



Population pharmacokinetics of tacrolimus to aid individualized dosing in kidney transplant recipients

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Objectives

- To identify predictable differences between kidney transplanted patients for initial dosing of tacrolimus
- To develop a population model suitable for Bayesian forecasting of tacrolimus dose
- To evaluate the use of hematocrit for tacrolimus target concentration intervention (TCI) [1]

Conclusions

- Initial dosing should be determined by *CYP3A5* *1/*3 genotype, sex, prednisolone dose (effects on F) and allometric scaling to fat free mass
- The model should be suitable for Bayesian forecasting during the first ten weeks after transplantation
- Measured blood concentrations should be adjusted using hematocrit to achieve a hematocrit standardized target concentration

Introduction

Tacrolimus

- Potent immunosuppressive agent widely used after organ transplantation
- Highly distributed into and bound to erythrocytes
- Initial dose is based on total body weight
- Hematocrit is not currently used for target concentration intervention (TCI)
- High variability between subjects and occasions in addition to apparently time varying pharmacokinetics makes TCI challenging
- Several population pharmacokinetic models have been developed for tacrolimus [2-5]
- PK models not commonly in clinical use for initial dosing or Bayesian forecasting even though there is wide agreement of their potential clinical value

Table 1. Patient, covariate and dosing characteristics

	New transplanted patients first ten weeks (n=44)			Stable transplanted patients (n=29)		
	Number	Median	Range	Number	Median	Range
Patients / occasions	(44 / 44)			(29 / 44)		
Total number of samples	1032			514		
Samples per patient (average)	24		(5 - 31)	13		(8 - 39)
Post transplant day on time of sampling			(1 - 90)	1 669		(26 - 5 697)
Sex (male / female)	(32 / 12)			(21 / 8)		
Body size						
Total body weight (kg)		80	(46 - 152)		84	(51- 131)
Fat free mass (kg)		59	(35 - 93)		61	(35 - 80)
<i>CYP3A5</i> genotype						
*1/*1	0			0		
*1/*3	8			3		
*3/*3	36			26		
Hematocrit (%) at day 1		31	(18 - 39)			
Hematocrit (%) at day 70		38	(30 - 45)			
Hematocrit (%) in stable phase				39		(29 - 58)
Tacrolimus dose (mg/day)		5	(2 - 14)		4	(2 - 12)
Prednisolone dose (mg/day)		15 ^a	(5 - 80)		5	(0 - 25)

Tested covariates that did not explain variability are not included in the table (age, height, fat mass, albumin, serum creatinine, C-reactive protein, liver function tests (ASAT, ALAT, bilirubin, alkaline phosphatase), methylprednisolone I.V. dose, use of other interactive drugs, acute rejection episodes)

^aPrednisolone dose is typically tapered from 20 mg to 10 mg during the first ten weeks

