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# Choosing the right dose of tacrolimus

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## ABSTRACT

Choosing the right dose of tacrolimus 'adapted to each individual patient' is a central question after transplantation. The pharmacokinetic behaviour of tacrolimus in paediatric patients is significantly influenced by clinical factors growth and maturation, as well as genetic factors. Large interindividual variability and narrow therapeutic index make dosage individualisation mandatory in children. CYP3A5 expressers require a 1.8-fold higher tacrolimus dose than non-expressers. A visual patient-tailored dosing chart, taking into consideration the child's weight, recent haematocrit level and CYP3A5 genotype, was developed based on a population pharmacokinetic–pharmacogenetic model, and can be used routinely to individualise tacrolimus starting dose. Area under the concentration-time curve-based dosage adaptation through limited sampling strategy and Bayesian estimation is more reliable than trough concentration. Therapeutic drug monitoring and dosage adaptation can be included in routine post-transplantation consultation and should be considered in the urgent situations (eg, rejection, adverse event, lack of compliance, change of coadministration drug with potential drug–drug interaction and other situations).

## INTRODUCTION

The treatment of choice for end-stage organ failure in children is, in most cases, organ transplantation. The progresses achieved in solid-organ transplantation are reflected by the increase in the long-term survival rates. Several paediatric renal transplant cohorts have demonstrated that patient survival exceeded 90% at 5 and 10 years post-transplantation and 70% at 20 years post-transplantation.[1]

Following transplantation, paediatric recipients require immunosuppressive therapy to prevent rejection. The protocols of immunosuppressive therapy vary widely among transplantation centres, but usually include the combination of a calcineurin inhibitor (CNI; such as tacrolimus or ciclosporin), with an antiproliferative agent (azathioprine or mycophenolate mofetil (MMF)), and corticosteroids. Mammalian target of rapamycin inhibitors, such as sirolimus and everolimus, are sometimes used in combination with, or instead of, a CNI.[2]

As these drugs exhibit high intraindividual and interindividual pharmacokinetic and pharmacodynamic variability and have a narrow therapeutic index,[3] major efforts have focused on defining pharmacokinetic–pharmacodynamic therapeutic target using blood or plasma concentrations of each immunosuppressant to individualise therapy. Therapeutic drug monitoring (TDM) is crucial in daily practice so as to optimise treatment efficacy, reduce rejections and prevent adverse reactions. Most transplantation centres use trough concentrations ($C_0$) and/or area under the concentration-time curve (AUC) to adjust the individual dose, with the primary goal being to maintain the $C_0$/AUC within a predefined therapeutic range according to the type of transplantation, post-transplant period and protocol of immunosuppression.[4] In adult organ transplant recipients, many factors influencing the response to immunosuppressants are identified, including time post-transplantation, comedications and hepatic/renal function.[3 4] In addition to these factors, the pharmacokinetics of immunosuppressants in paediatric patients is also significantly influenced by growth and maturation-related changes, responsible for age-related differences in drug disposition. Dosage individualisation is more challenged in children, but with high-expected benefits.

## IMMUNOSUPPRESSIVE THERAPY: TACROLIMUS–MYCOPHENOLATE MOFETIL

The achievements in paediatric organ transplantation outcome have been obtained, along with the optimal use of immunosuppressive therapy. A randomised control trial in 196 children who had renal transplants has demonstrated that tacrolimus was more effective than ciclosporin in preventing acute rejection after transplantation.[5] Meta-analysis, including more than 4000 such children and adults, has achieved the same conclusion, although this was at the expense of increased diabetes and neurological and gastrointestinal side effects in patients treated with tacrolimus.[6]

