Microsampling in transplant recipients: time to reshape tacrolimus from trough concentration to AUC?

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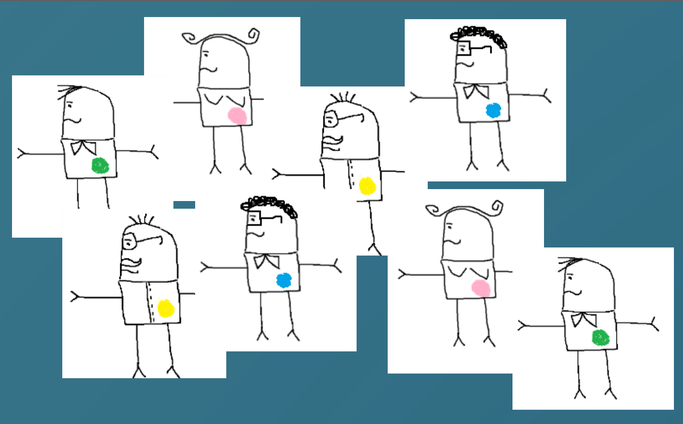
Introduction

Therapeutic drug monitoring (TDM) is an important tool in preventing acute rejection (AR) and drug-related adverse events in solid organ transplantation (SOT). For tacrolimus (TAC), it is usually conducted by measuring trough concentrations (Cmin) of the drug assuming an adequate correlation between this single point measurement and total exposure of the drug (reflected by the area under the curve of drug concentrations (AUC)). The main limiting factor to the recourse to AUC measurement is the high number of samples required to properly evaluate TAC exposure. Microsampling devices allowing measuring TAC concentration on a single blood drop obtained through fingerprick has now overcome these difficulties.

The aim of this study is to evaluate the relationship between TAC Cmin and AUC in solid organ transplant patients.

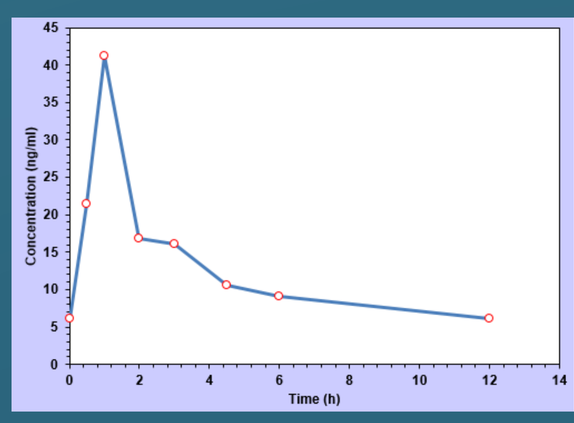
Methods

Liver and kidney transplant recipients presenting various issues (suspicion of rejection, rapid kidney deterioration, high Cmin variability…)



Benefiting from a tacrolimus area under the curve measurement using microsampling devices (Mitra, Neoteryx, CA, USA) and analyzed by LC-MS/MS

Pharmacokinetic parameters estimated with a non-compartmental analysis using the PKSolver software[1]



Results

21 patients included (20 kidney and 1 liver transplant patients)

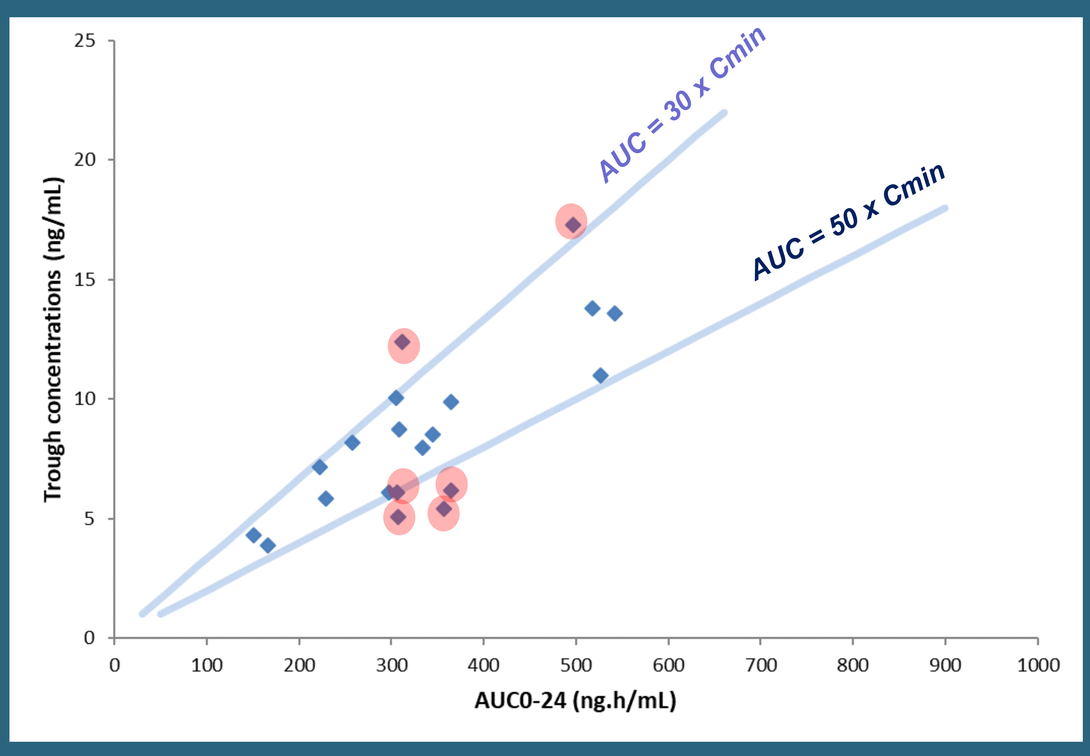
- 6 Immediate-release formulations
- 5 prolonged-release formulations
- 10 LCP-tacro formulations

n=8

Patients characteristics

Pharmacokinetic parameters		
Parameter	**Median**	**Inter-Quartile Range**
Daily dose (mg/d)	11	5-17
AUC0-24 (ng.h/mL)	312	297-364
Cmin (ng/mL)	8.1	6.0-10.3
Cmax (ng/mL)	27.5	17.6-33.0
Tmax (h)	3.5	2-6
AUC/Cmin	39.2	31.4-47.9
AUC/dose (ng.h/mL/mg)	31.3	23.7-57.4

Main objective



Large variability on Cmin (CV = 41%) and AUC (CV = 34%) even higher when correcting for dosage AUC/dose (CV = 57%)

6 patients out of 21 (28.5%) outside the 30-50 x Cmin AUC

3 patients out 4 of patients with AUC > 50 x Cmin cotreated with calcium channel blockers

CV : coefficient of variation

Conclusion

Microsampling approaches allows accessing AUC in solid organ transplant patients. Tacrolimus TDM using AUC might be beneficial to patients by individualizing dosage to real exposure and avoiding using an AUC surrogate (Cmin). This proof-of-concept study showed the feasibility and interest of the approach. In this selected population of patients **more than 1 patient out of 4 display Cmin badly reflecting their tacrolimus exposure**. As proposed by the recent IATDMCT consensus on tacrolimus therapeutic drug monitoring[2], AUC should be implemented in the standard management of transplant recipients.

References:

[1]PKSolver, Zhang et al., *Comput Methods Programs Biomed*. 2010; [2]Brunet et al., *Ther Drug Monit* 2019.