Oral

[O26-3] O26-3: Pharmacogenomics (1)

Chairs: Ichiro Ieiri, Japan / Vincent Haufroid, Belgium
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[O26-3-1] Tacrolimus updated guidelines through population-based pharmacokinetics modeling: how to benefit more from CYP3A pre-emptive genotyping prior to kidney transplantation

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Background

Tacrolimus (Tac) is a profoundly effective immunosuppressant that reduces the risk of rejection after solid organ transplantation. However, its use is hampered by its narrow therapeutic window along with its highly variable pharmacological (pharmacokinetic [PK] and pharmacodynamic [PD]) profile. Part of this variability is explained by genetic polymorphisms affecting the metabolic pathway. The integration of *CYP3A4* and *CY3A5* genotypes in tacrolimus population-based PK (PopPK) modeling approaches has been proven to accurately predict the dose requirement to reach the therapeutic window. The objective of the present study was to develop an accurate PopPK model in a cohort of 59 kidney transplant patients to deliver this information to clinicians in a clear and actionable manner.

Methods

We conducted a non-parametric nonlinear effects PopPK modeling analysis in Pmetrics®. 59 Patients were genotyped for the *CYP3A4*22* and *CYP3A5*3* alleles and were classified into 3 different categories (poor metabolizers (PM), Intermediate metabolizers (IM) or extensive metabolizers (EM)). Probability of target attainment analysis was performed with 5 simulated doses and 6 different trough concentration targets to propose new guidelines according to *CYP3A* profile

Results

A one-compartment model with double gamma absorption route described very accurately the tacrolimus PK. In covariate analysis, only *CYP3A* genotype was retained in the final model (Δ-2LL=-73). Our model estimated that tacrolimus concentrations were 33% $IC_{95\%}$[20-26%] and 41% $IC_{95\%}$[36-45%] lower in *CYP3A* IM and EM when compared to PM, respectively. Our PTA analysis results suggest that a starting dose around 0.07 mg/kg bodyweight b.i.d. for PM, 0.13 mg/kg bodyweight b.i.d. for IM and 0.2 mg/kg bodyweight b.i.d. for EM would better fit that a universal dosage for everyone.

Conclusions

With the present analysis, we add a slight nuance to the CPIC tacrolimus dosage guidelines according to *CYP3A5*3* allelic status by considering the decrease of function caused by the *CYP3A4*22* allele. Subsequently, after therapy initiation, this tool would also probably benefit the clinician if used in a Bayesian

adaptive control system.