Population pharmacokinetics of tacrolimus in paediatric liver transplant recipients, a model to describe early post-transplantation apparent clearance

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Abstract

In this study 1) the predictive capacity of two previously derived population pharmacokinetic models of tacrolimus in paediatric liver transplant recipients were tested during Bayesian forecasting 2) a new population pharmacokinetic model was developed focusing on the immediate post-transplant period and 3) this new model was applied in a simulation exercise to devise a new dosing scheme for initial oral dosing of tacrolimus. Pharmacokinetic, demographic and covariate data were collected retrospectively from patient records. The Abbottbase PKS program was used for Bayesian forecasting. Actual tacrolimus concentrations were compared to those predicted by the program and bias and precision determined. The NONMEM program was used for building of a new population pharmacokinetic model. Factors screened for influence on the pharmacokinetic parameters were weight, age, sex, post-operative day, whole/cut-down donor liver, haematocrit, serum albumin, bilirubin, serum creatinine, creatinine clearance, liver function tests and country of origin. Data were collected from 20 patients for Bayesian forecasting and from 73 patients for population pharmacokinetic modelling. Predictive performance of the two previous population models was poor in the immediate post-transplant period (range of precision, bias). Tacrolimus pharmacokinetics appeared to change rapidly over this period. During the first and third month after transplantation use of only one previous sample during Bayesian forecasting providing the best predictive performance. The final population model estimated a typical apparent clearance of tacrolimus of 0.148 L/h/kg₀.⁷₅ immediately following the transplantation, increasing to a maximum of 1.37 L/h/kg₀.⁷₅ and typical apparent distribution volume of 27.2 L/kg. An alternative initial dosing schedule was developed based on an initial loading dose followed by a maintenance dose that increased with time, with drug dosing based on allometric scaling.

Keywords: tacrolimus, paediatric liver transplantation, population pharmacokinetics, Bayesian forecasting, dosage prediction
**Introduction**

Tacrolimus is a potent immuno-suppressant agent used to prevent and treat rejection in paediatric liver transplantation. Tacrolimus has a narrow therapeutic window and displays considerable between and within-subject pharmacokinetic variability. It is imperative that doses of tacrolimus are quickly individualised to reduce occurrence of adverse events such as rejection, drug toxicity and infections. Therapeutic drug monitoring (TDM) of tacrolimus is therefore routinely performed. The dosage of tacrolimus needed to achieve therapeutic concentrations in paediatric liver transplantation is highly variable between patients and hard to predict especially in the immediate post-transplant period (1).

To date seven population pharmacokinetic studies of tacrolimus in adult liver transplant recipients (2-8) and four studies in children (9-12) have been performed. Factors reported to influence the apparent clearance (CL/F) of tacrolimus include patient hepatic and renal function, body size, age (in paediatrics), time post-transplant and transplant type (whole or cut-down graft). Factors reported to influence the apparent volume of distribution (V/F) of tacrolimus include patient size and haematocrit level.

A population model may be useful in predicting the optimal drug dosage regime in a new patient when implemented in a Bayesian software program. Bayesian forecasting is a TDM tool where individual pharmacokinetic parameters are estimated for each patient based on patient characteristics, dosing history and observed concentrations (13). These techniques can be used to predict the most appropriate dosage regime to reach or maintain a desired drug concentration. The number of blood collections needed and the time to reach targeted drug concentrations can be reduced (13-16).

In several pharmacokinetic studies to date, the CL/F of tacrolimus has been reported to increase significantly during the first weeks post-transplant (2, 11, 17-21). Possible explanations have included enzyme induction by concomitant steroid therapy, donor organ recovery or altered protein levels. Two previous population pharmacokinetic studies of tacrolimus, both in adults, have focused on predicting early post-transplant CL/F of tacrolimus (2, 17).

The transplantation clinic at the Karolinska University Hospital in Stockholm, Sweden, currently utilizes a per-kg dosing schedule for initial oral dosing of tacrolimus in pediatric liver transplant recipients. Patients weighing more than 20 kg received an initially oral dose of tacrolimus of 0.1 mg/kg, twice daily from six hours pre-transplantation to up to day seven post-transplantation. Patients weighing less than 20 kg received an initial oral dose of tacrolimus of 0.15 mg/kg twice daily over this period. Thereafter, tacrolimus dosing is guided by TDM based on tacrolimus trough concentrations. The first weeks after transplantation are characterized by highly variable tacrolimus exposure. This occurs at a critical time in terms of graft acceptance (22, 23).