The best immunosuppressive regimen in paediatric organ transplant recipients is still under discussion, because a powerful randomised controlled study, involving children treated with different immunosuppressive combinations is practically unfeasible to perform in this special category of population. However, the immunosuppressive regimen of tacrolimus, MMF and prednisone has become the most common combination in children who had organ transplants. According to the North American Paediatric Renal Trials and Collaborative Studies report, the triple therapy of ciclosporin, azathioprine and prednisone were once used in the majority of patients (80%–85%) from 1987 to 1993. There were marked changes following the introduction of tacrolimus and MMF. The percentage of children who had a transplant treated with ciclosporin has decreased from 81% in 1996 to <2% in 2009, along with the increased tacrolimus usage from 6% to 74% in the same period. The same trend has been observed for azathioprine and MMF. Azathioprine usage has decreased from 49% in 1996 to 3% in 2009, whereas MMF increased from 9% to 60% in the same period.[7]

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## BIBLIOGRAPHICAL SEARCH

A narrative review was conducted, and a bibliographical search was performed electronically using PubMed. Searches were performed with the following keywords: 'tacrolimus population pharmacokinetics children'; 'tacrolimus CYP3A5/pharmacogenetics children' with the limit of 'human'. All studies published in April 2014 or earlier were included in the analysis. The bibliography of each article was examined, and selected articles were read carefully.

## TACROLIMUS

Tacrolimus is a calcineurin inhibitor. An initial oral dose of 0.15 mg/kg twice daily is recommended for paediatric organ transplant recipients.[8] However, with this standard dose, adolescents are overdosed, whereas young children are underdosed,[9 10] indicating that a uniform milligram/kilogram basis dosing regimen is not adapted across all paediatric age ranges because of a non-linear relationship between weight and clearance in children. Tacrolimus is a new prolonged-release once-daily formulation of tacrolimus. Limited data (mainly pharmacokinetic data) were reported in children who had liver and renal transplants.[11 12] It is recommended that patients receiving stable treatment with tacrolimus twice daily can be switched to tacrolimus once daily, on a daily milligram-for-milligram basis, followed with close TDM.

### Therapeutic drug monitoring

Tacrolimus $C_0$ target concentrations of 10–20 ng/mL during the immediate post-transplantation period and 5–15 ng/mL, thereafter, are commonly used for all types of paediatric organ transplantations (table 1). The concentration-controlled trial in renal transplant adults has found significant trend for increasing toxicity with increasing maximum level of tacrolimus $C_0$ and for decreasing rates of rejection with increasing minimum level of tacrolimus $C_0$.[13] Given the extremely high interindividual variability of pharmacokinetics in children, the dosing individualisation of tacrolimus is mandatory.

Although target $C_0$ has been widely used for tacrolimus TDM, the major limitation is the weak correlation between $C_0$ and AUC both in adults and children. Thus, AUC-guided tacrolimus TDM has been proposed with a target of 150–200 h*ng/mL. Numerous limited sampling strategies based on regression linear method[14 15] and Bayesian estimator[16 17] have been developed and validated in children. These tools will facilitate AUC-guided tacrolimus TDM by providing limited blood sampling and accurate AUC prediction.

### Population pharmacokinetic models of tacrolimus

A total of nine studies described the population pharmacokinetics of tacrolimus in children who had organ transplants (table 2).[18–26] Seven studies were conducted in children who had liver transplants and two in children who had renal transplants. Either one-compartment (n=7) or two-compartment (n=2) models with first-order elimination were fitted to the tacrolimus paediatric pharmacokinetic data. The number in the studied population ranged from 16 to 100 and covered the paediatric age range. The typical apparent oral clearance (CL/F) was highly variable, ranging from 0.12 to 2.18 L/h/kg among the published studies. The identified factors influencing the dosage with tacrolimus are illustrated in table 3.

**Table 1** Target trough concentration

| Time post-transplantation | $C_0$ target concentration (ng/mL) |
|---|---|
| 0–1 month | 10–20 |
| 1–3 months | 10–15 |
| >3 months | 5–10 |

$C_0$, trough concentrations.