References

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Results

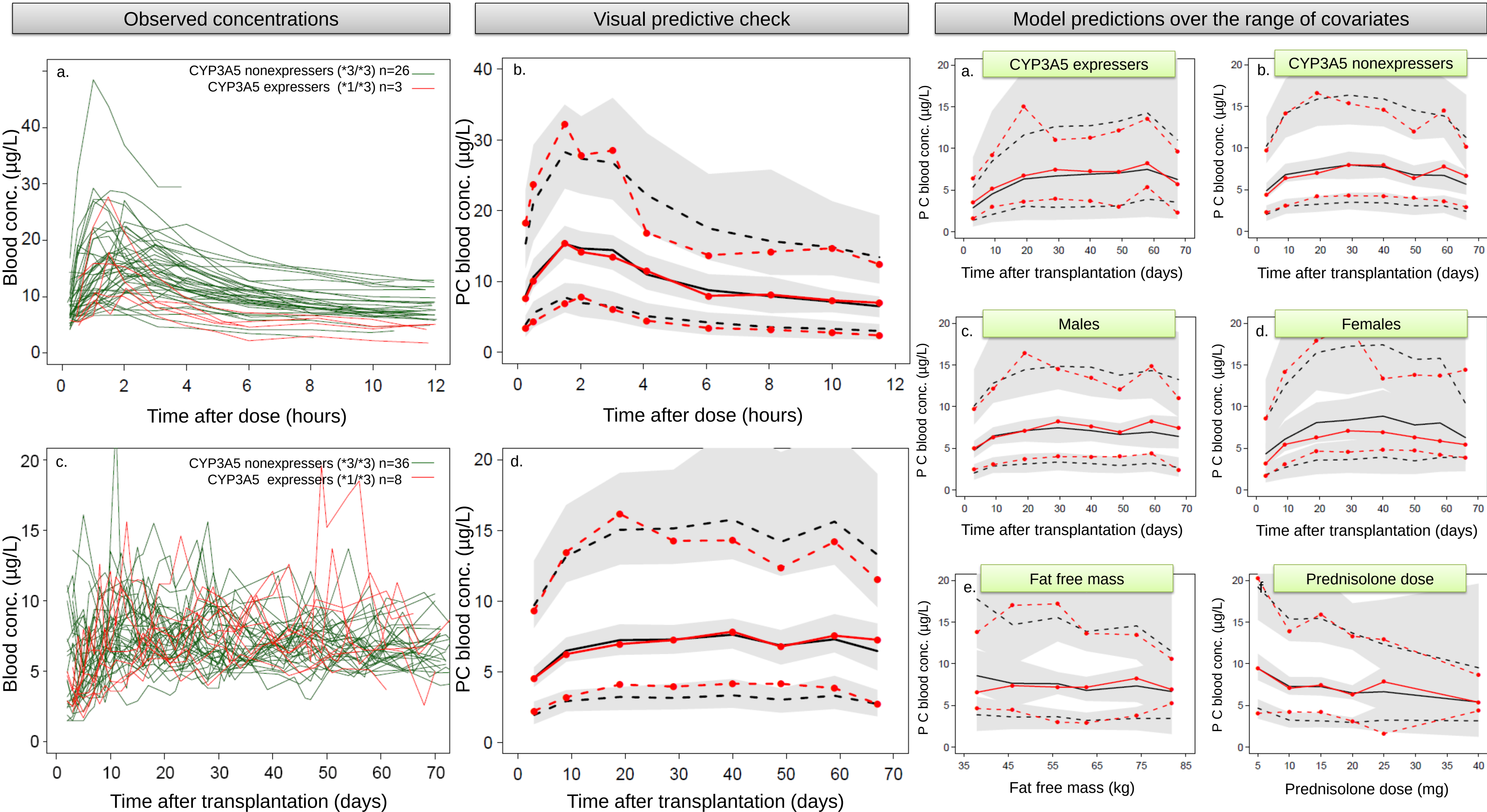


Fig. 1. (a) Observed blood concentrations during a dosing interval at steady state; (b) corresponding prediction corrected visual predictive check (pcVPC); (c) observed trough blood concentrations first seventy days after transplantation; (d) corresponding pcVPC. Solid red line is median observed blood concentration, dashed red lines are 90% observation interval, solid black line is median predicted blood concentrations, dashed black lines are the 90% prediction interval. Gray shaded area represents 95% confidence interval of each prediction interval. PC, prediction corrected

Fig. 2. pcVPCs over the range of covariates in: (a) *CYP3A5* expressers (*1/*3), (b) *CYP3A5* nonexpressers (*3/*3), (c) males, (d) females, (e) over the range of fat free mass and (f) over the range of prednisolone doses. (a)-(d) are shown for prediction corrected trough concentrations relative to post transplant day. PC, prediction corrected