The aims of this study were 1) to test two previously developed population models of tacrolimus in paediatric liver transplant recipients (10, 11) for their predictive ability when employed in Bayesian forecasting, in a new cohort of patients given each individual’s dosing history and covariate values 2) to develop a population pharmacokinetic model of tacrolimus in the largest paediatric liver transplant population to date that focused on the immediate post-transplant period and 3) to apply the population pharmacokinetic model in a simulation study to obtain a covariate based dosing scheme for initial oral dosing of tacrolimus before TDM guided dosing begins.
METHODS

Predictive performance of previous models

Data were collected retrospectively from 20 paediatric liver transplant patients at the Karolinska University Hospital in Stockholm, Sweden to test the predictive performance of two previously developed population models (2,3) when employed in Bayesian forecasting. As data were available as part of the routine clinical care of patients, this study was considered to be a clinical audit by decision of the regional Ethics Committee, and no further ethics clearance was required. All data was anonymized immediately after collection to prevent identification of patients.

Tacrolimus dosage history, trough concentration measurements and patient covariate values were recorded in the first, third and twelfth months after transplant. Tacrolimus trough concentrations had been measured daily (before the morning dose) in the first month post-transplant, twice weekly in the third month and weekly in the twelfth month post-transplant. Trough concentrations of 10-20 ng/mL, 5-15 ng/mL and 2-10 ng/mL were targeted over these three periods respectively. Tacrolimus concentrations were measured using an EMIT® 2000 Tacrolimus Assay (Siemens Healthcare). This immunoassay has a predictable range of 2-30 ng/mL. In between-day variation for controls of 5-15 ng/mL is 6.8-7.5 % (24).

Sixteen recipients from Singapore (10) and 35 recipients from Australia (11) have previously been used to develop population pharmacokinetic models of tacrolimus in paediatric liver transplantation, here called the Sam and Staatz models respectively (Table 1). Both

<table>
<thead>
<tr>
<th>Table 1: Models used in Bayesian Forecasting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical value</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td><strong>Sam et al. (10)</strong></td>
</tr>
<tr>
<td>CL (L/h)</td>
</tr>
<tr>
<td>Factor for age on CL (/year)</td>
</tr>
<tr>
<td>V (L)</td>
</tr>
<tr>
<td>Factor for BSA on V (/m²)</td>
</tr>
<tr>
<td>F (%)</td>
</tr>
<tr>
<td>Factor for body weight on F (/kg)</td>
</tr>
<tr>
<td>Factor for Bili&gt;200 μM on F</td>
</tr>
<tr>
<td>Residual error (ng/mL)</td>
</tr>
<tr>
<td><strong>Staatz et al. (11)</strong></td>
</tr>
<tr>
<td>CL/F – cut-down (L/h)</td>
</tr>
<tr>
<td>– whole (L/h)</td>
</tr>
<tr>
<td>V/F (L)</td>
</tr>
<tr>
<td>Residual error (ng/mL)</td>
</tr>
</tbody>
</table>

*Factors for parameters incorporated as percent change in typical value per unit of influencing factor for age, body surface area and weight, and in percent change if bilirubin above 200μM.*
models are one compartmental with first order absorption and elimination. Under the Sam model, typical population CL/F was estimated to be 7.4 L/h and typical population V/F was estimated to be 198 L. Parameter between-subject variability estimates were CV%CL = 34%, CV%CL = 33% and CV%V = 24%. Under the Staatz model, typical population CL/F was estimated to be 5.75 L/h in cut-down liver recipients and 44 L/h in whole liver recipients and typical population V/F was estimated to be 617 L. Parameter between-subject variability estimates were CV%CL/F (cut-down) = 144%, CV%CL/F (whole liver) = 297%, CV%V/F = 42%.