### Impact of pharmacogenetics on tacrolimus pharmacokinetics, and adverse events

Tacrolimus is almost completely metabolised by CYP3A4 and CYP3A5 and is a substrate of the P-gp encoded by the multidrug-resistance 1 gene (ABCB1). Table 4 summarises the pharmacogenetic studies of tacrolimus conducted in children who had organ transplants.[27–43] It has been consistently demonstrated that CYP3A5 expressers (CYP3A5*1 carriers) had a lower dose-adjusted $C_0$ and higher CL/F, thus requiring higher tacrolimus doses in order to reach the same steady-state $C_0$ when compared with CYP3A5 non-expressers (CYP3A5*3/*3 carriers). This finding has been demonstrated in children who had heart, liver and renal transplants and in different ethnicities (Caucasian, Japanese, African–American and Mexican), supporting a CYP3A5-based pharmacogenetic-dosing strategy of tacrolimus which allows CYP3A5 expressers to achieve the target concentration more rapidly and decrease the potential toxicity associated with high concentrations in CYP3A5 non-expressers. Table 5 shows the tacrolimus dose for CYP3A5 expressers and non-expressers. CYP3A5 expressers require a 1.8-fold (mean of reported studies) higher dose than non-expressers. Interestingly, Hooper *et al*[39] reported that CYP3A5 non-expressers had an increased risk of toxicity with coadministration of nicardipine. The same caution was highlighted in our recent case report concerning coadministration of tacrolimus and amlodipine.[44] The impact of CYP3A5 genotype on tacrolimus drug–drug interactions merits further research. Close monitoring was recommended when the comedications were changed in children who had transplants.

For CYP3A4, CYP3A4*1B (–392 A>G mutation) was the most studied. Although it was reported to be associated with a lower hepatic activity,[45] no study has shown significant correlation between CYP3A4*1B and tacrolimus pharmacokinetics in children. The novel CYP3A4*22 is a good candidate to consider in further paediatric pharmacokinetic studies, as Gijsen *et al*[42] have shown that tacrolimus dose requirement was significantly lower for CYP3A4*22 carriers when compared with CYP3A4*1/*1 carriers in children who had heart transplant. This effect was reported to be independent of the CYP3A5*3 genotype.

With regard to ABCB1, it limits the absorption of tacrolimus by active extrusion from the enterocyte back into the gut lumen. Japanese children who had liver transplant with higher ABCB1 mRNA expression were associated with high apparent oral clearance (CL/F), thus requiring higher doses in order to reach the target concentrations.[20 29] However, the impact of ABCB1 single nucleotide polymorphism (SNP) on tacrolimus paediatric pharmacokinetics is still controversial. Most studies failed to demonstrate significant genotype-pharmacokinetics correlation probably because the SNP is a weak probe of ABCB1 expression. Haplotype analysis (3435C>T; 2677G>T/A; 1236C>T) is more powerful. Hawwa *et al*[34] have demonstrated that in children who had liver transplant, ABCB1 T-T-T carrier had a higher risk of nephrotoxicity and dose-adjusted $C_0$.

## DISCUSSION

Children with transplanted organs are in a continuous and dynamically changing state of growth and developmental

