TACROLIMUS BAYESIAN DOSE ADJUSTMENT IN A LARGE POPULATION OF PAEDIATRIC RENAL TRANSPLANT RECIPIENTS

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Introduction

ISBA is an online expert system (**https://pharmaco.chu-limoges.fr**) routinely used since 2005 for estimating the AUC of immunosuppressive drugs through PK modelling and Bayesian estimation, and proposing dose adjustments to reach predefined exposure targets.

Objectives

We retrospectively analysed the ISBA database to describe tacrolimus (Tac) pharmacokinetics and exposure, evaluate the efficiency of ISBA dose recommendations and propose Tac $AUC_{0\text{-}12h}$ target ranges in paediatric kidney allograft recipients.

Methods

We analysed 1935 requests for Tac dose adjustment in 419 patients aged <19 years treated with immediate-release Tac, posted by 21 French renal transplantation centers.
We studied the variability of Tac exposure and the efficiency of AUC dose adjustment.
Using the AUC vs. C0 regression equations at different periods post-transplantation periods, we derived $AUC_{0\text{-}12h}$ target ranges from the C0 target ranges.

Conclusions

- Tac $AUC_{0\text{-}12h}$ intra-individual variability is rather low in paediatric kidney transplant recipients
- Based on its (rather loose) correlation with C0, we propose target ranges for Tac $AUC_{0\text{-}12h}$ in this population, very close to those previously reported for adults (1)
- ISBA efficiently helps to reduce Tac underexposure or overexposure.
- Estimating the AUC/C0 ratio may help to determine personalized C0 targets.

References

1. Saint-Marcoux et al. Lessons from routine dose adjustment of tacrolimus in renal transplant patients based on global exposure. Ther Drug Monit. 2013;35(3):322-7

Results

Demographics

- 419 patients from 21 French KTR centres → 1935 Tac $AUC_{0\text{-}12h}$
- Tacrolimus dose: 3.5 ± 2.2 (0.5 – 20.0) mg bid
- Patient age: 12.3 ± 4.7 (2.0 – 18.9) years

Variability of AUC0-12h

- Inter-individual: 40% over all post-transplant periods
- Intra-individual: 32.3% over all post-transplant periods,
  25.8% when restricted to a 3-month time span

Age effect

- No age effect on tacrolimus C0 or AUC
- Tacrolimus dose increase significantly with age
- Cmax, C0/dose, Cmax/dose, AUC/dose decrease significantly

AUC/C0 does not vary with age or post-transplantation period

Table 1: $AUC_{0\text{-}12h}$ ranges proposed for pediatric KTR

	Post-Tx period	<M3	M3 – M12	>M12
C_0 target range: 3-7 ng/mL	AUC range proposed in paediatrics	85-155	80-140	70-130
	AUC range proposed in adults (1)	*75-140*	*80-140*	*75-130*
C_0 target range: 5-10 ng/mL	AUC range proposed in paediatrics	120-200	110-190	100-170
	AUC range proposed in adults	*110-190*	*110-180*	*100-170*
C_0 target range: 8-12 ng/mL	AUC range proposed in paediatrics	170-240	155-220	140-200
	AUC range proposed in adults	*NA*	*150-210*	*140-200*
C_0 target range: 10-15 ng/mL	AUC range proposed in paediatrics	200-285	185-265	170-245
	AUC range proposed in adults	*190-270*	*180-250*	*NA*

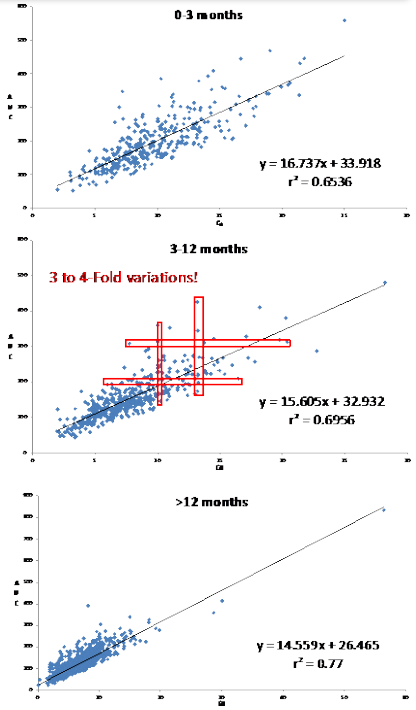

Figure 1: $AUC_{0\text{-}12h}$ vs. C0

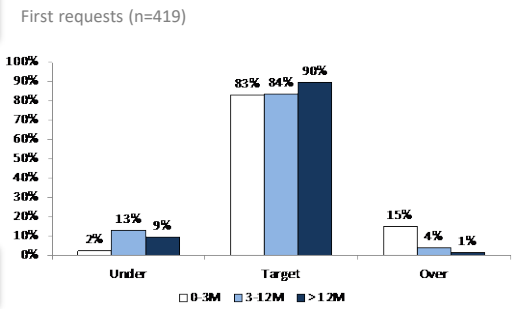

Figure 2: % of 1st requests in the recommended AUC target ranges

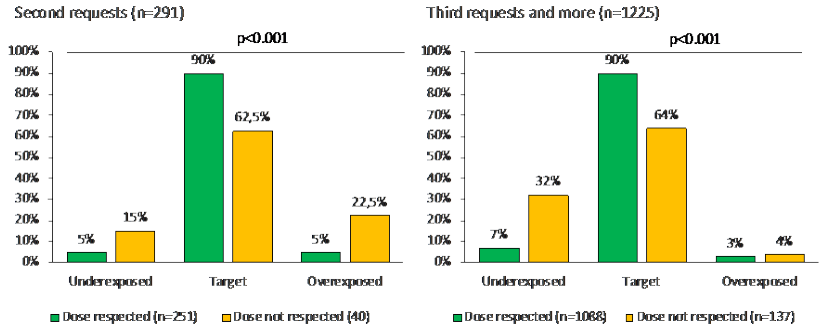

Figure 3: % requests of rank ≥2 in the recommended AUC ranges