The AbbottBase Pharmacokinetic System version 1.10 (Abbott Diagnostics, Chicago Ill., USA) was used for Bayesian forecasting. Individual pharmacokinetic parameters were estimated for each patient based on dosing history, covariate values and observed concentrations. Patient information was incorporated into the program via the setup menu. Only CL/F and V/F were estimated in the program. The absorption rate constant (ka) was fixed to 4.48 h\(^{-1}\) (25). The assay coefficient of variation was set to 7.5%. No time weighting factor was considered. In applying the covariate effects in the Sam model, adjusted initial estimates for CL/F and V/F were calculated and input in the parameter estimation dialogue of the software.

Under the Staatz model patient covariates such as weight, age and type of transplant were entered into the PKS program directly. Tacrolimus trough concentrations were predicted given the patient’s dosage history. Measured tacrolimus blood concentrations were integrated chronologically. Therefore the first concentration could be used in the prediction of the second, and the first and second concentrations could be used in the prediction of the third and so on.

Bias and precision of the two models were calculated in terms of mean prediction error (MPE) and root mean squared error (RMSE) (26), as well as 95% confidence intervals. MPE provides a measure of bias and RMSE provides a measure of imprecision. The lower the value of the MPE and the RMSE the closer the predicted measurement is to the observed measurement. Over four time periods (day 1-14, day 15-30, 3\(^{rd}\) month, > 1 year) the use of one, three, five or ten previous samples for prediction of the sequential sample were compared.

Development of a population model for the immediate post-transplant period

Data were collected retrospectively from a further 18 paediatric liver transplant recipients at the Karolinska University Hospital and pooled with the first 20 patients plus 35 Australian paediatric liver transplant recipients utilized for development of the Staatz model. Ethical clearance was granted by the University of Queensland Medical Research Ethics Committee regarding the Australian patients, whereas the additional Swedish data fell under the same jurisdiction as in the forecasting study and no further ethics approval was needed. These 73 patients were used to develop a population pharmacokinetic model of tacrolimus that focused on the early post-transplantation period.

Tacrolimus trough concentrations measured in Swedish patients (38 subjects) were analyzed using the EMIT 2000\(^{®}\) assay. Tacrolimus trough concentrations measured in Australian patients (35 subjects) were analysed using a validated high-performance liquid chromatography-tandem mass spectrometry assay (27). This assay is specific for the parent drug, tacrolimus, and is linear over the range of 0.2 to 100 ng/mL (\(r^2>0.99\)). The within-day and between-day imprecision is <8%.

Population modeling was performed using the software program NONMEM v.6.2 (ICON, Ellicott City, MD, USA) with the aid of the PsN toolkit to execute runs, and to perform step-wise covariate model building (28, 29). The population
analysis was undertaken using the first order conditional estimation method (FOCE) with interaction. Maximum likelihood estimates ($\theta$'s and $\eta$'s) were sought for CL/F and V/F. The absorption rate constant ($k_a$) was fixed to 4.48 h$^{-1}$.

Post processing of NONMEM output was undertaken with Xpose (Version 4.0) programmed in the statistics package R. Between-subject variability ($\eta$'s) in pharmacokinetic parameters was assumed to be log-normally distributed and covariance between parameters was examined. Additive, proportional and combined error structures were tried during modelling of residual random error.

A number of models were tested in an attempt to describe changes in tacrolimus CL/F in the immediate post-transplant period including a piecewise linear model; an enzyme turn-over model (with and without time dependence in the enzyme induction rate); and a model with CL increasing in a sigmoidal fashion with time (with and without a baseline CL/F at the time of transplantation (CL$_{0/F}$), here called the sigmoidal CL$_{max}$ model.

Under the piecewise linear model (equation 1), CL/F increased linearly with increasing post-operative day (POD), if the time post-transplant was less than an internal break-point time, IBP. At post-transplant times greater than the IBP, CL/F was then either constant or increased linearly with increasing post-operative day at a different rate. The IBP time was estimated during modeling.

Under an enzyme turn-over model (equation 2), CL/F was assumed to be dependent of the rate of induction of a metabolic enzyme. Metabolic activity was described by an enzyme formation rate, $k_{in}$, and a degradation rate, $k_{out}$. Tacrolimus CL/F was also influenced by metabolic activity at time 0, i.e the time of transplantation; $k_0$. This model works on the hypothesis that CL/F is linked to induction of a metabolic enzyme, and the half-life of human CYP3A4 could be obtained from a previous enzyme induction study (31).