**Table 2** Population pharmacokinetic studies of tacrolimus in paediatric organ transplant recipients

| Study | Population | Number of patients | Age (years) | Weight (kg) | PK model | Oral clearance (L/h/kg)* | Factors affecting clearance |
|---|---|---|---|---|---|---|---|
| Sam *et al*[18] | Children who had liver transplants | 16 | 3.7 (1.1–13.9) | 12.0 (6.9–20.5) | One-compartment model with first-order absorption and first-order elimination | 0.12 | Age |
| Staatz *et al*[19] | Children who had liver transplants | 35 | 5.7 (0.5–16.6) | 20.2 (6.4–43.5) | One-compartment model with first-order absorption and first-order elimination | 0.28 (cut-down liver recipients)<br>2.18 (whole-liver recipients) | Transplant type, age, liver function (AST, GGT) |
| Fukudo *et al*[20] | Children who had liver transplants | 100 | 1.2† (0.1–15) | 8.6† (3.4–61) | One-compartment model with first-order elimination | 0.65 (day 30 post-transplantation) | Weight, AST, time post-transplantation, intestinal ABCB1 mRNA level and recipient's CYP3A5 genotype |
| Zhao *et al*[21] | Children who had renal transplants | 50 | 10 (2–18) | 30.1 (10.6–62) | Two-compartment model with first-order, lagged time absorption and first-order elimination | 0.61 | Weight, Haematocrit, CYP3A5 genotype |
| Wallin *et al*[22] | Children who had liver transplants | 73 | 3.5 (0.4–16.9) | 15.4 (4–80) | One-compartment model with first-order absorption and first-order elimination | – | Weight, time post-transplantation |
| Zhao *et al*[23] | Children and young adults who had renal transplants | 22 | 15.2 (5.6–22.8) | 45.2 (16.7–70) | One-compartment model with first-order, lagged time absorption and first-order elimination | 0.63 | Weight, CYP3A5 genotype |
| Guy-Viterbo *et al*[24] | Children who had liver transplants | 42 | 1.4† (0.5–10.9) | 10.2† (5.5–31.4) | Two-compartment model with first-order absorption and first-order elimination | – | Weight, haematocrit, time post-transplantation, |
| Musuamba *et al*[25] | Children who had liver transplants | 82 | 1.0† (0.3–14.1) | 9.0† (5.3–66.8) | One-compartment model with first-order absorption and first-order elimination | 1.11 | Weight, haematocrit, liver transplant size to body weight ratio, time post-transplantation, comedication of CYP3A inhibitors |
| Jalil *et al*[26] | Children who had liver transplants | 43 | 5 (0.7–17.6) | 21.6 (6.1–70.0) | One-compartment model with first-order absorption and first-order elimination | 0.6 | Time post-transplantation, CYP3A5 genotype |

Values are expressed as mean (range).
*Total CL/F divided by mean or median weight.
†Median (range).
AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase.

**Table 3** Factors affecting tacrolimus dosages in children

| Factors | Effects on dose |
|---|---|
| Developmental factor | Increase of dosage with increase in age and weight |
| Age | |
| Weight | |
| Liver function | Decrease of dosage in patients with liver dysfunction |
| AST | |
| GGT | |
| Biological factor | Increase of dosage in patients with low haematocrit level (<33%) |
| Haematocrit | |
| Transplantation | Higher dose in patients with whole liver transplant compared with cut-down liver transplant recipients |
| Transplant type | Decrease of dosage with increase in time post-transplantation |
| Time post-transplantation | |
| Liver transplant size to body weight ratio | |
| Drug metabolism and transporter | Higher dose in CYP3A5 expresser compared with CYP3A5 non-expresser |
| CYP3A5 genotype | Higher dose in patients with higher intestinal ABCB1 mRNA level |
| Intestinal ABCB1 mRNA level | Decrease of dosage in patients coadministrated with CYP3A inhibitor |
| Comedication of CYP3A inhibitor | |

AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase.

changes in physiological parameters, which results in marked differences in the pharmacokinetic behaviour of immunosuppressants during childhood. In clinical practice, immunosuppressant doses in children who had organ transplants are given based solely on body weight or body surface area, and the dosage was empirically modified based on TDM results. However, it is now clear that this is not an optimal strategy.

The pharmacometric and pharmacogenetic approaches have the advantages of tailoring the doses of the immunosuppressant. Traditional TDM services will significantly benefit from the application of modelling-based dose individualisation in paediatric patients. It has been demonstrated that optimal immunosuppression during the immediate phase of post-transplantation is a prognostic factor for good graft function, reduction of acute rejection episodes and significant influence of long-term graft outcomes.

Population pharmacokinetic models have been published in children who had liver and renal transplants. The main challenge regarding the model-based dosage individualisation is how to account for the factors influencing the dose of tacrolimus, linked to growth and maturation, transplantation, biological and clinical conditions, liver function and drug metabolism and transporter. The performance of prediction of individual dose depends on the variability. Despite the continuous efforts to identify covariates influencing the pharmacokinetic parameters, the remaining (inexplicable) pharmacokinetic variability remains high, which influences the important role of dosage adaptation. The Bayesian estimation method can be used to address this issue.

