

Evaluation of dosing strategies to achieve targeted tacrolimus exposure after adult kidney transplantation

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Aims

- To examine the extent of target achievement of tacrolimus using different dosing strategies
 - Weight-based (mg/kg)**
 - Mechanism-based**
 - Bayesian forecasting**

Conclusions

- Weight-based dosing** was only slightly worse compared to **Mechanism-based dosing** for target achievement, resulting in 32 % vs. 37 % of concentrations within the acceptable range, respectively
- Bayesian forecasting** substantially improved target achievement to 65 % of the concentrations. However, 35% were still outside the suggested acceptable range. To improve this, between-occasion variability associated with tacrolimus oral bioavailability needs to be further characterised so that it can be predicted

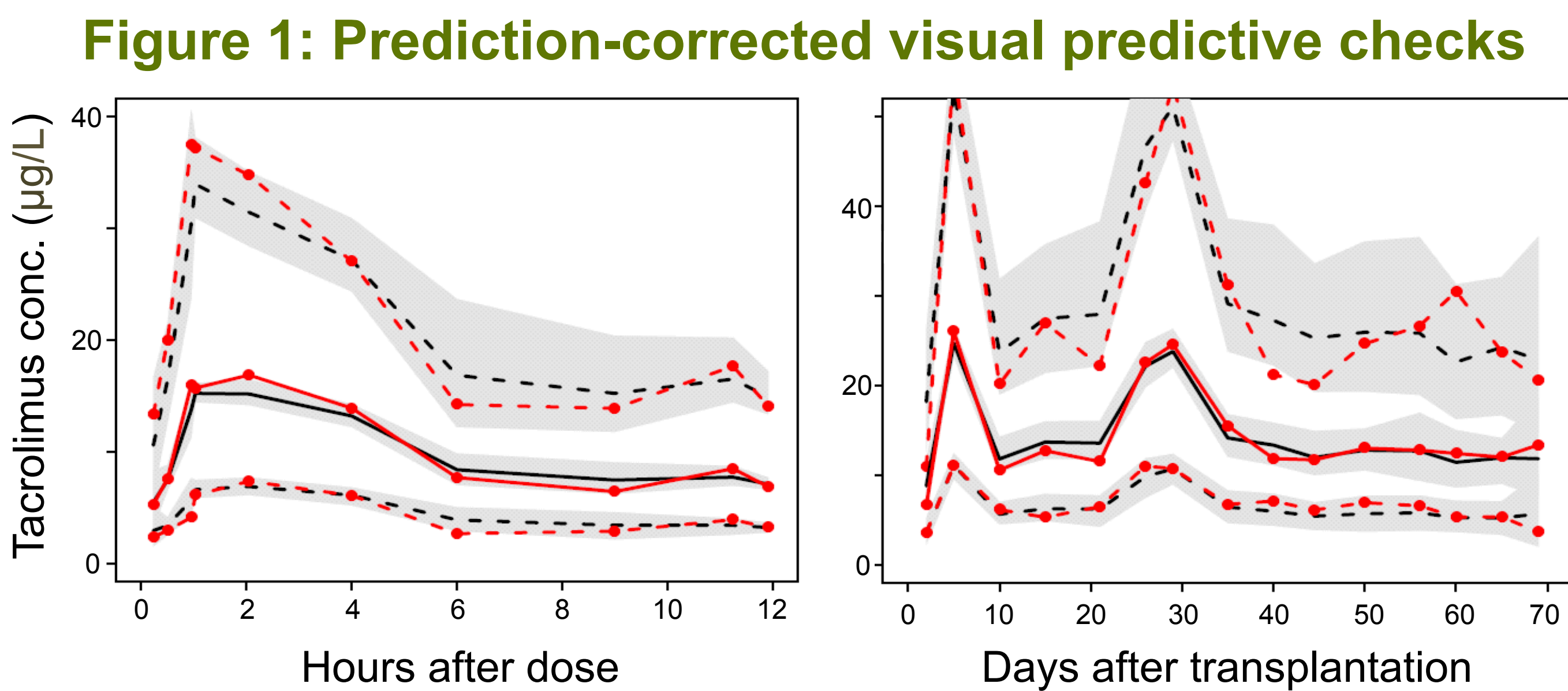
Background and theory-based model

- Tacrolimus is used to prevent rejection after kidney transplantation. Its dosing is complicated by a narrow therapeutic range and large pharmacokinetic variability between subjects and dosing occasions
- We previously developed a theory-based population pharmacokinetic model based on 3100 tacrolimus whole blood concentrations in 242 kidney transplanted adults (Table 1, Figure 1) [1]