Under a sigmoidal CL$_{max}$ model, CL is allowed to change as a function of POD, increasing with a sigmoidal shape from CL$_{0/F}$ at time of transplantation to a maximum level CL$_{max}$, with a shape factor, $\gamma$. The parameter $T_{CL(50)}$ denotes the time when half the increase towards CL$_{max}$ is achieved (2, 17).

$$CL = CL_{0} + \left( \frac{CL_{max} \cdot POD}{T_{CL(50)} + POD} \right)$$

Allometric scaling was applied on the base model with CL/F scaled by weight$^{0.75}$ and V/F by weight. Allometric scaling of CL to weight$^{0.75}$ has been shown to better reflect physiological changes in drug elimination with weight than a linear relationship, especially in paediatric populations (32, 33). Total body weight, lean body weight (LBW) (James formula) (34) and non-lean body weight (i.e. body weight minus LBW), were evaluated as size measures. Covariates screened for influence on the pharmacokinetic parameters were age, sex, post-operative day, whole/cut-down donor liver, haematocrit, serum albumin, bilirubin, serum creatinine (S-Crea), creatinine clearance (CrCl) and liver function tests (aspartate aminotransferase (AST), alanine aminotransferase (ALT), $\gamma$-glutamyltransferase (GGT),

$$\frac{dCL}{dt} = k_{in} - k_{out} \cdot CL ; k_{in} = k_0 + \left( \frac{k_{max} \cdot POD}{T_{50} + POD} \right) ; k_{out} = \frac{\ln 2}{\frac{1}{T_{50,CYP3A4}}}$$

$$\frac{dCL}{dt} = \theta_{early} \cdot POD \left( 1 - \frac{POD_{50}}{IBP_{50} + POD_{50}} \right) + \theta_{late} \cdot POD \left( \frac{POD_{50}}{IBP_{50} + POD_{50}} \right)$$

$$\theta_{early}$$

$$\theta_{late}$$

POD$^{50}$

IBP$^{50}$

POD$^{50}$

IBP$^{50}$

POD$^{50}$

IBP$^{50}$

POD$^{50}$
alkaline phosphatase (ALP), luteine dehydrogenase (LDH)). CrCL was calculated using the Schwartz formula (35), with an upper bound of 200 ml/min/1.73m² for patients with extremely low S-Crea levels. As different assay methods and dosage regimens were used in Swedish and Australian patients, country of origin was also examined as a covariate and for its influence on residual random error.

Primary covariate selection was made by generalized additive modelling (GAM) using Xpose. Potentially useful covariates were tested in linear, piece-wise linear and exponential relationships with the pharmacokinetic parameters in NONMEM using the stepwise covariate model building function in the PsN-package (28, 29). Nested models were compared statistically using a likelihood ratio test on the differences in objective function value (OFV). A step-wise covariate search was carried out in NONMEM with a forward inclusion criteria of p<0.01 and a backward elimination criteria of p<0.001. During each step in the model building process, improvements to the model were also assessed by evaluation of agreement between observed and predicted tacrolimus blood concentration, increases in precision of parameter estimates and reduction in between subject variability and residual error. Final covariate selection was made based upon possible mechanisms of effect and clinical significance. Covariate relations were regarded clinically significant if the effect on the typical parameter value was greater than 15%.

Shrinkage of the final empirical Bayes estimates and residual errors were calculated, to ensure the GAM method and goodness-of-fit plots were reliable in covariate screening and for diagnostics (36).

Bootstrap methods were used to assess uncertainty in the final population model parameter estimates with the assistance of the PsN toolkit (28, 29). Under this technique repeated random sampling, with replacement, of the original data set produces new data sets of the same size but with a different combination of subjects (28, 37). As the number of bootstrap samples approaches infinity, the sample standard deviations of the parameters approach the ‘true’ (but unknown) standard deviations. Mean parameter estimates obtained from 500 bootstrap runs were compared to population mean values.

