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

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Background
The immunosuppressant everolimus is increasingly applied in renal transplantation. Its extensive PK variability and narrow therapeutic index necessitate TDM-guided dose adaptation. Whereas most centers rely on conventional TDM, more sophisticated model-based approaches are available. We externally validated a previously published mechanistic population PK model, intended for model-informed precision dosing (MIPD) of everolimus.

Methods
The validation dataset included trough concentrations (C_0) and PK curves (0-6h), collected retrospectively from routine TDM. The evaluated model accounts for saturable erythrocyte-binding of everolimus in whole blood (WB) and estimates plasma PK parameters using paired everolimus and hematocrit (Hct) observations, enabling Hct-correction. Model appropriateness was evaluated with a prediction-corrected VPC. Model performance for its intended use; to predict a future C_0 or AUC using prior PK data, was evaluated with a fit-for-purpose analysis, stratified on the early (≤6 months) and late (>6 months) posttransplant periods. Bias and precision were expressed as the mean (MPE) and mean absolute (MAPE) prediction error. The percentage of predictions within ±10-30% of observations (P_{10}-P_{30}) were also assessed. Lastly, TDM target attainment of observed and Hct-normalized C_0 and AUC were assessed..

Results
4132 PK observations were available from 173 renal transplant recipients. The VPC showed adequate model appropriateness. The fit-for-use analysis showed accurate and precise predictions for C_0 in the early (MPE: 8.1±2.5%, MAPE: 26.8±2.1%, P_{10}: 30.9%, P_{30}: 71.1%) and late (MPE: 4.7±2.0%, MAPE: 25.4±1.4%, P_{10}: 28.2%, P_{30}: 70.7%) periods, and for AUC in the early (MPE: -9.7±5.1%, MAPE: 13.3±3.9%, P10: 50.0%, P_{30}: 90.6%) and late (MPE: -0.13±4.8%, MAPE: 13.3±2.8%, P_{10}: 37.5%, P_{30}: 95.8%) periods. Hct-correction yielded TDM decision differences on 16.4% and 15.5% of occasions as compared to TDM based on the observed C_0 and AUC. Whereas this study included renal transplant recipients exclusively, our results can likely be extrapolated to oncology patients as everolimus PK in these populations is similar.

Conclusion
Our model accurately and precisely predicted future everolimus exposure, demonstrating its utility for everolimus MIPD. Additionally, we illustrated the potential added value of Hct-normalized everolimus TDM, which poses a promising strategy to further optimize everolimus therapy. These results provide reassurance to clinically implement this methodology for further evaluation.