A population pharmacokinetic model to predict the starting dose of tacrolimus following pediatric renal transplantation

L.M. Andrews[1]: L.Andrews@erasmusmc.nl

D.A. Hesselink[2] , T. van Gelder[1,2], B.C.P. Koch[1], E.A.M. Cornelissen[3], R.J.M. Brüggemann[4], R.H.N. van Schaik[5], S.N. de Wildt[6], K. Cransberg[7], B.C.M. de Winter[1]

Aim

- To describe the population pharmacokinetics of twice-daily immediate-release tacrolimus (Tac) in the first weeks after pediatric renal transplantation
- To develop a dosing guideline for the starting dose

Background

- Tac has a narrow therapeutic window and large pharmacokinetic variability.
- Multiple factors (e.g. bodyweight, age, drug interactions, hematocrit, ethnicity, treatment with glucocorticoids and CYP3A genotype) affect the PK of Tac
- The starting dose is currently based solely on bodyweight (0.3 mg/kg/day) and then adjusted by means of TDM

Conclusion

- The pharmacokinetics of Tac in the first six weeks after pediatric renal transplantation could be accurately described with a two-compartment model.
- CYP3A5 expressers had a 2 times higher CL/F. An increase in eGFR from 30 to 90 ml/min resulted in 19% higher CL/F, whereas a decrease in hematocrit levels from 0.3 to 0.25 L/L corresponded with a 20% higher Tac CL/F. Deceased donor was associated with a 35% higher Tac CL/F than living donor.
- The tacrolimus weight-normalized starting dose should be higher in patients with lower bodyweight, CYP3A5 expressers and patients receiving a kidney from a deceased donor.

Methods

A total of 722 blood samples were collected from 46 children treated with Tac over the first six weeks after renal transplantation. Tac was determined using LC-MS/MS or immunoassay.

One- and two compartment models were tested using NONMEM 7.2® (FOCE+I) and PsN® version 4.6.0. Pirana® software was used as an interface between NONMEM®, R (version 3.2.2) and Xpose (version 4).

Inter-individual (IIV) and inter-occasion variability (IOV) were exponentially modeled. Covariates were analysed using forward inclusion ($p<0.05$) backward elimination ($p<0.001$).

Model selection based on minimum objective function values, parameter precision, error estimates, shrinkage values and goodness of fit plots. Bootstrap was performed and the final model was internally and externally validated (VPC).

Simulations were performed to illustrate the effect of the significant covariates on Tac concentrations. To develop a dosing guideline, simulations were performed using a model which only included covariates that significantly influence the starting dose.

Table 1. Parameter estimates

Parameter	Final model	Simulation model	Bootstrap of the final model	
			Estimate	95% CI
tlag (h)	0.37	0.43	0.40	0.30-0.45
ka (L/h)	0.56	0.43	0.58	0.40-1.25
CL/F (L/h)	50.5	54.9	54.0	43.5-68.1
V1/F (L)	206	119	211	122-363
Q/F (L/h)	114	147	116	82-187
V2/F (L)	1520	1900	1544	1052-2140
Covariate effect on CL				
CYP3A5*3/*3	1.04	1.00	1.02	0.85-1.21
CYP3A5*1/*1 or *1/*3	1.98	1.82	1.91	1.56-2.43
eGFR (ml/min/1.73 m2)	0.19	-	0.18	0.04-0.32
Donor living	0.74	0.74	0.70	0.55-0.86
Hematocrit < 0.3 (L/L)	-0.44	-	-0.42	-0.87-0.24
IIV (%)				
ka	188	119	195	139-256
CL/F	25	30	24	17-34
V1/F	69	115	82	20-122
V2/F	62	89	59	31-87
IOV (%)				
CL/F	18	19	18	11-23
V2/F	35	26	35	22-49
Residual variability				
Additional				
Immunoassay	1.01	0.81	0.88	0.01-2.56
LC-MS/MS	0.28	0.73	0.70	0.01-1.26
Proportional				
Immunoassay	0.13	0.13	0.11	0.001-0.29
LC-MS/MS	0.21	0.21	0.20	0.15-0.24

Results

- The final structural model was a two-compartment model with allometric scaling for bodyweight (Table 1)
- Higher bodyweight, lower eGFR and higher hematocrit levels resulted in lower total Tac CL. CYP3A5 expressers and recipients who received a kidney from a deceased donor had a significantly higher Tac CL.
- The model was successfully externally validated.
- Dosing guidelines were developed with a target C_0 of 12,5 ng/mL (Table 2)

Table 2. Dosing guideline starting dose

		CYP3A5 expresser	CYP3A5 non-expresser
Weight (kg)	Donor	Dose (mg/kg/day)	Dose (mg/kg/day)
10	Living	0.89	0.44
	Deceased	1.33	0.61
20	Living	0.76	0.37
	Deceased	1.06	0.53
30	Living	0.63	0.33
	Deceased	1.00	0.46
40	Living	0.61	0.31
	Deceased	0.91	0.44
50	Living	0.60	0.30
	Deceased	0.82	0.42
60	Living	0.55	0.30
	Deceased	0.80	0.40
70	Living	0.53	0.30
	Deceased	0.78	0.38

[1]Dept. of Hospital Pharmacy, Erasmus MC; [2]Dept. of Internal Medicine, Erasmus MC; [3]Dept. of Pediatric Nephrology, Radboud UMC; [4]Dept. of Hospital Pharmacy, Radboud UMC, [5]Dept. of Clinical Chemistry, Erasmus MC; [6]Dept. of Pharmacology and Toxicology, Radboud UMC; [7]Dept. of Pediatric Nephrology, Erasmus MC.