and $T(C)$ represent the individual parameter value and the typical individual parameter value, respectively, $\theta$ represents the parameter to be estimated, $\text{Cov}_{\text{median}}$ is the population median for the covariate, and $\text{Cov}_i$ is the covariate of the i-th individual.
The potential covariates included gender, age, weight, albumin, alanine transaminase, aspartate transaminase, creatinine, urea, total protein, total bile acid, direct bilirubin, total bilirubin, haematocrit, haemoglobin, co-medications (phenobarbitone and omeprazole), and pharmacogenetics. Objective function value (OFV) changes were identified using covariate inclusion, and a decrease in OFV $>3.84$ ($P<0.05$) and an increase in OFV $>6.64$ ($P<0.01$) were considered to be sufficient for significance in the final model.\(^{21,22}\)

**Model evaluation**

The results of bootstrapping with 1000 repetitions with different random sampling, medians, and 2.5th to 97.5th percentiles, were used to evaluate the final model pharmacokinetic parameters. Goodness-of-fit plots and prediction-corrected visual predictive check plots were used to evaluate the final model.\(^{23}\)

**Simulation**

The simulation was made up of the following two parts: (I) individuals who carry the $CYP3A5^*3/*3$ allele; and (II) individuals who carry the $CYP3A5^*1$ allele. Seven weight groups (5, 10, 20, 30, 40, 50, and 60 kg) were simulated using 1000 virtual patients with different initial dosages. Based on previously published reports, the sirolimus target concentration in paediatric kaposiform haemangioendothelioma patients was fixed at 10 to 15 ng/ml.\(^{24,25}\)

**Results**

**Patients’ data**

There were 14 patients enrolled in the study, with an average age of $1.53 \pm 1.40$ years. Nine patients were male and five were female. Other demographic information on the patients and drug combinations are shown in Table 1. Partial basic clinical information from some patients that were collected in a previous study\(^{13}\) and the pharmacogenetics analysis and Hardy–Weinberg equilibrium are shown in Table 2. Table 2 also shows the Pearson chi-squared test result of each gene was $>0.05$, which meets the Hardy–Weinberg equilibrium.

**Modelling and validation**

The final model was as follows:

\[
\frac{CL}{F} = 7.55 \times \left(\frac{WT}{70}\right)^{0.75} \times (1 - (-0.999) \times CYP3A5) \tag{vi}
\]

\[
\frac{V}{F} = 1840 \times \left(\frac{WT}{70}\right) \tag{vii}
\]

where WT and $CYP3A5$ represent weight and $CYP3A5$ genotype, respectively. For individuals who carry the

| Table 1. Demographic data of patients and drug combinations. |
|------------------------------------------------------------|
| Characteristic                                      | Mean $\pm$ SD |
|------------------------------------------------------------|
| Gender (male/female)                                      | 9/5           |
| Age (years)                                               | $1.53 \pm 1.40$ |
| Weight (kg)                                               | $8.87 \pm 4.12$ |
| Albumin (g/l)                                             | $40.41 \pm 2.86$ |
| Alanine transaminase (IU/l)                              | $29.96 \pm 18.92$ |
| Aspartate transaminase (IU/l)                            | $44.65 \pm 14.42$ |
| Creatinine ($\mu$mol/l)                                   | $23.52 \pm 5.38$ |
| Urea (mmol/l)                                             | $17.57 \pm 46.25$ |
| Total protein (g/l)                                       | $60.71 \pm 3.92$ |
| Total bile acids ($\mu$mol/l)                             | $5.36 \pm 3.11$ |
| Direct bilirubin ($\mu$mol/l)                             | $1.89 \pm 3.02$ |
| Total bilirubin ($\mu$mol/l)                              | $5.35 \pm 3.76$ |
| Haematocrit (%)                                           | $33.72 \pm 2.77$ |
| Haemoglobin (g/l)                                         | $110.65 \pm 9.63$ |
| Number of co-medications                                  | 1            |
| Phenobarbitone                                            | 1            |
| Omeprazole                                                 | 2            |

SD, standard deviation.
CYP3A5*3/*3 allele, the value of CYP3A5 is 0, and for individuals who carry the CYP3A5*1 allele, the value of CYP3A5 is 1.

Figure 1 shows the goodness-of-fit plots for the final population model (goodness-of-fit plots for the base population model are shown in Supplementary Figure 1S), and Figure 2 showed the visual predictive check plots for the final model, indicating the predictive power of the final model. As shown in Table 3, the median values from bootstrapping were similar to the values estimated in the final model, and the absolute value of all the bias was <12%, showing that the final model was dependable.

