Population pharmacokinetics and pharmacogenetics of everolimus in renal transplant patients on a calcineurin inhibitor free regimen

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Aim

- Describe pharmacokinetics of everolimus in renal transplant patients following oral administration of everolimus twice daily in absence of CNI's and to identify covariates explaining variability.

Conclusions

- The concentration time profile of oral everolimus was best described by a two compartment pharmacokinetic model with lag-time.
- The demographic covariate Ideal Weight explained 15.4 % of the variability in distribution volume of the central compartment.
- *ABCB1, CYP3A5, CYP2C8, Pregnane X receptor* do not significantly influence everolimus pharmacokinetics.

Introduction

- Everolimus (Certican®, Novartis, Basel, Switserland) is an orally administered immunosuppressive agent targeting the mTOR receptor.
- Everolimus is indicated for prevention of acute and chronic rejection of solid organ transplants.
- Everolimus is characterized by its high variability in pharmacokinetics and narrow therapeutic window (1-2).
- Explaining variability in pharmacokinetics could help to predict everolimus dosage to quickly reach and maintain adequate exposure during therapy.

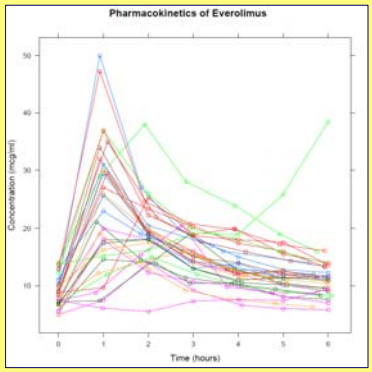

Figure 1:
Concentration time curves of 32 renal transplant patients receiving 3 mg everolimus twice daily measured with LC-MS/MS showing large variability in pharmacokinetics.

Materials & Methods

- 53 stable renal transplant recipients on everolimus and prednisolone studied from 6 months up to 2 years after transplantation (3).
- Therapy started with 3 mg everolimus twice daily following routine TDM with a target AUC of 120 mcg*h/L.
- Dataset consisted out of 786 whole blood samples collected from 35 males and 18 females determined with LC-MS/MS.
- Development of population pharmacokinetic base model.
- Covariate analysis with demographic covariates such as Weight, Height, Age, Hematocrit, IWT, BSA, BMI, Albumin, Sex, and pharmacogenetic covariates *ABCB1, CYP3A5, CYP2C8 and Pregnane X Receptor .*
- Analysis was performed using NONMEM 7.1.2, R-Statistics and Pirāna (5).

Results

Table 1: Baseline characteristics of the patients included in the everolimus population PK/PG analyses

	Mean	SD	Median	Range
Male	35			
Female	18			
Age (yrs)	50			22-71
Caucasion (%)	81			
Weight (kg) *	80.5	16.3	77.2	52 - 128.8
Body surface Area (m^2) **	1.96	0.23	1.93	1.51 - 2.52
Lean Body Mass (kg) **	60.4	8.6	59.4	43.2 - 79.9
Ideal Body Weight (kg) **	68	7.5	68.3	52 - 83.1
Height (m) **	173.6	10.2	174	152 - 194
Creatinine clearance (ml/min)*	116	34.1	116	59 - 226
Everolimus Dose (mg)*	2.44	0.75	2.25	0.75 - 4.5
Hematocit (L/L)	0.38	0.04	0.38	0.26 - 0.48
Albumin (g/L)	42.36	3.64	43	25 - 49

* During trial, ** At first TDM moment

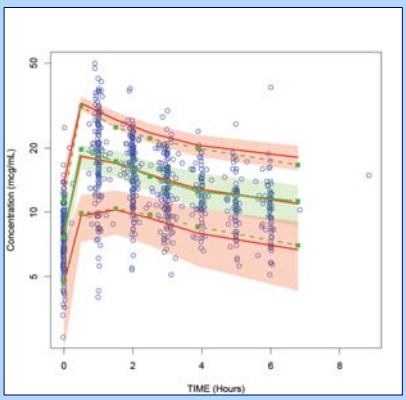

Figure 2:
Prediction corrected Visual predictive check with 80 % prediction interval. The observed concentrations are shown as open circles. The dashed lines with squared symbols represent the observation intervals. The solid lines represent the prediction interval. The shaded areas around the prediction intervals represent the 95 % confidence interval around each of the prediction interval.

Table 2: *Summary of model parameter estimates*

	Base Model		Final Model		1000 bootstrap runs	
PK Parameter	Mean Value	RSE(%)	Mean Value	RSE(%)	Median Value	95% CI
CL	18	4,5	17,9	4,5	18,0	16.4 to 19.7
F (fixed)	1	0	1	0	1,0	1 to 1
V_c (L)	153	5,7	148	6,2	146,7	130.0 to 166.4
Q (L/h)	56,1	6	55,7	6,8	55,7	49.1 to 64.1
V_p (L)	495	9,7	498	13,8	491,9	325.1 to 1209.3
k_a (h-1)	7,36	8,8	7,55	14,2	8,0	5.1 to 15.1
Lagtime	0,714	3,3	0,709	2,1	0,714	0.67 to 0.80
Dose CL (TDM effect)	0,505	16,8	0,532	15,9	0,545	0.3 to 0.7
Θ_{IWT} on Vc/F	-	-	-1,41	27,1	-1,4	-2.30 to -0.56
Interindividual variability						
IIV CL (CV%)	26,4	18,8	26,2	18,7	24,9	13.5 to 35.0
IIV Vc (CV%)	32,5	20,2	27,7	14,7	26,6	16.3 to 35.7
IIV Ka (CV%)	110,5	17,6	108,6	20,2	104,9	45.9 to 152.0
Interoccasion variability						
IOV Ka (CV%)	131,1	13,3	135,6	14,7	140,8	99.5 to 189.3
IOV F (CV%)	25,9	7,2	25,9	6,9	25,9	22.2 to 29.4
Random residual variability						
σ^1 (proportional error)	14,0		13,9		13,9	11.8 to 16.2

Table 3: *Genotype distribution in study Population (N=53)*

SNP	Frequency						ABCB HAP1	ABCB HAP2	N	Haplotype frequency (%)		CYP2C8 HAP1	CYP2C8 HAP2	N	Haplotype frequency (%)	
ABCB1 C1236t (rs1128503)	8	T/T	25	C/T	20	C/C	CCG	CCG	13	CCG	0.52	CT	CT	47	CT	0.94
ABCB1 G2677T (rs2032582)	6	G/G	25	G/T	22	T/T	CCG	CTG	2	TTT	0.33	TC	CT	6	TC	0.06
ABCB1 T3435C (rs1045642)	7	T/T	30	C/T	16	C/C	CCG	TTT	19	TCG	0.08					
ABCB1 129CT (rs3213619)	50	T/T	3	C/T	0	C/C	CCT	TTT	1	CTG	0.04					
CYP2C8 (rs10509681)			47	T/T	6	C/T	CTG	TTT	2	CTT	0.02					
CYP2C8 (rs11572080)			6	C/T	47	C/C	CTT	CCG	1	CCT	0.01					
CYP3A5*3 (rs776746)	47	G/G	4	G/A	2	A/A	TCG	CCG	7							
CYP3A5 *6 (rs10264272)	0	G/G	53	A/G	0	A/A	TTT	CTT	1							
PXR (NR1|2) G-24113A (rs2276706)	7	T/T	23	C/T	23	C/C	TTT	TCG	2							
PXR(NR1|2) A+7635G (rs6785049)	7	G/G	20	A/G	26	A/A	TTT	TTT	5							

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