There is increasing evidence to support a potential benefit for CYP3A5 genotyping before starting a tacrolimus-based immunosuppressive treatment in children who had organ transplants. Indeed, CYP3A5 genotyping may help clinicians to choose the better starting dose regimen for tacrolimus compared with the universal milligram/kilogram dose usually prescribed. In adult renal transplant recipients, CYP3A5 genotype-based dosing regimen has been proposed (0.075 mg/kg for CYP3A5 non-expresser, 0.150 mg/kg for CYP3A5 expressers). Thervet *et al*[46] conducted a randomised clinical trial to evaluate the clinical benefits of this new dosing guideline and showed that an a priori CYP3A5 genotyping to individualise the starting dose resulted in a more rapid achievement of target tacrolimus $C_0$ with less dose adjustments than the universal 0.1 mg/kg twice daily dosing regimen. However, a substantial percentage (57%) of patients did not reach the target $C_0$ window at day 3, indicating that factors other than CYP3A5 genotype contribute to the interindividual variability of tacrolimus pharmacokinetics.

As variability is even higher in paediatric patients, the children should benefit more from the model-based dosage individualisation approach as demonstrated in adults. However, the randomised control trial is still missing in children and the clinical benefits still need to be confirmed.

## Clinical practice recommendation to tailor tacrolimus dose

A model-based tacrolimus paediatric dosing individualisation approach to integrate the combined pharmacometric and pharmacogenetic methods can be applied in paediatric clinical practice.

### Patient-tailored starting dose

A visual patient-tailored dosing chart was developed based on a population pharmacokinetic–pharmacogenetic model (figure 1). To use this dosing chart, the child's weight, recent haematocrit level and CYP3A5 genotype should be known.

Imagine patient 'X', CYP3A5 non-expresser (*3/*3), with a weight of 30 kg and a haematocrit of 36%. We want to achieve a $C_0$ of 15 ng/mL; so now we can check in the visual dosing chart and find that a dosing regimen of 0.1 mg/kg is appropriate for this patient.

### Therapeutic drug monitoring

The first TDM can be taken 2–3 days after starting treatment. It is often based on $C_0$. If $C_0$ falls into the target, no dosage adaption is required before the next TDM. If $C_0$ is outside the recommended target, a control sample is required before dosage adaptation.

### Dosage adaptation

When dosage adaption is required, AUC-based adaption is more reliable than $C_0$-based. The predefined sampling schedule is available in the pharmacology lab. The individual pharmacokinetic parameters can be calculated through the limited sampling