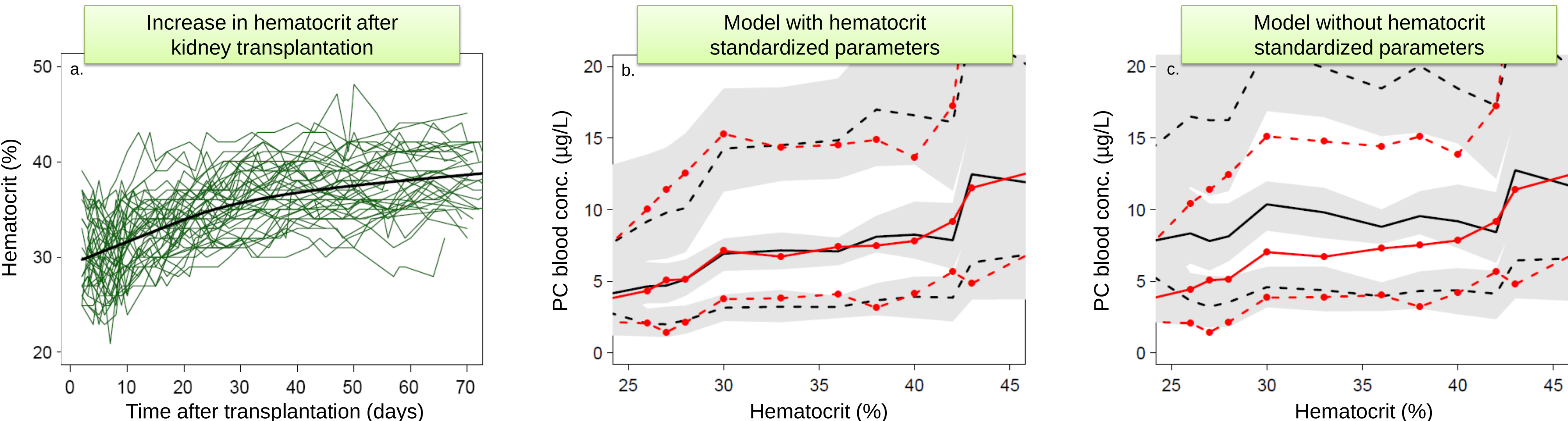


Fig. 3. (a) Hematocrit as a function of time after transplantation; (b) PC observations and predictions as a function of hematocrit; (c) PC observations and predictions as a function of hematocrit without hematocrit standardization. Parameters were not reestimated. PC, prediction corrected

Table 2. Backward elimination of covariates

	ΔOFV
Hematocrit on F	94.7
Time after transplantation on F	90.5
<i>CYP3A5</i> *1/*3 on F	35.5
Prednisolone on F	30.2
Allometric scaling to FFM	15.2
Sex on F	8.7

Table 3. Selected BS results from alternative model

BS results from alternative model with <i>CYP3A5</i> *1/*3 on CL/F and F		
	BS	C.I.
	average	2.5 - 97.5
<i>CYP3A5</i> on CL/F	1.07	0.80 - 1.44
<i>CYP3A5</i> on F	0.51	0.35 - 0.80
BS, bootstrap; C. I., Confidence interval		

Relative bioavailability was decreased by 53% in *CYP3A5* expressers, by 27% in females, by up to 21% with higher prednisolone doses and was 104% higher immediately after transplantation. The two latter effects were best described by sigmoid E_{max} models (Pred₅₀ 16 mg/day, Day₅₀ 1.4 days).

Allometric scaling to fat free mass revealed a relationship between PK and body size in kidney transplanted adults. Studies using total body weight have not found a relationship with size [2-5].

A linear hematocrit associated change in blood concentration explained the time related changes in pharmacokinetics after day 2. Assuming $F=0.2$ [6], the blood clearance of tacrolimus (2.7 L/h/60 kg fat free mass) means it has a low extraction ratio. Pharmacologically active unbound drug clearance should not be affected by changes in hematocrit. Hematocrit based standardization of measured and target concentrations may lead to more consistent clinical effects.

Methods

- 1032 trough concentrations and 44 full PK profiles
- NONMEM 7.2
- First order conditional method with interaction
- Model selection used parameter plausibility, VPC and change in objective function (ΔOFV)
- Two compartments, BOV tested on all parameters
- Study specific first order absorption with lag time
- Study specific residual error with BSV