Current treatment guidelines in the summary of product characteristics (SPC) suggests an initial oral dose of tacrolimus of 0.15-0.20 mg/kg/day divided into two doses (38) until TDM can be used to guide therapy. At the Karolinska University Hospital TDM is initiated after the seventh day post-transplantation with a tacrolimus trough of 10-20 ng/ml targeted in the first month. In order to evaluate the current treatment protocol in the first seven days after transplantation simulations of 500 typical patients were performed with the final model, using either the current dose/kg strategy or a dosing strategy derived from the final model developed. Median tacrolimus trough concentration and the 95% prediction interval were compared between the current and proposed dosing strategy.

RESULTS

Patients and data collection
605 tacrolimus concentration time-points were collected from 20 paediatric liver transplant recipients for evaluation of Bayesian forecasting. 3284 tacrolimus concentration time-points were collected from 73 paediatric liver transplant recipients for building of a new population model. Patient characteristics are displayed in Table 2. The median tacrolimus dose in the total population during the initial days prior to TDM, was 0.20 mg/kg/day (range 0.04-0.5 mg/kg/day). Twenty-seven percent of the
tacrolimus trough concentrations during this period were in the target range of 10-20 ng/mL, 26% undershot the target and 47% were over target.

**Bayesian forecasting**

Table 3 summaries the predictive performance of Bayesian forecasting in terms of MPE and RMSE under the Sam and Staatz models with differing amount of prior information and over different study periods. The Staatz model showed somewhat better overall predictive performance than the Sam model. Predictive performance improved with time post-transplant. Use of only one previous sample showed the best predictive performance during the first and third months post-transplant, use of three samples was somewhat better in the twelfth month based on both bias and precision. Predictive performance was significantly worse when five or ten previous samples were used in the Bayesian feedback process. MPE of the
Staatz model went from 51% during the first month post-transplant to 1.2% in the twelfth month if based on three previous samples, and RMSE improved from 107% to 60%.

**Population modeling**

A one-compartment model with first-order absorption and elimination was considered adequate for modeling the data. Concentration measurements were logarithmically transformed due to the wide distribution of data. Residual error was modeled using two components corresponding to an additive and a proportional error on the logarithmic scale, with an exponential interindividual variability term. Allometric scaling was applied to the base model for CL/F and V/F reducing the model objective function value (OFV) by 43 points. A change in CL/F with time post-transplant was evident and was best described by a sigmoidal CL$_{\text{max}}$/F model with the addition of a CL$_{0}$/F parameter. The turnover model improved the objective function by 43 points, the piecewise linear model by 857 points and the sigmoidal CL$_{\text{max}}$/F model by 934 points. Covariate analysis suggested a negative relationship between patient age and CL$_{\text{max}}$/F and a positive relationship between bilirubin level and time to 50% of maximum CL/F (T$_{\text{CL50/F}}$). Inclusion of these covariate relations reduced the OFV, but made only a minor impact (less than 1%) on between subject variability and residual error. Bootstrap analysis showed that confidence intervals associated with addition of these covariates into the model included zero. The final population model thus included no other covariates than patient weight and time post-transplantation (Table 4). Typical values were 0.148 L/h/kg$^{0.75}$, 1.37 L/h/kg$^{0.75}$ and 27.2 L/kg for CL$_{0}$/F, CL$_{\text{max}}$/F and V/F, respectively.

A plot of model-predicted versus observed concentrations for the final model based on individual parameter estimates is shown in Figure 1a. Shrinkage in estimated between subject variability in system parameters (η’s) and residual error (ε) were less than 5% and 2%, respectively. Examination of a plot of individual weighted residuals (IWRES) (39) versus time after dose (Figure 1b) confirmed the appropriateness of a one-compartment pharmacokinetic model. Internal validation with a bootstrap showed all parameters to have adequate confidence intervals (Table 5).