**Table 4** Pharmacogenetic studies of tacrolimus in paediatric organ transplant recipients

| Study | Population | Ethnicity | Number of patients | Gene/Allele/SNP | Effect on PK/PD/adverse events |
|---|---|---|---|---|---|
| Goto *et al*[27] | Children and adults who had liver transplants | Japanese | 69 | ABCB1 −1G>A, 61A>G; 307T>C; 1199G>A; 1236C>T; 2677G>T/A; 3435C>T; +139C>T; +44C>T; −76T>A | No impact on PK |
| Zheng *et al*[28] | Children who had heart transplants | Caucasian/ African–American | 65 | CYP3A5*3 | ↓ $C_0$/dose for CYP3A5*1 carriers |
| | | | | ABCB1 3435C>T; 2677G>T/A | ↓ $C_0$/dose for ABCB1 3435CC or ABCB1 2677GG carriers |
| Goto *et al*[29] | Children who had liver transplants | Japanese | 181 | CYP3A5*3 | ↓ $C_0$/dose for CYP3A5*1 carriers |
| | | | | ABCB1 | ↓ $C_0$/dose for patients with higher ABCB1 expression level |
| Tada *et al*[30] | Children who had renal transplants | Japanese | 39 | CYP3A5*3 | ↓ AUC/dose and ↑ dose for CYP3A5*1 carriers |
| | | | | ABCB1 3435C>T | No impact on PK |
| Fukudo *et al*[20] | Children who had liver transplants | Japanese | 65 | CYP3A5*3 | ↑ CL/F for CYP3A5*1 carriers |
| | | | | ABCB1 | ↑ CL/F for patients with higher ABCB1 expression level |
| Masuda *et al*[31] | Children and adults who had liver transplants | Japanese | 164 | CYP3A4 | No impact on PK |
| | | | | ABCB1 | ↓ $C_0$/dose, ↑ acute cellular rejection and ↓ survival rate for patients with higher ABCB1 expression level |
| Ferraresso *et al*[32] | Children and young adults who had renal transplants | Caucasian | 30 | CYP3A5*3 | ↑ dose and ↑ blood pressure for CYP3A5*1 carriers |
| Zhao *et al*[21] | Children who had renal transplants | Caucasian | 50 | CYP3A5*3 | ↑ CL/F for CYP3A5*1 carriers |
| | | | | CYP3A4*1B | No impact on PK |
| | | | | ABCB1 3435C>T; 2677G>T/A; 1236C>T | No impact on PK |
| Chen *et al*[33] | Children and adults who had renal transplants | Chinese | 67 | CYP3A5*3 | ↓ $C_0$/dose, ↓ nephrotoxicity and ↑acute rejection for CYP3A5*1 carriers |
| Hawwa *et al*[34] | Children who had liver transplants | Caucasian/Asian/ black Caribbean | 51 | ABCB1 3435C>T; 2677G>T/A; 1236C>T | ↑ $C_0$/dose and ↑ nephrotoxicity for ABCB1 T-T-T carriers |
| Turolo *et al*[35] | Children who had renal transplants | Caucasian | 87 | CYP3A5*3 | ↓ $C_0$/dose for CYP3A5*1 carriers |
| | | | | CYP3A4*1B | No impact on PK |
| | | | | ABCB1 3435C>T; 2677G>T/A; 1236C>T | No impact on PK |
| de Wildt *et al*[36] | Children who had renal and liver transplants | Mixed | 90 | CYP3A5*3 | ↑ dose for kidney transplant CYP3A5*1 carriers, but no impact for liver transplant children |
| | | | | ABCB1 3435C>T; 2677G>T/A; 1236C>T | ↑ dose for liver transplant ABCB1 T-T-T carriers, but no impact for renal transplant children |
| Ferraris *et al*[37] | Children who had renal transplants | Caucasian | 48 | CYP3A5*3 | ↓ $C_0$/dose for CYP3A5*1 carriers |
| Gijsen *et al*[38] | Children who had heart transplants | Mixed | 39 | CYP3A5*3 | ↑ dose for CYP3A5*1 carriers |
| | | | | ABCB1 3435C>T; 2677G>T/A; 1236C>T | No impact on PK |
| Hooper *et al*[39] | Children who had renal transplants | Mixed | 38 | CYP3A5*3 | ↑ risk of toxicity for CYP3A5 non-expressers with coadministration of nicardipine |
| García-Roca *et al*[40] | Children who had renal transplants | Mexican | 167 | CYP3A5*3 | ↑ dose for CYP3A5*1 carriers |
| Zhao *et al*[23] | Children and adolescents who had renal transplants | Caucasian | 22 | CYP3A5*3 | ↑ CL/F for CYP3A5*1 carriers |
| Durand *et al*[41] | Children who had liver transplants | Caucasian | 179 | CYP3A5*3 | ↑ dose for CYP3A5*1 carriers |
| Gijsen *et al*[42] | Children who had heart transplants | Mixed | 60 | CYP3A5*3 | ↑ dose for CYP3A5*1 carriers |
| | | | | CYP3A4*22 | ↑ dose for CYP3A4*1/*1 carriers |
| Gijsen *et al*[43] | Children who had renal transplants | Mixed | 43 | POR*28 | ↓ $C_0$/dose for CYP3A5*1+POR*28 carriers |

AUC, area under the concentration-time curve; $C_0$, trough concentrations; PD, pharmacodynamics; PK, pharmacokinetics; SNP, single nucleotide polymorphism.