### Simulation

As shown in Figure 3, with the same body weight, the sirolimus clearance rates in individuals with CYP3A5*3/*3 and CYP3A5*1 were 1:1.999, and with the same CYP3A5 genotype, low body-weight individuals had a higher sirolimus clearance rate than those with a high body weight. In Figure 4, the 95% confidence interval of the simulation from an initial dose of 0.20 mg/kg that was split into two doses was between nearly 10 and 15 ng/ml of the target concentrations in CYP3A5*3/*3 individuals. As shown in Figure 5, in individuals with CYP3A5*1, for a weight of 5 to 30 kg, the initial dose

| Table 2. Pharmacogenetics analysis and Hardy–Weinberg equilibrium. |
|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
|                         |                         |                          |                          |                          |                          |
|                         | Gene                    | Variation                | Genotype                 | Frequency                | %                         | P value*                  |
| ABCB1                   | rs1045642               | A/A                      | 3                        | 21.43                    | N.S.                     |
|                         |                         | A/G                      | 8                        | 57.14                    |                          |
|                         |                         | G/G                      | 3                        | 21.43                    |                          |
| ABCC4                   | rs1751034               | C/C                      | 2                        | 14.28                    | N.S.                     |
|                         |                         | C/T                      | 6                        | 42.86                    |                          |
|                         |                         | T/T                      | 6                        | 42.86                    |                          |
| ABCC8                   | rs757110                | A/A                      | 2                        | 14.29                    | N.S.                     |
|                         |                         | A/C                      | 9                        | 64.29                    |                          |
|                         |                         | C/C                      | 3                        | 21.42                    |                          |
| CYP2C19                 |                         | *1/*1                    | 7                        | 50.00                    | –                        |
|                         |                         | *1/*2                    | 4                        | 28.57                    |                          |
|                         |                         | *2/*2                    | 3                        | 21.43                    |                          |
| CYP3A4                  |                         | *1A/*1A                  | 6                        | 42.86                    | –                        |
|                         |                         | *1A/*1G                  | 6                        | 42.86                    |                          |
|                         |                         | *1B/*1B                  | 1                        | 7.14                     |                          |
|                         |                         | *1G/*1G                  | 1                        | 7.14                     |                          |
| CYP3A5                  |                         | *1/*1                    | 1                        | 7.14                     | –                        |
|                         |                         | *1/*3                    | 6                        | 42.86                    |                          |
|                         |                         | *3/*3                    | 7                        | 50.00                    |                          |
| UGT1A1                  |                         | *1/*1                    | 7                        | 50.00                    | –                        |
|                         |                         | *1/*6                    | 4                        | 28.57                    |                          |
|                         |                         | *28/*80                  | 2                        | 14.29                    |                          |
|                         |                         | *28/*28/*80              | 1                        | 7.14                     |                          |
| UGT1A8                  | rs1042597               | C/C                      | 2                        | 14.29                    | N.S.                     |
|                         |                         | C/G                      | 9                        | 64.29                    |                          |
|                         |                         | G/G                      | 3                        | 21.42                    |                          |

*Pearson Chi-squared test.

N.S., not significant; –, no data.
of 0.23 mg/kg was split into two doses, which obtained the optimal probability to achieve the target concentrations. For a body weight of 30 to 60 kg, 0.20 mg/kg was split into two doses to obtain the optimal probability to achieve the target concentrations.

**Discussion**

The incidence of kaposiform haemangioendothelioma, a rare kind of vascular tumour, is estimated to be 0.07/100,000 children per year.\(^\text{26}\) It is associated with some life-threatening complications such as airway obstruction, severe infection, and characteristic consumptive coagulopathy, as well as Kasabach–Merritt phenomenon.\(^\text{26,27}\) Thus, a treatment for kaposiform haemangioendothelioma is required.

