Model-informed precision dosing of everolimus: external validation in adult renal transplant recipients

**Background & aim**

- Everolimus is an immunosuppressive drug from the class of mammalian target of rapamycin (mTOR) inhibitors, used for graft rejection prophylaxis in renal transplantation.
- Everolimus efficacy is challenged by extensive between-subject PK variability and a narrow therapeutic index. This necessitates an individualized dosing approach, typically established using whole blood trough concentration TDM.  
- Unfortunately, TDM target attainment rates are often unsatisfactory and patients with on-target everolimus exposure may still develop organ rejection. This illustrates a need for improved monitoring of everolimus therapy.
- As everolimus displays erythrocyte partitioning, hematocrit-corrected whole blood exposure has been suggested as a more informative TDM marker. Furthermore, model-informed precision dosing (MIPD) has introduced options for more sophisticated dose adaptation.
- We have previously developed a mechanistic population PK model, intended for everolimus MIPD, which enables estimation of hematocrit-corrected whole blood exposure.
- Here, we externally evaluated this model for its utility for everolimus MIPD in a retrospective cohort of renal transplant recipients.

**Methods**

- The retrospective external dataset included 2933 whole blood trough concentrations and 322 abbreviated AUC$_{0-12}$, from routine everolimus TDM in 173 renal transplant recipients treated at Leiden University Medical Center.
- First, the appropriateness of the population PK model for application in renal transplantation was evaluated with a prediction-corrected visual predictive check (VPC).
- Second, a fit-for-use validation was conducted to evaluate if the model could accurately and precisely predict future everolimus exposure from prior PK data. Prediction bias and imprecision were expressed as the mean (MPFE) and mean absolute percentage prediction error (MAPE), stratified on six months after transplantation.
- Third, the model was used to calculate dose adaptation advice, which were then compared to conventional TDM-guided dose adaptation advice (data not shown).
- Fourth, the model was used to calculate hematocrit-corrected trough concentrations and AUC$_{0-12}$ by normalizing the observations to the expected mean population hematocrit (0.38). The extents of differences between the observed and hematocrit-corrected everolimus trough concentrations and AUC$_{0-12}$ exceeding ±20% were then quantified, as these would result in different TDM dose adaptation recommendations.
- The population PK modelling was performed using NONMEM® 7.30 (Icon Development Solutions, Ellicott City, MD, USA), with Perl-speaks-NONMEM Toolkit 4.8.1 and Piranha 2.9.7 as modelling interface. Data handling, visualization and statistics were performed with R 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) and RStudio 1.2.5001 (RStudio Inc. Boston, MA, USA).

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**Discussion**

- No full AUC$_{0-12}$ curves were available. Alternatively, AUC$_{0-12}$ were estimated with the model using 4-6 PK samples within 0-6h after everolimus intake. This may have slightly biased the fit-for-use results for AUC$_{0-12}$ based MIPD.
- Whereas we only included renal transplant recipients, our results can likely be extrapolated to oncology patients, as everolimus PK is similar in these populations.

**Conclusions**

- The population PK model accurately and precisely predicts future exposure from prior PK observations, demonstrating its utility for everolimus MIPD.
- The model provides a practical means of performing TDM based on hematocrit-corrected whole blood exposure, which poses a promising strategy to further optimize everolimus therapy.