



Population pharmacokinetics of tacrolimus in adult kidney transplant recipients

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Background

- Tacrolimus is a potent immunosuppressant agent used following transplantation which has a narrow therapeutic index and displays large between- and within- subject pharmacokinetic (PK) variability

Aims

To develop a population PK model of tacrolimus in adult kidney transplant recipients, then to use this model to:

- Compare CYP3A5 genotype based initial dosing to standard per-kilogram based initial dosing of tacrolimus
- Predict the best starting regimen of tacrolimus, based on patient genotype, to achieve a trough concentration between 6 and 10 µg/L on day 5 post-transplant

Methods

- NLME model developed in NONMEM® 7.12 (FOCE+I) and PsN®
- Covariates investigated: patient age, sex, weight, height, race, albumin, creatinine, liver function tests (bilirubin, AST, ALT, ALP, GGT), haematocrit, creatinine clearance, use of CYP3A4 and proton pump inhibitors, free and total prednisolone exposure (AUC and C_{max}), post-operative day (POD) and CYP3A5 genotype (rs776746)
- Model evaluated based on nonparametric bootstrap, goodness of fit and prediction-corrected visual predictive check (pcVPC) plots
- Starting dose regimens compared by simulating tacrolimus trough concentrations on day 5 post-transplant

Results

- 1554 concentration-time points from 173 patients analysed (Table 1)
- 2-compartment model with first order absorption after a lag time and first order elimination best described the data (Table 2)
- Higher CL/F in CYP3A5 *1 allele carriers, heavier patients, patients with lower haematocrit and those in the immediate post-transplant period
- Covariate inclusion reduced unexplained IIV from 49% to 30% for CL/F and from 114% to 47% for V1/F. No trends suggesting model misspecification were identified in plots (Figure 1)
- A fixed dose of 6 mg bd (Figure 2b) and per-kilogram dose of 0.075 mg/kg bd (Figure 2d) was too low in CYP3A5 expressers, with >66% of patients predicted to achieve a trough concentration <6 µg/L
- Highest percent of target attainment was achieved in CYP3A5 expressers on a starting dose of 10 mg bd or 0.115 mg/kg bd

Conclusion

- To reduce risk of under immunosuppression in the immediate post-transplant period CYP3A5 expressers are likely to benefit from a tacrolimus starting regimen of 10 mg bd or 0.115 mg/kg bd

Table 1: Characteristics of study patients

Number of patients (n)	173
Post-operative days (days)	23 [2-104]
Age (y)	50 [33-64]
Body weight (kg)	79 [59-101]
CYP3A5 6986A>G genotype ^b (n)	
AA (*1/*1)	3
GA (*1/*3)	23
GG (*3/*3)	146
Haematocrit (fraction)	0.33 [0.25-0.40]
Free prednisolone C _{max} (nmol/L)	162 [85-260]

a = Median or number [10th-90th percentile]; b = Genotypes were in Hardy-Weinberg equilibrium