**Table 5** Tacrolimus dosage for CYP3A5 expresser and non-expresser

| Study | Time post-transplantation | Dosage of tacrolimus (mg/kg/day) | | Ratio† |
|---|---|---|---|---|
| | | CYP3A5*1 carriers | CYP3A5*3/*3 | |
| *Renal transplantation* | | | | |
| Tada *et al*[30] | 1 M | 0.271±0.110 | 0.150±0.056 | 1.8 |
| Ferraresso *et al*[32] | 1 W | 0.26 (0.1–0.36) | 0.21 (0.12–0.41) | 1.2 |
| | 2 W | 0.3 (0.13–0.3) | 0.24 (0.05–0.36) | 1.3 |
| | 1 M | 0.3 (0.11–0.5) | 0.18 (0.03–0.44) | 1.7 |
| | 2 M | 0.26 (0.1–0.38) | 0.16 (0.05–0.36) | 1.6 |
| | 7 M | 0.19 (0.11–0.35) | 0.11 (0.05–0.27) | 1.7 |
| | 13 M | 0.19 (0.08–0.32) | 0.08 (0.03–0.22) | 2.4 |
| Turolo *et al*[35] | 1 W | 0.28±0.02 | 0.22±0.1 | 1.3 |
| | 1 M | 0.44±0.16 | 0.24±0.1 | 1.8 |
| | 2 M | 0.4±0.12 | 0.18±0.08 | 2.2 |
| de Wildt *et al*[36] | 2 W | 0.28 (0.14–0.42) | 0.18 (0.02–0.70) | 1.6 |
| Ferraris *et al*[37] | 12 M | 0.21±0.03 | 0.13±0.01 | 1.6 |
| García-Roca *et al*[40] | 6 M | 0.17 for CYP3A5*1/*1<br>0.14 for CYP3A5 *1/*3 | 0.07 | 2.0‡ |
| *Heart transplantation* | | | | |
| Gijsen *et al*[38] | 2 W | 0.28 | 0.12 | 2.3 |
| *Liver transplantation* | | | | |
| Durand *et al*[41] | Steady-state | 0.29±0.20 | 0.18±0.23 | 1.6 |

Values are expressed as mean±SD or median (range).
†Ratio of tacrolimus dosage in children with CYP3A5*1 carriers and CYP3A5*3/*3 (mean or median values were used for calculation).
‡Tacrolimus dosages in children with CYP3A5 *1/*3 and *1/*3 were used to calculate the ratio.
M, month; W, week.