Fortunately, sirolimus, the prototypical inhibitor of the mammalian target of rapamycin (mTOR), plays an important role in conditions involving disorders of the mTOR cell signalling pathway,\(^\text{28}\) and it also has substantial antitumor activity.\(^\text{29}\)
Figure 2. Prediction-corrected visual predictive check for the final model. The 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, respectively. Partial concentration values were collected in a previous study.\textsuperscript{13}

Table 3. Parameter estimates of the final model and bootstrap validation.

| Parameter       | Estimate | SE (%) | Median | 95% Confidence interval | Bias (%) |
|-----------------|----------|--------|--------|-------------------------|----------|
| CL/F (L/hour)   | 7.55     | 15.2   | 7.42   | [3.68, 10.10]           | −1.72    |
| V/F (L)         | 1840     | 12.7   | 1860   | [31, 2190]              | 1.09     |
| Ka (hour\(^{-1}\)) | 0.485 (fixed) | −     | −      | −                       | −        |
| \(\theta_{CYP3A5}\) | −0.999  | 40.3   | −1.000 | [−1.985, −0.255]        | 0.10     |
| \(\omega_{CL/F}\) | 0.348   | 17.0   | 0.307  | [0.102, 0.423]          | −11.78   |
| \(\sigma_1\)   | 0.390    | 7.3    | 0.386  | [0.327, 0.448]          | −1.03    |

The 95% confidence interval was displayed as the 2.5th, 97.5th percentile of the bootstrap estimates. CL/F, apparent oral clearance (L/hour); V/F, apparent volume of distribution (L); Ka, absorption rate constant (hour\(^{-1}\)); \(\theta_{CYP3A5}\), the coefficient of CYP3A5 genotype; \(\omega_{CL/F}\), inter-individual variability of CL/F; \(\sigma_1\), residual variability, proportional error; Bias, prediction error, Bias = (Median − Estimate)/Estimate \times 100%; −, no data.
For example, sirolimus has been administered to patients after liver transplant, kidney transplant, heart transplant, lung transplant, hematopoietic stem cell transplant, neurofibromatosis type 1, tuberous sclerosis complex, and others. Sirolimus has also been widely used to treat paediatric kaposiform haemangioendothelioma. However, with considerable pharmacokinetic variability in between individuals, it is difficult to determine an initial dosing regimen in paediatric kaposiform haemangioendothelioma patients. Thus, the present study aimed to recommend the initial dose of sirolimus in paediatric kaposiform haemangioendothelioma patients based on population pharmacokinetics and pharmacogenomics.

Figure 3. CL/F of sirolimus in paediatric kaposiform haemangioendothelioma patients. (a) Individuals with CYP3A5*3/*3; (b) individuals with CYP3A5*1. CL, clearance; F, bioavailability.

Figure 4. Initial dose recommendation for sirolimus in paediatric kaposiform haemangioendothelioma patients with CYP3A5*3/*3.
In our study, we found the final covariates that affect sirolimus clearance, which were weight and the \textit{CYP3A5} genotype. The sirolimus clearance rates in individuals with \textit{CYP3A5*3/*3} or \textit{CYP3A5*1} were 1:1.999 at the same body weight. Additionally, in patients with the same genotype \textit{CYP3A5}, patients with a low body weight had a higher sirolimus clearance rate than those with a high body weight, meaning that children with a lighter weight need larger doses than heavier children. We also simulated different initial dosing regimens in different body weights and \textit{CYP3A5} genotypes, and the sirolimus target concentrations were fixed to 10 to 15 ng/ml, in accordance with previous publications.\textsuperscript{24,25} In individuals with \textit{CYP3A5*3/*3}, the initial dose recommendation for sirolimus, 0.20 mg/kg split into two doses, was for a body weight of 5 to 60 kg and the 95% confidence interval of the simulated sirolimus concentrations was between almost 10 and 15 ng/ml. Thus, the initial dose recommendation for sirolimus in pediatric kaposiform haemangioendothelioma patients with \textit{CYP3A5*3/*3} was 0.20 mg/kg split into two doses. The same initial dose (0.20 mg/kg split into two doses) for individuals with \textit{CYP3A5*1} who weighted 30 to 60 kg, can obtain the optimal target concentrations within the treatment window. Patients who carry \textit{CYP3A5*1} with a weight of 5 to 30 kg need a larger dose, and based on the simulation, we recommend 0.23 mg/kg split into two doses. Additionally, the probability of achieving the target concentrations from the recommended initial dosing regimens (0.23 mg/kg split into two doses for a body weight of 5 to 30 kg and 0.20 mg/kg split into two doses for a body weight of 30 to 60 kg) in individuals with \textit{CYP3A5*1} were all above 80%.

As a retrospective clinical study, this study has some limitations. Because of the low incidence of the pediatric kaposiform haemangioendothelioma in children, collecting patient data was extremely difficult,
which was why there was a small number of patients in this study. Additionally, the present study had a poor fit and large confidence intervals, which may be because our modelling data came from a real-world dataset with a sparse sampling schedule, and it may not be sufficiently intensive. Therefore, a large-scale, prospective, intensive sampling-point study is needed to verify our results in the future.