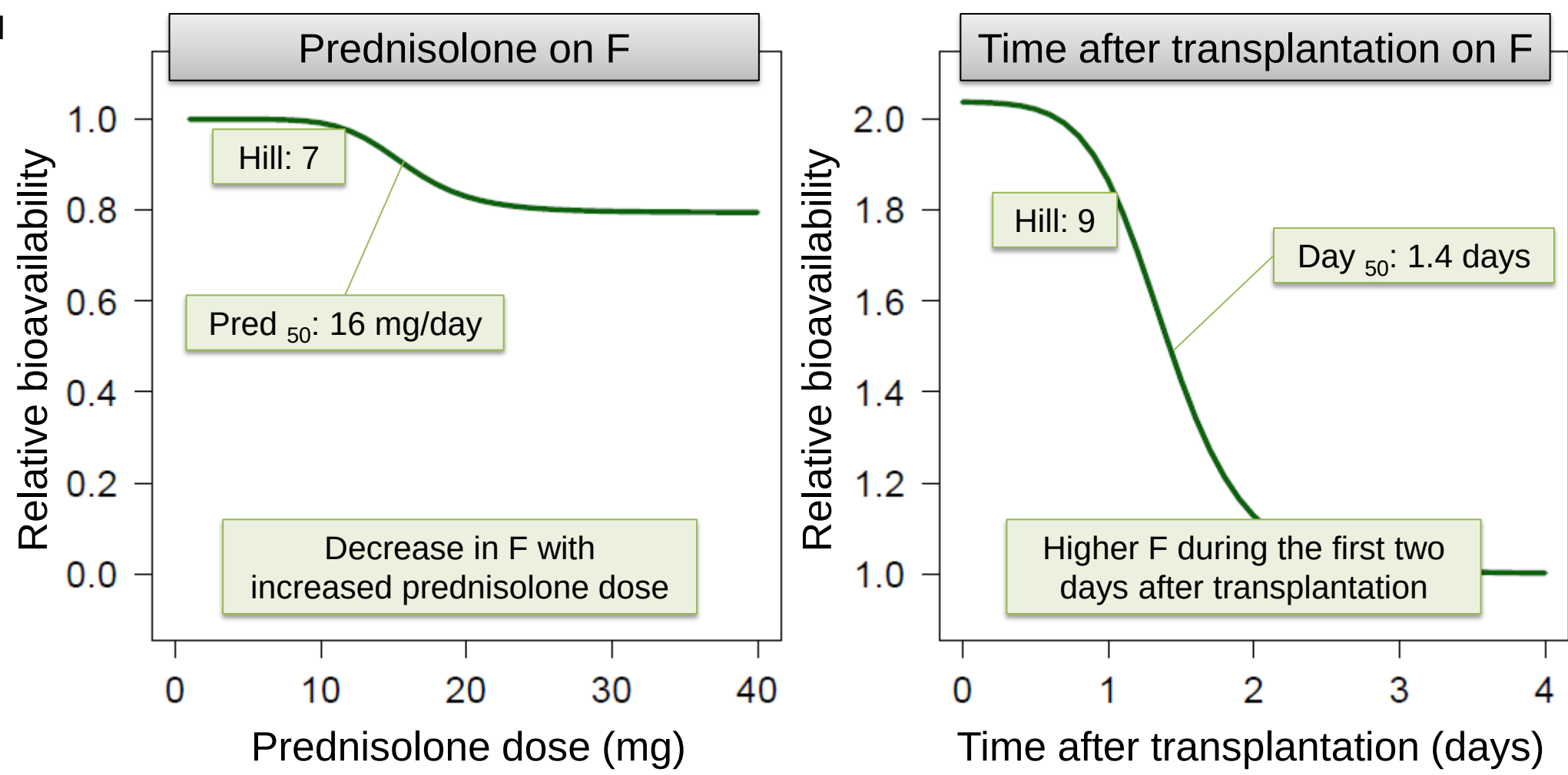


Fig. 4. Effects of prednisolone dose and time after transplantation on bioavailability. Day 0 is the day of surgery. Tacrolimus therapy typically starts this morning.

Table 4. Standardized^a parameter estimates using original data and 500 non-parametric bootstraps

	Predictable effects			Variability (bootstrap)	
	Original data	BS average	C.I. 2.5 - 97.5	BSV (%)	BOV (%) 2.5 - 97.5
CL/F (L/h) ^a	13.9	13.7	11 - 16	33	24 - 42
V ₁ /F (L/h) ^a	74.5	72.8	37 - 99	30	0.003 - 84
Q/F (L/h) ^a	19.4	19.2	11 - 31	99	56 - 128
V ₂ /F (L/h) ^a	371	374	267 - 520	62	32 - 95
Relative F				17	14 - 21
Covariates on F, factor for					
<i>CYP3A5</i> *1/*3	0.47	0.47	0.37 - 0.60		
Sex (female)	0.75	0.73	0.58 - 0.90		
Prednisolone > 16 mg ^b	0.82	0.79	0.64 - 0.89		
First 2 days ^b	1.85	2.04	1.52 - 2.99		
Residual variability					
study 1, 4 (%)				17.4	16 - 19
study 2 (fraction of 1, 4)				0.54	0.4 - 0.7
study 3 (fraction of 1, 4)				0.69	0.5 - 0.8

^a Standardized to male, fat free mass=60 kg, hematocrit =45%, *CYP3A5* nonexpresser, prednisolone dose < 15 mg. BS, bootstrap; C. I., Confidence interval. BSV, between subject variability; BOV, between occasion variability

^b Described by a sigmoidal E_{max} model, where only max effect is included in table. See fig. 3 for details

CL/F, apparent clearance; V₁/F, apparent central volume of distribution; Q/F, apparent intercompartmental clearance; V₂/F, apparent peripheral volume of distribution; F, bioavailability; *CYP3A5*, Cytochrome P450 3A5