**Simulation of a new dose schedule**

Our findings suggested that the current initial dosage schedule of tacrolimus
Table 3: Accuracy and precision of Bayesian forecasting expressed in terms of mean prediction error (MPE) and root mean squared error (RMSE)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1 sample</th>
<th>3 samples</th>
<th>5 samples</th>
<th>10 samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median conc. (ng/ml)</td>
<td>Prediction model</td>
<td>MPE</td>
<td>RMSE</td>
<td>MPE</td>
</tr>
<tr>
<td>Day 1-14</td>
<td>Sam (5,24.2)</td>
<td>14%</td>
<td>56%</td>
<td>51%</td>
</tr>
<tr>
<td>Day 15-30</td>
<td>Staatz (11,62)</td>
<td>11%</td>
<td>49%</td>
<td>26%</td>
</tr>
<tr>
<td>Day 3rd month</td>
<td>9.9 ng/ml</td>
<td>13%</td>
<td>49%</td>
<td>26%</td>
</tr>
<tr>
<td>Day 1 year</td>
<td>6 ng/ml</td>
<td>1%</td>
<td>68%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Table 4: Final model population pharmacokinetic parameter estimates, relative standard errors (RSE) and 95% confidence interval (CI) obtained from bootstrapping (500 samples)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical estimate (RSE)</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final model</td>
<td>CL\text{max} (mL/h/kg\textsuperscript{0.75})</td>
<td>1.37 (10%)</td>
</tr>
<tr>
<td></td>
<td>ω\text{Cl\text{max}} (%)</td>
<td>65 (19%)</td>
</tr>
<tr>
<td></td>
<td>CL\text{min} (mL/h/kg\textsuperscript{0.75})</td>
<td>0.148 (24%)</td>
</tr>
<tr>
<td></td>
<td>T\text{CL50} (days)</td>
<td>5.38 (8%)</td>
</tr>
<tr>
<td></td>
<td>T\text{tCl50} (%)</td>
<td>54 (30%)</td>
</tr>
<tr>
<td></td>
<td>Gamma</td>
<td>3.78 (6%)</td>
</tr>
<tr>
<td></td>
<td>V (L/kg)</td>
<td>27.2 (32%)</td>
</tr>
<tr>
<td></td>
<td>Cov (%)</td>
<td>90 (22%)</td>
</tr>
<tr>
<td></td>
<td>Additive error (ng/ml)</td>
<td>1.63 (5%)</td>
</tr>
<tr>
<td></td>
<td>Proportional error (%)</td>
<td>29.2 (8%)</td>
</tr>
<tr>
<td></td>
<td>ω (%)</td>
<td>29 (24%)</td>
</tr>
</tbody>
</table>

ω = between subject variability.

Table 5: Dose suggestion for the initial therapy based on final model population pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Day</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day of transplantation</td>
<td>0.135 mg/kg twice daily</td>
</tr>
<tr>
<td>Day 1 post-transplantation</td>
<td>0.135 mg/kg twice daily</td>
</tr>
<tr>
<td>Day 2 post-transplantation</td>
<td>0.07 mg/kg\textsuperscript{0.75} twice daily</td>
</tr>
<tr>
<td>Day 3 post-transplantation</td>
<td>0.09 mg/kg\textsuperscript{0.75} twice daily</td>
</tr>
<tr>
<td>Day 4 post-transplantation</td>
<td>0.14 mg/kg\textsuperscript{0.75} twice daily</td>
</tr>
<tr>
<td>Day 5 post-transplantation</td>
<td>0.19 mg/kg\textsuperscript{0.75} twice daily</td>
</tr>
<tr>
<td>Day 6 post-transplantation</td>
<td>0.24 mg/kg\textsuperscript{0.75} twice daily</td>
</tr>
</tbody>
</table>
in paediatric liver transplant recipients at the Karolinska University Hospital should be revised based on a lower initial CL/F immediately post-transplant. The current hospital guidelines of 0.1-0.15 mg/kg twice daily were compared to a model based dosing strategy. In order to achieve a correct initial concentration a loading dose should be calculated as \( C_{\text{target}} \times V/F \), meaning it will be dependent on the patient weight. This should be followed by a maintenance dose based rather on CL/F and dosing interval, meaning dose will be dependent on weight^{0.75} and time. Based on our final model to achieve a steady-state target concentration of 20 ng/ml, an initial loading dose 0.54 mg/kg, followed by a twice daily maintenance dose of only 0.057 mg/kg^{0.75} increasing with time post-transplantation. In order to avoid extremely high concentrations in patients with a low volume of distribution, or to limit consequences by errors in administration, the loading dose could be divided over the first four dose occasions, as according to Table 5. Simulations were made for a typical individual of 15.4 kg based on a) a standard dose of 0.1 mg/kg twice daily b) the new proposed schedule without a loading dose, c) the new proposed schedule including a loading dose and d) the new proposed schedule with the loading dose divided on the first four occasions. The predicted median concentrations and 95% prediction intervals are depicted in Figure 2. The concentration-time profiles of tacrolimus in a typical individual weighing 20 kg compared to a 10 or 40 kg individual, after administration of a) the current dosage schedule 0.1 mg/kg twice daily if >20 kg and 0.15 mg/kg twice daily if <20 kg, followed by b) the new proposed dosage regimen, with loading dose divided into four dose occasions, are displayed in Figure 3.