In conclusion, these are the first recommendations for the initial sirolimus dose in paediatric kaposiform haemangioendothelioma patients based on population pharmacokinetics and pharmacogenomics. The present study may provide practical value for sirolimus clinical use in paediatric kaposiform haemangioendothelioma patients.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

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References
1. Asleh R, Briasoulis A, Kremers WK, et al. Long-term sirolimus for primary immunosuppression in heart transplant recipients. J Am Coll Cardiol 2018; 71: 636–650. DOI: 10.1016/j.jacc.2017.12.005.
2. Engle JA and Fair C. Sirolimus and mirabegron interaction in a hematopoietic cell transplant patient. J Oncol Pharm Pract 2018; 24: 627–631. DOI: 10.1177/1078155217726161.
3. Kieu V, Jhangiani K, Dadwal S, et al. Effect of isavuconazole on tacrolimus and sirolimus serum concentrations in allogeneic hematopoietic stem cell transplant patients: a drug-drug interaction study. Transpl Infect Dis 2019; 21: e13007. DOI: 10.1111/tid.13007.
4. Kikuchi M, Shigeta K, Tanaka M, et al. Estimation of blood sirolimus concentration based on tacrolimus concentration/dose normalized by body weight ratio in lung transplant patients. Ther Drug Monit 2019; 41: 615–619. DOI: 10.1097/FTD.0000000000000649.
5. Zhang ZH, Li LX, Li P, et al. Sirolimus in liver transplant recipients with hepatocellular carcinoma: an updated meta-analysis. J Invest Surg 2019; 32: 632–641. DOI: 10.1080/08941939.2018.1447053.
6. Blatt J, Stavas J, Moats-Staats B, et al. Treatment of childhood kaposiform hemangioendothelioma with sirolimus. Pediatr Blood Cancer 2010; 55: 1396–1398. DOI: 10.1002/pbc.22766.
7. Jahnel J, Lackner H, Reiterer F, et al. Kaposiform hemangioendothelioma with Kasabach–Merritt phenomenon: from vincristine to sirolimus. Klin Pediatr 2012; 224: 395–397. DOI: 10.1055/s-0032-1323823.
8. Ji Y, Chen S, Xiang B, et al. Sirolimus for the treatment of progressive kaposiform hemangioendothelioma: a multicenter retrospective study. Int J Cancer 2017; 141: 848–855. DOI: 10.1002/ijc.30775.
9. Kai L, Wang Z, Yao W, et al. Sirolimus, a promising treatment for refractory Kaposiform hemangioendothelioma. J Cancer Res Clin Oncol 2014; 140: 471–476. DOI: 10.1007/s00432-013-1549-3.
10. Reichel A, Hamm H, Wiegering V, et al. Kaposiform hemangioendothelioma with Kasabach–Merritt syndrome: successful treatment with sirolimus. J Dtsch Dermatol Ges 2017; 15: 329–331. DOI: 10.1111/ddg.12987.
11. Zimmerman JJ and Kahan BD. Pharmacokinetics of sirolimus in stable renal transplant patients after multiple oral
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dose administration. *J Clin Pharmacol* 1997; 37: 405–415.
12. MacDonald A, Scarola J, Burke JT, et al. Clinical pharmacokinetics and therapeutic
drug monitoring of sirolimus. *Clin Ther* 2000; 22: B101–B121.
13. Wang DD, Chen X and Li ZP. Population
pharmacokinetics of sirolimus in pediatric
patients with kaposiform hemangioendothe-
lioma: a retrospective study. *Oncol Lett*
2019; 18: 2412–2419. https://doi.org/10.
3892/ol.2019.10562. DOI: 10.3892/ol.2019.10562.
14. Lampen A, Zhang Y, Hackbarth I, et al. Metabolism and transport of the macrolide
immunosuppressant sirolimus in the small
intestine. *J Pharmaco Exp Ther* 1998; 285:
1104–1112.
15. Paine MF, Leung LY and Watkins PB. New
insights into drug absorption: studies with
sirolimus. *Ther Drug Monit* 2004; 26:
463–467.
16. Sattler M, Guengerich FP, Yun CH, et al. Cytochrome P-450 3A enzymes are respon-
sible for biotransformation of FK506 and
rapamycin in man and rat. *Drug Metab
Dispos* 1992; 20: 753–761.
17. Crowe A and Lemaire M. In vitro and in
