



Population pharmacokinetics of sirolimus in adult kidney transplant patients

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OBJECTIVE OF THE STUDY

- to explore factors that significantly contribute to sirolimus (SRL) pharmacokinetic variability
- to develop population pharmacokinetic model using therapeutic drug monitoring (TDM) data

METHODS

Table 1. Characteristics of patients

CHARACTERISTIC		NUMBER (%) / Mean ± Sd	RANGE
Gender	M	18 (72%)	
	F	7 (28%)	
Graft origin	Living donor	23 (92%)	
	Cadaver	2 (8%)	
Age (years)		43.03 ± 12.45	16 – 64
Weight (kg)		77.1 ± 18.79	44 – 128
Haematocrit		0.33 ± 0.05	0.18 – 0.83
Proteinaemia (g/L)		69.27 ± 6.33	44 – 83
Triglycerides (mmol/L)		2.53 ± 1.07	0.58 – 6.64
Total cholesterol (mmol/L)		6.17 ± 1.25	2.62 – 9.45
Aspartate aminotransferase (IU/L)		27.71 ± 28.81	9 – 274
Sirolimus dose (mg/day)		3.57 ± 2.29	0.5 – 15
trough concentration (ng/mL)		9.85 ± 4.81	0.5 – 38.4
Mycophenolate mofetil dose (mg/day)		1118.93 ± 446.94	0 – 2000
Corticosteroids dose (mg)		10.95 ± 6.93	0 – 60

Bioanalytical assay

- Total concentrations of SRL in whole blood were assessed using CMEA method (Architect® Abbott Laboratories)

Pharmacokinetic analysis

- NONMEM® (version 7.2.0), PSN® (version 3.5.3)
- Graphic presentation - Xpose®, R®, Pirana®
- FOCEI; ADVAN2 TRANS2
- Vd i ka were fixed at 13.5 L/kg and 2.2 h⁻¹
- Interindividual variability - exponential model
- Residual variability - slope-intercept error model
- STEPWISE COVARIATE MODEL BUILDING (forward inclusion/backward elimination)

Validation

- Bootstrap method - 1000 simulations
- Numerical Predictive Check (NPC) – 1000 simulations

CONCLUSIONS

Dose and AST levels outside the upper reference range explained in part sirolimus interindividual variability.

The results from the study allow individualization of SRL dosing in routine patient care, especially useful for patients with compromised liver function.

RESULTS

Table 2. Inclusion of covariates in the base model

	COVARIATE	ΔOFV	p value
FORWARD INCLUSION	DSRL	40.129	<0.001
	AST	16.579	<0.001
BACKWARD ELIMINATION	AST	16.579	<0.001
	DSRL	25.489	<0.001

DSRL – sirolimus daily dose; AST – aspartate aminotransferase

Final model equation

$$CL / F = 12.1 \cdot \left(\frac{DSRL}{3} \right)^{0.301} \cdot 0.647^{AST}$$

Table 3. Final model parameters of real and bootstrap simulated data

PARAMETER	FINAL MODEL		BOOTSTRAP	
	Estimate	Standard error	Median	Standard error
Θ_{CL}^a (l/h)	12.1	0.804	12.03	0.769
Θ_{AST}^b	0.647	0.0928	0.652	0.0844
Θ_{DSRL}^b	0.301	0.0785	0.300	0.0749
ω_{CL}^c	0.0746	0.0293	0.0734	0.0272
Wa ^d (ng/ml)	2.030	0.322	2.025	0.305
Wp ^d	-0.248	0.0370	-0.247	0.0346

^a, typical value of tacrolimus clearance;

^b, influential factors for covariates (AST - Aspartate aminotransferase greater than 37 IU/L, DSRL – daily sirolimus dose);

^c, variance for clearance;

^d, residual variability (Wa – additive error, Wp – proportional error).

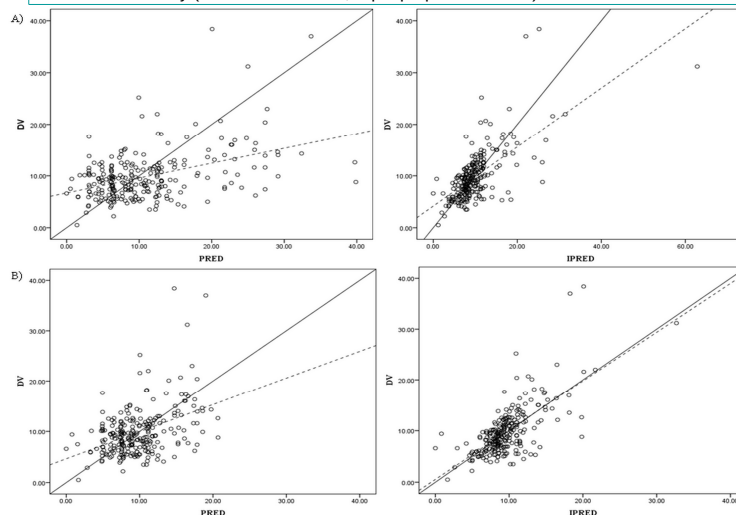


Figure 1. Observed sirolimus concentration (DV) versus population (PRED) and individual model predicted (IPRED) concentration (ng/ml) for A) base model and B) final model. Line of identity (solid); regression line (dashed).

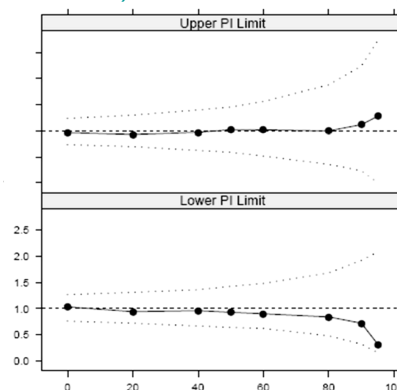


Figure 2. Numerical Predictive Check of the final population model for sirolimus. Circles present lower and upper limits of prediction intervals (%) observed in the data. Dashed lines indicate 95% CIs of the lower and upper limits of simulation-based prediction intervals (%).

References:

1. Jiao Z, Shi XJ, Li ZD, Zhong MK (2009). Population pharmacokinetics of sirolimus in de novo Chinese adult renal transplant patients. *Br J Clin Pharmacol* 68 (1):47-60.
2. Djebli N, Rousseau A, Hoizey G, Rerolle JP, Toupance O, Le Meur Y, Marquet P (2006). Sirolimus population pharmacokinetic/pharmacogenetic analysis and bayesian modelling in kidney transplant recipients. *Clin Pharmacokinet* 45 (11):1135-1148.