![Figure 2: Median and 95 percent prediction interval of a) standard dose of 0.15 mg/kg twice daily; b) model based dose; c) model based dose with loading dose and d) model based dose with loading dose divided over four occasions](image-url)
Discussion

A population pharmacokinetic model of tacrolimus is required that can be used in a Bayesian forecasting program to assist with drug dosing in the immediate post-transplant period in paediatric liver transplant recipients. Previously published population pharmacokinetic models of tacrolimus in pediatric liver transplantation when applied during Bayesian forecasting do not adequately predict the pharmacokinetics of tacrolimus in the first critical weeks of treatment. Some of these models were not developed for the immediate post-transplant period. A similar study of prediction of trough concentrations in adult transplantation showed poor performance in this early phase (5). A pharmacokinetic model for tacrolimus has been developed using data from the early post-transplant period which aimed at explaining not only steady-state pharmacokinetics, but also the initial change in apparent drug clearance of tacrolimus. Different modelling equations were tested to describe tacrolimus apparent clearance in the immediate post-transplant period.

Several authors have described a need for increased tacrolimus doses with time post-transplantation in adult kidney and liver transplantation (20, 21, 40, 41). Previous publications by Antignac et al (2) have suggested that the change in apparent clearance could be a function of improvement in metabolic activity. However the time frame may be too long (~10 days) to reflect organ recovery, and this pattern has been observed not only in liver transplantation but also in kidney function (17). It has been suggested that the increase in clearance could be attributed to an induction of metabolic activity by concomitant steroid usage. A correlation between tacrolimus clearance and steroid dosage has been shown in kidney transplant recipients (17, 41). Patients in this study were initiated on steroid doses of 1 g pre-cortalone i.v./20mg prednisolone p.o. (dose reduced with 50% if <30 kg) which would have been high enough to cause induction. Another explanation might be auto-induction of metabolism, however this is contradicted by the lack of indication of time dependent clearance in bone marrow transplantation (42). In paediatric bone marrow recipients high steroid dosages are generally only used in cases of graft-versus-host disease.

Apparent clearance and distribution estimates obtained in this study corresponded well with previous values in paediatric populations (9, 12, 43), and when scaled to adult weight corresponded well with values reported in adult populations (2, 44).

This study was based on retrospective data and as such some uncertainty exists in dose and sample time records, especially
in the outpatient setting. Covariate testing was limited to information routinely collected in the clinic. For example no information was available on patient CYP3A5 genotype in this study which has been demonstrated to influence patients dosing requirements for tacrolimus \(^{(45)}\). Neither was acute and chronic rejection episodes recorded in a manner allowing them to be tested as covariates for hepatic clearance. The majority of tacrolimus concentrations measured in this study represented trough levels, whereas a prospective trial would allow more informative sampling schedules.

The usefulness of our final model for Bayesian forecasting needs to be evaluated in a new population. The AbbottBase PKS program could not be used as it does not support the time varying clearance functions here suggested, but could be set up to be used for the later treatment period. A Microsoft Excel based macro for individualizing initial dosing based on the time-dependent clearance model, including a Bayesian tool for dose adjustment could be developed in the future \(^{(42)}\) to allow for Bayesian forecasting in the clinical setting.

Our final population model was used to suggest a revised dosage strategy allowing on an initial loading dose followed by a maintenance dose that increased with time, with drug dosing based on allometric scaling. Such a strategy would allow quicker obtainment of tacrolimus target concentrations while accounting for a lower initial CL/F of tacrolimus immediately post-transplant. The safety and precision of the revised dose recommendations still remains to be evaluated.

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References


