

Tacrolimus in pediatric liver recipients: population pharmacokinetic analysis during the first year post transplantation

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Background

Tacrolimus (TAC), an immunosuppressive drug, is difficult to handle in pediatric liver transplantation (PLT) because of its narrow therapeutic window and its high pharmacokinetic (PK) variability. Previous studies characterized TAC PK in PLT but mainly focused on the early post transplant period. However, acute rejection may occur up to one year post transplantation (PT). Moreover, an important pediatric growth is expected during this first year PT with potential influence on TAC PK. Therefore, it is important to characterize TAC PK during all the first year post PLT.

Aim

To describe the TAC PK after oral administration in pediatric patients during the first year post transplantation
To identify and model the effect of demographic and clinical factors on TAC PK variability in this population

Methods

Retrospective TAC doses and routine TDM trough levels from 82 pediatric liver allograft recipients during the first year post transplantation were used to develop a population PK model using mixed effects modelling (NONMEM version 7.2). Patient's demographics, biochemical test results and physiological characteristics such as patient age, body weight, liver size/body weight, co-medications, hematocrit, time post-transplantation were tested as covariates to explain interindividual variability. Data from 42 and 40 patients were used for model building and model validation, respectively.

Results and discussion

Structural model characteristics

A two-compartment model with first-order elimination best described the TAC PK.
Apparent volumes of central (V_1/F) and peripheral (V_2/F) compartments, intercompartmental clearance (Q/F) and maximal blood clearance (CL/F) estimates were 253L, 100L, 115L/day and 314L/day, respectively.
The absorption first order rate (K_a) and V_2/F were fixed to 4.5h⁻¹ and 100L respectively, based on literature data. (table 1)

Covariate model

Time after transplantation, liver size/body weight ratio and hematocrit levels significantly influenced drug elimination whereas bodyweight was the only covariate retained for its significant influence on distribution volume.
Time after transplantation was imputed as a continuous covariate on CL following an E-max model (eq.1). The other covariates were included in the model in a power manner.

$$\frac{CL}{F} = \theta_{CL} \times \left(1 - \frac{CL_{MAX} \times TIME}{CL_{50} + TIME} \right) \quad \text{Equation 1}$$

Parameters (units)	Estimates [Bootstrap CI]	IIV/IOV [Bootstrap CI]
θ_{CL} (L/day)	0.001 [0.0007-0.0013]	0.3[0.27-0.32] / 0.1[0.09-0.13]
θ_{T50} (days)	17.4 [12.5-21.6]	-
θ_{CLMAX}	314 [129-493]	-
θ_{Ka} (h ⁻¹)	4.5 [-]	-
θ_{V1} (L)	253 [193-326]	0.6[0.5-0.7]
θ_{V2} (L)	100 [-]	-
θ_Q (L/day)	115 [97-138]	-
θ_{wt} on V_1	0.9 [-]	-
$\theta_{size/wt}$ on CL	0.12 [0.04-0.21]	-
θ_{Hct} on CL	-0.85 [-1.12—0.58]	-
ϵ_{prop}	0.02 [0.018-0.023]	NA
ϵ_{add} (ng/mL)	1.78 [1.63-1.95]	NA

Table 1 : Final model parameters

Diagnostic plots

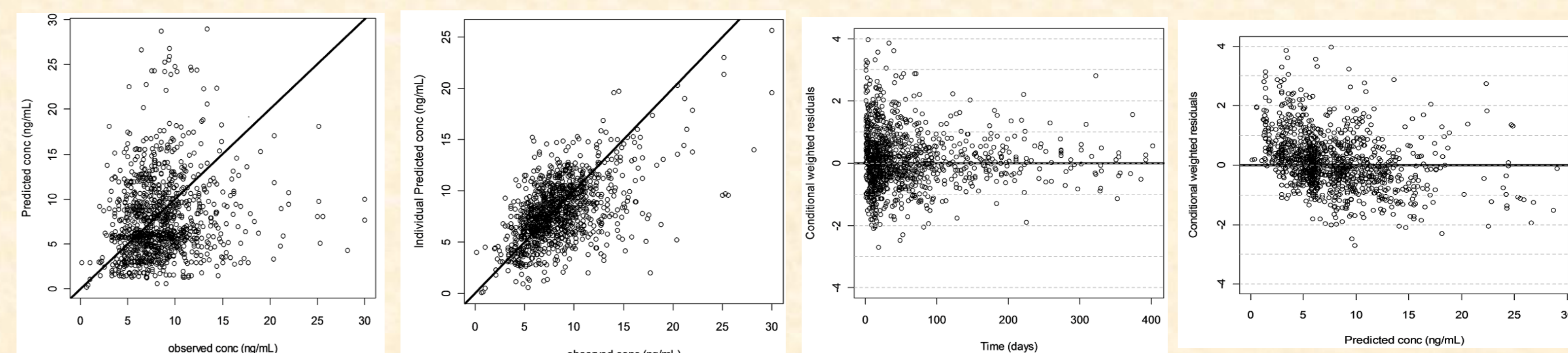


Figure 1: Goodness of fit plots for the final population pharmacokinetic model.

Internal and external validation of the model

The final model was internally validated by visual predictive check and 1000 bootstraps. The model shows good predictive performance and good accuracy and precision in the parameter estimation. External validation showed that the model was able to predict an external dataset from another cohort of 40 pediatric liver transplanted patients.

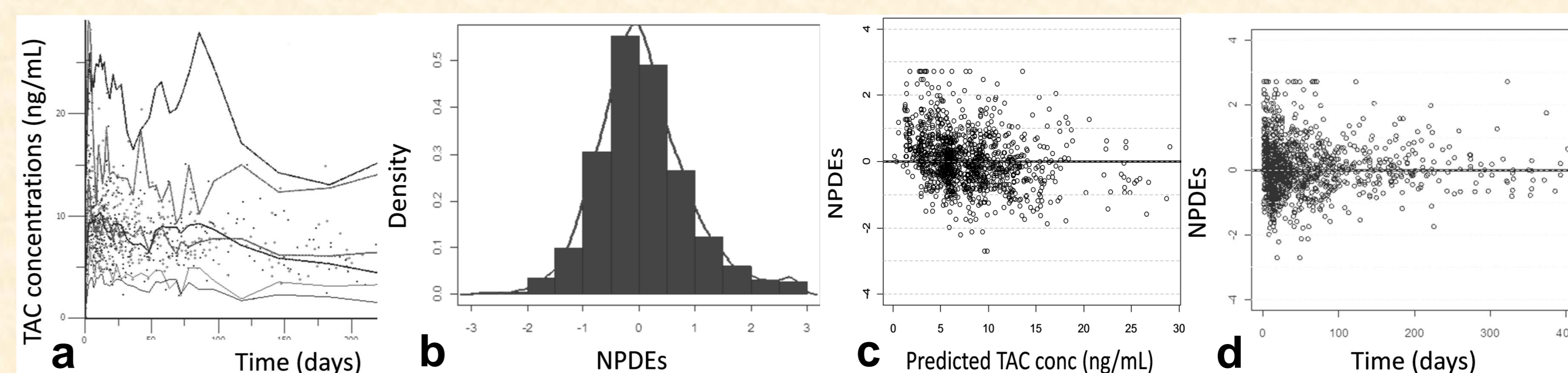


Figure 2: a) Scatter plot visual predictive check from the final model. b) c) and d) Diagnostic plots for internal model validation (NPDEs)

Conclusions

We developed a population PK model for TAC throughout the first year after PLT. Once implemented in a Bayesian based dosage individualization software, this model could serve as a unique tool for dose adjustment.