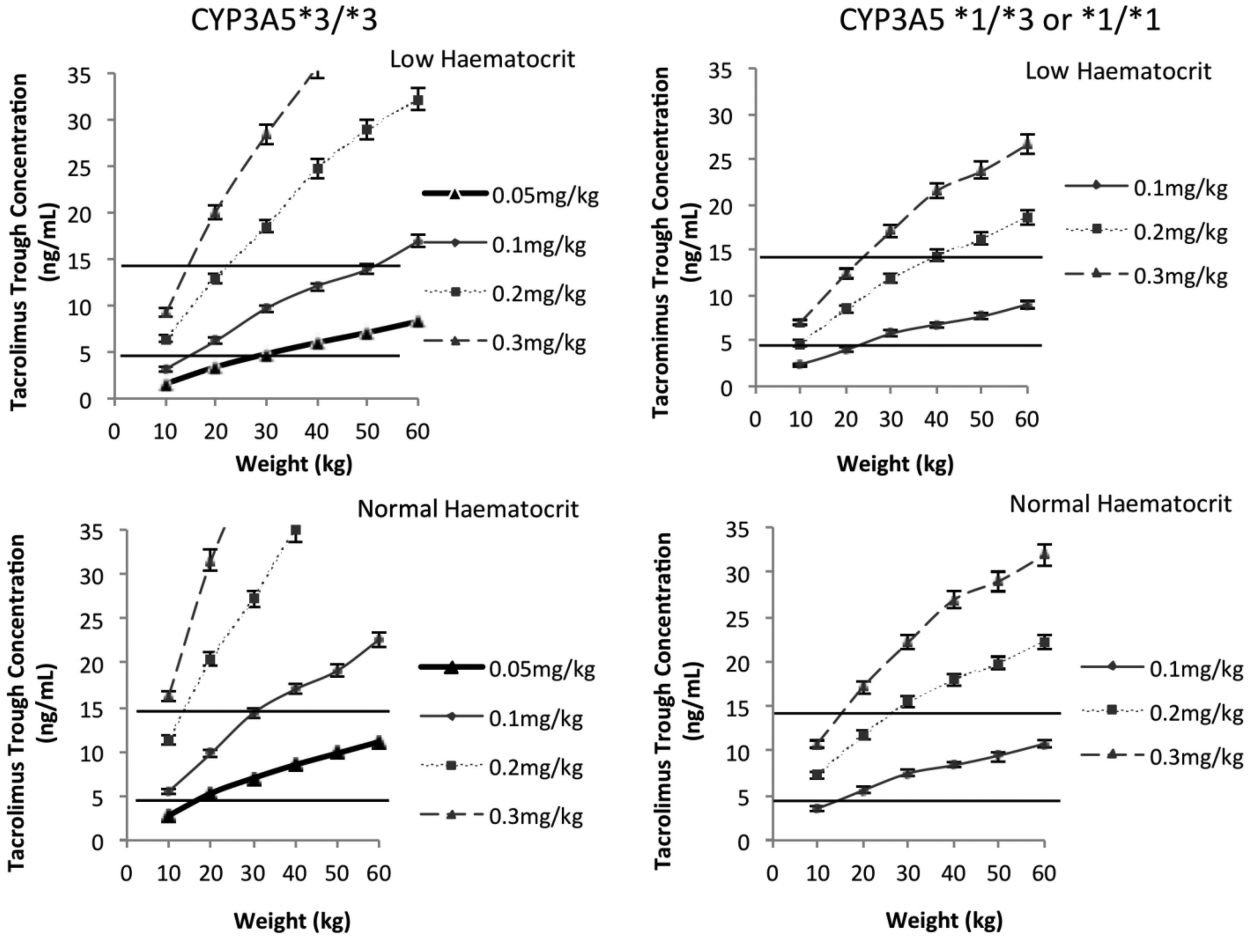


**Figure 1** Patient-tailored dosing chart of tacrolimus in paediatric renal transplant recipients (adapted from our previous publication, Zhao *et al*[21]). Low haematocrit level <33%; normal haematocrit level ≥33%.

strategy, or Bayesian estimation, by a clinical pharmacologist. The dosage adaptation needs to be discussed between pharmacologist and nephrologist, taking into consideration both clinical condition and individual pharmacokinetic parameters.

### Follow-up

A regular TDM follow-up can be adapted to the clinical practice, such as at 1 month, 6 months and the annual post-transplantation consultation. In the following situations, TDM and dosage adaptation should be considered: rejection, adverse events (eg, nephrotoxicity, neurotoxicity, gastrointestinal toxicity and so on), lack of compliance, change of coadministration drugs with potential drug–drug interaction (eg, antihypertension drug, proton pump inhibitor and so on).

In summary

- Use lower dose if haematocrit is low.
- Use higher dose if patient is CYP3A5 expresser.
- AUC-based dosage adaption is more reliable than $C_0$.
- TDM should be routinely performed.

## CONCLUSION AND PERSPECTIVES

Model-based dosage individualisation will shorten intensive concentration-controlled period in an early post-transplant period, during which immunosuppression should be optimal in order to reduce acute rejection and improve patient outcomes. The integration of current discoveries in paediatric clinical practice needs a close collaboration between nephrologist and clinical pharmacologist.

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# Choosing the right dose of tacrolimus

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## Notes