situ absorption of SDZ-RAD using a
human intestinal cell line (Caco-2) and a
single pass perfusion model in rats: compar-
ison with rapamycin. *Pharm Res* 1998; 15:
1666–1672.
18. Masuda S and Inui K. An up-date review on
individualized dosage adjustment of calcine-
urin inhibitors in organ transplant
patients. *Pharmac Ther* 2006; 112:
184–198. DOI: 10.1016/j.pharmthera.
2006.04.006.
19. Anderson BJ and Holford NH. Mechanism-
based concepts of size and maturity in phar-
macokinetics. *Annu Rev Pharmacol Toxicol*
2008; 48: 303–332. DOI: 10.1146/annurev.
pharmtox.48.113006.094708.
20. Anderson BJ and Holford NH. Tips and
traps analyzing pediatric PK data. *Paediatr
Anaesth* 2011; 21: 222–237. DOI: 10.1111/
j.1460-9592.2011.03536.x.
21. Wang DD, Chen X and Li ZP. Wuzhi cap-
sule and haemoglobin influence tacrolimus
elimination in paediatric kidney transplanta-
tion patients in a population pharmacokinetics analysis: a retrospective
study. *J Clin Pharm Ther* 2019; 44:
611–617. DOI: 10.1111/jcpt.12828.
22. Wang DD, Chen X, Fu M, et al. Model
extrapolation to a real-world dataset: evalua-
tion of tacrolimus population pharmacoki-
netics and drug interaction in pediatric liver
transplantation patients. *Xenobiotica* 2020;
50; 371–379. DOI: 10.1080/
00498254.2019.1631505.
23. Wang D, Chen X, Xu H, et al. Population
pharmacokinetics and dosing regimen opti-
misation of tacrolimus in Chinese pediatric
hematopoietic stem cell transplantation
patients. *Xenobiotica* 2020; 50: 178–185.
DOI: 10.1080/00498254.2019.1601791.
24. Adams DM, Trenor CC 3rd, Hammill AM,
et al. Efficacy and safety of sirolimus in the
treatment of complicated vascular anomal-
ies. *Pediatrics* 2016; 137: e20153257. DOI:
10.1542/peds.2015-3257.
25. Mizuno T, Fukuda T, Emoto C, et al.
Developmental pharmacokinetics of siroli-
mus: implications for precision dosing in
neonates and infants with complicated vas-
cular anomalies. *Pediatr Blood Cancer* 2017;
64: e26470. DOI: 10.1002/pbc.26470.
26. Croteau SE, Liang MG, Kozakewich HP,
et al. Kaposiform hemangioendothelioma:
atypical features and risks of Kasabach–
Merritt phenomenon in 107 referrals. *J Pediatr*
2013; 162: 142–147. DOI: 10.1016/j.
pedsurg.2012.06.044.
27. Iwami D, Shimaoka S, Mochizuki I, et al.
Kaposiform hemangioendothelioma of the
mediastinum in a 7-month-old boy: a case
report. *J Pediatr Surg* 2006; 41: 1486–1488.
DOI: 10.1016/j.jpedsurg.2006.04.013.
28. Fasolo A and Sessa C. Current and future
directions in mammalian target of rapamy-
cin inhibitors development. *Expert Opin
Investig Drugs* 2011; 20: 381–394. DOI:
10.1517/13543784.2011.541154.
29. Wu K, Cohen EE, House LK, et al. Nonlinear population pharmacokinetics of
sirolimus in patients with advanced cancer.
*CPT Pharmacometrics Syst Pharmacol* 2012;
1: e17. DOI: 10.1038/psp.2012.18.
30. Alfano G, Fontana F, Mori G, et al. Antiviral activity of sirolimus in an HIV-
positive kidney transplant recipient. *Int J STD AIDS* 2019; 30: 919–922. DOI: 10.1177/0956462419839520.

31. Rossano JW, Jefferies JL, Pahl E, et al. Use of sirolimus in pediatric heart transplant patients: a multi-institutional study from the Pediatric Heart Transplant Study Group. *J Heart Lung Transplant* 2017; 36: 427–433. DOI: 10.1016/j.healun.2016.09.009.

32. Scott JR, Courter JD, Saldana SN, et al. Population pharmacokinetics of sirolimus in pediatric patients with neurofibromatosis type 1. *Ther Drug Monit* 2013; 35: 332–337. DOI: 10.1097/FTD.0b013e318286dd3f.

33. Lee YI, Lee JH, Kim DY, et al. Comparative effects of topical 0.2% sirolimus for angiofibromas in adults and pediatric patients with tuberous sclerosis complex. *Dermatology* 2018; 234: 13–22. DOI: 10.1159/000489089.