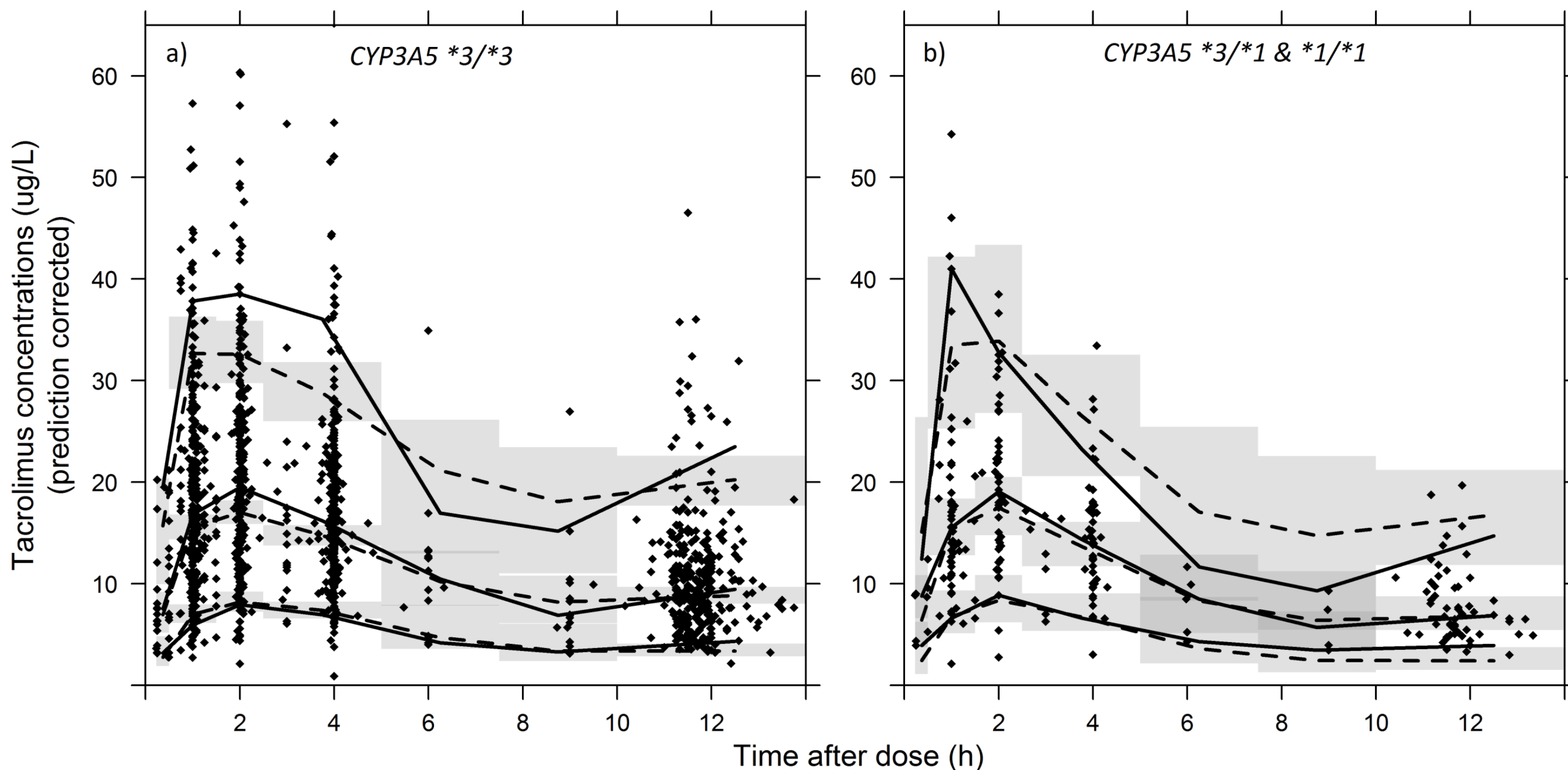
Table 2: Parameter estimates and bootstrap results for final model

	Estimate	Bootstrap (n=1,000) Median (95% non-parametric CI)
CL/F (L/h) (θ _{CL/F})	25.5	26.2 (24.0 to 28.5)
IIV _{CL/F} (%)	29.5	28.9 (20.6 to 36.6)
IOV _{CL/F} (%)	29.9	29.1 (24.4 to 33.9)
θ _{CYP3A5}	1.60	1.64 (1.41 to 1.92)
θ _{HAEM}	-1.01	-1.13 (-2.06 to -0.32)
θ _{POD}	-0.21%	-0.21% (-0.31 to -0.08%)
V1/F (L) (θ _{V1/F})	113.0	106.7 (70.6 to 158.2)
IIV _{V1/F} (%)	46.8	51.0 (19.4 to 96.1)
IOV _{V1/F} (%)	126.5	115.6 (91.7 to 148.4)
θ _{Pred}	-0.28%	-0.30% (-0.30 to -0.28%)
Q/F (L/h)	67.9	67.0 (48.8 to 86.3)
V2/F (L)	1060	986 (648 to 1268)
IIV _{V2/F} (%)	89.4	102.9 (79.3 to 137.6)
ka (h ⁻¹)	0.35	0.35 (0.25 to 0.46)
IIV _{ka} (%)	47.6	44.9 (31.9 to 55.7)
Lag-time (h)	0.44	0.44 (0.37 to 0.47)
Proportional RUV (%)	18.3	19.0 (17.2 to 21.2)

$$CL/F_i = \theta_{CL/F} \times \theta_{CYP3A5}^x \times (1 + \theta_{HAEM}(HAEM - 0.33)) \times \left(\frac{WT}{70}\right)^{0.75} \times (1 + \theta_{POD}(POD - 22.7))$$
$$V1/F_i = \theta_{V1/F} \times (1 + \theta_{Pred}(Pred_{Cmax,free} - 155.5))$$

x = 1 for CYP3A5 expressers (*1/*1 and *1/*3) and x = 0 for CYP3A5 non-expressers (*3/*3); HAEM = haematocrit (fraction); IIV = inter-individual variability; IOV = inter-occasion variability; POD = Post-operative day (capped at 180 days); Pred_{Cmax,free} = C_{max} value of free prednisolone (nmol/L); RSE = relative standard error; RUV = residual unexplained variability; WT = body weight (kg)

Figure 1: pc-VPC based on final model in CYP3A5 (a) non-expressers and (b) expressers



The upper, middle and lower continuous lines represent the 95th, 50th and 5th percentiles of the observations. The upper, middle and lower dashed lines represent the 95th, 50th and 5th percentiles of the simulated data from the final model. The grey shaded areas are the 95% confidence intervals for the percentiles of the simulated data for each bin.

Figure 2: Fraction of patients below, in and above the tacrolimus trough target range of 6-10 µg/L, based on 100 simulated datasets

