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)). Another 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 obtain 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.

Method:

Consecutive AUC measurements proposed to transplant recipients treated by TAC were analyzed. Eight fingerprick samples were drawn to patients using Mitra©microsampling devices (Neoteryx, CA, USA). TAC blood levels were measured using a validated LC-MS/MS method (Tron *et al.*, Submitted) and AUC and pharmacokinetic parameters estimated using a non-compartmental analysis approach (PK Solver, Zhang *et al.*, Comput Methods Programs Biomed. 2010). The following data were collected: gender, weight, drug formulation and dosage, organ transplanted and potential interacting treatment.

Results:

Fifteen patients (14 kidney and 1 liver recipients) have been included during 10 months in the study (9 LCP-Tacro, 4 Prolonged-release and 2 Immediate-release tacrolimus). A moderate correlation has been observed between Cmin and AUC (R^2 = 0.69). Median AUC0-24 over Cmin ratio was 40.3 (IQR 30.9-44.9). Two patients had very high AUC/Cmin ratio (above 60) and both were co-treated with calcium channel antagonists which are known to inhibit CYP3A4.

Conclusion:

This preliminary results shows how loose can be the relationship between AUC and Cmin. Measuring AUC offers proper evaluation of TAC exposure compared to Cmin. Microsampling approaches allows access to AUC with minimally invasiveness in transplant recipients making it a convenient strategy to reevaluate the exposure-effect relationship in SOT.