Table 1: Population parameter estimates

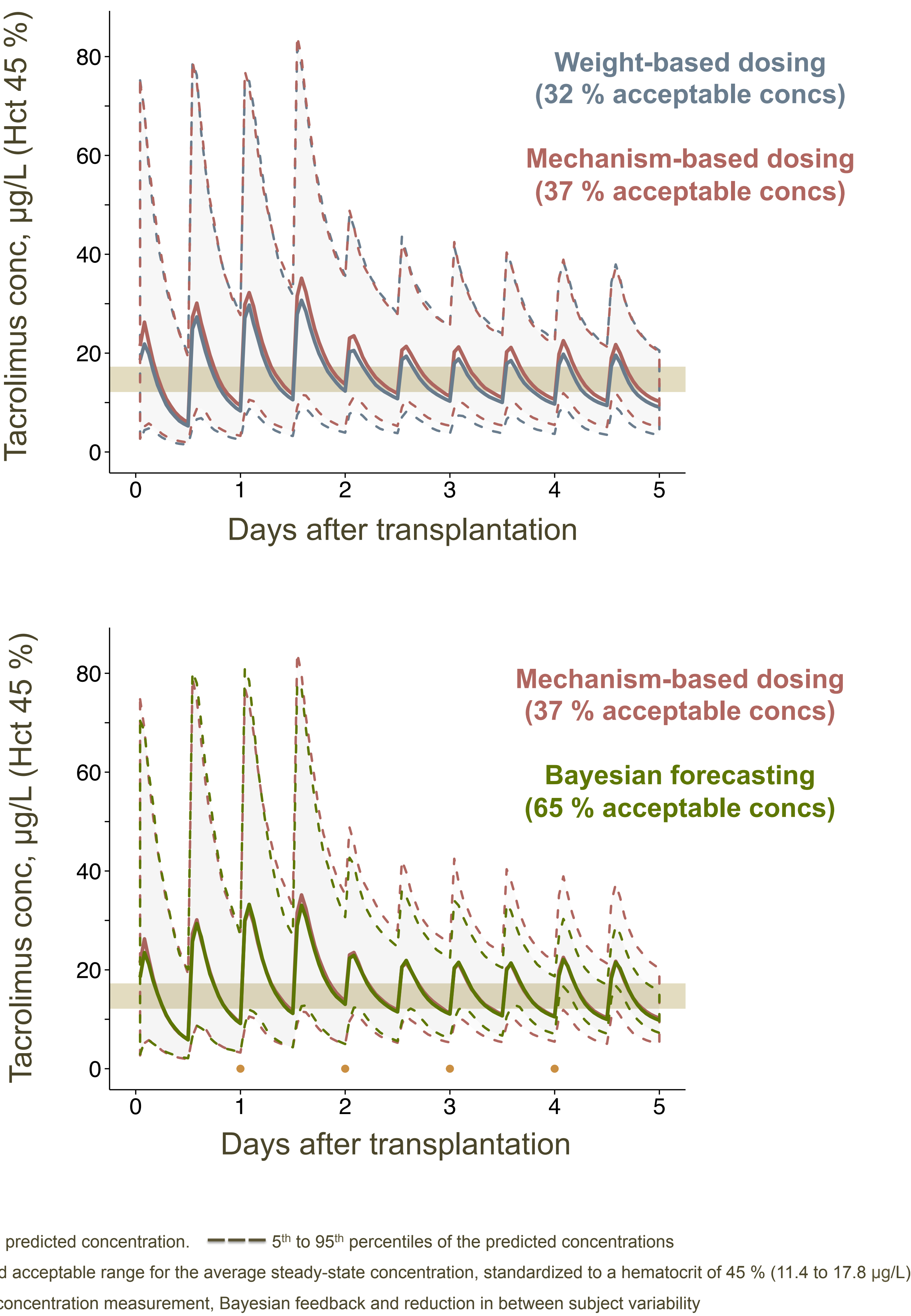
Parameter		Estimate (Hct 45 %)*	BSV (CV %)	BOV (CV %)
CL (L/h)	$\times (FFM/60)^{3/4}$	16.1	40 %	
	$\times \theta_{CYP3A5}^{*1/*X}$	1.30		
V1 (L)	$\times FFM/60$	125	54 %	
Q (L/h)	$\times (FFM/60)^{3/4}$	23.8	63 %	
V2 (L)	$\times FFM/60$	636	57 %	
Bioavailability (F)		1**		23 %
	$\times \theta_{CYP3A5}^{*1/*X}$	0.82		
	$\times \theta_{Day\ 1\ and\ 2\ post-transplant}$	2.68		
	$\times Prednisolone\ induction\ function$			
	$E_{max}\ (%)$	-67 %		
	$ED_{50}\ (mg)$	35 mg		
Absorption rate (h^{-1})		1.0		120 %
Absorption lag (h)		0.4		
Residual error (%)		14.9		

*Standardized to hematocrit (Hct) of 45 % and FFM of 60 kg (FFM 60 kg was typical of total body weight 70kg in our study population). **Defined as population value.
BOV= between occasion variability, BSV= between subject variability, CYP3A5= cytochrome P450 3A5; FFM= fat free mass



Results

Figure 2: Concentration-time profiles in 1000 simulated individuals using various dosing strategies



— Median predicted concentration. — 5th to 95th percentiles of the predicted concentrations
Suggested acceptable range for the average steady-state concentration, standardized to a hematocrit of 45 % (11.4 to 17.8 µg/L)
• Times of concentration measurement, Bayesian feedback and reduction in between subject variability

Methods

- Simulated concentration-time profiles of 1000 subjects

Doses based on

- total body weight** (0.04 mg/kg/12 hours)
- CL and F from population pharmacokinetic parameter values and **mechanism-based** individual covariates to achieve a target concentration:
 - fat free mass
 - CYP3A5 genotype
 - prednisolone dose
- as in (ii), but designed to imitate the effect of **Bayesian dose adjustment** by tapering of between-subject variability to zero over the first five days without a change in between-occasion variability

Target concentration

- average steady-state concentration of **14.2 µg/L** (standardized to a hematocrit of 45 %) [2] with a suggested acceptable range defined as 80-125 % of the target concentration [3]

References

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- Holford NHG, Buclin T. Ther Drug Monit 2012;34:565–8.

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