DEVELOPMENT OF A POPULATION PHARMACOKINETIC META-MODEL FOR EVEROLIMUS FROM SIMULATED DATABASE

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Individual Profiling and Prevention of Risks
with Immunosuppressive Therapies
and Transplantation

Introduction

- Everolimus (EVE) is a selective mTOR (Mammalian Target of Rapamycin) inhibitor commonly used as immunosuppressive therapy in combination with, or as a replacement to, calcineurin inhibitors in order to reduce their nephrotoxic effects. EVE is also used alone or in combination with inhibitors of other pathways as a treatment of metastatic renal cell carcinoma, advanced breast cancer, neuroendocrine tumors and tuberous sclerosis complex.
- Although the dose used in the two groups of indications is quite different, its use is not without limitations. Indeed, EVE is characterized by a narrow therapeutic range which can lead to therapeutic failure or toxicity, and significant interindividual pharmacokinetic variability explained at least in part by its metabolism by cytochrome P450 3A4 and its transport by P-glycoprotein. As a result, therapeutic drug monitoring is deemed necessary in transplantation, while surprisingly it is not currently performed in oncology.
- For the purpose of dose optimization, population pharmacokinetic (PKpop) models were developed in small and homogeneous patient groups with given diseases. Ter Heine *et al.* published a mechanistic Pkpop model for everolimus in cancer and transplant patients and proposed alternative dosing regimens [1] .
- The objective of the present study was the development of a PKpop meta-model for everolimus using a simulated patients' data generated based on previously published PK parameters values from EVE PKpop across indications.

Methods

- A literature review was performed in Pubmed to find PKpop models of everolimus published up to June 4, 2018 (Figure 1).
- Five patient characteristics databases were independently generated using R software starting from demographic characteristics, dosing regimen and biological parameters (mean, range and variance) described respectively in the 5 published PKpop models [2–6],
- The virtual patient demographics in the databases were used to simulate corresponding detailed concentration-time profiles according to the structural and error model, the significant covariates and the dosing regime published for each of the models. These simulated datasets were evaluated by ensuring that each of them allowed the estimation of pharmacokinetic parameters similar to the original (published) model described in the literature.
- The five simulated datasets were pooled, and the meta-dataset served to build a PKpop meta-model using a top-down approach.
- This model was externally validated on an independent dataset of 499 PK observations from 89 real kidney, liver or heart transplant recipients.
- Virtual patient generation, model development and validation were all performed using NONMEM 7.3.

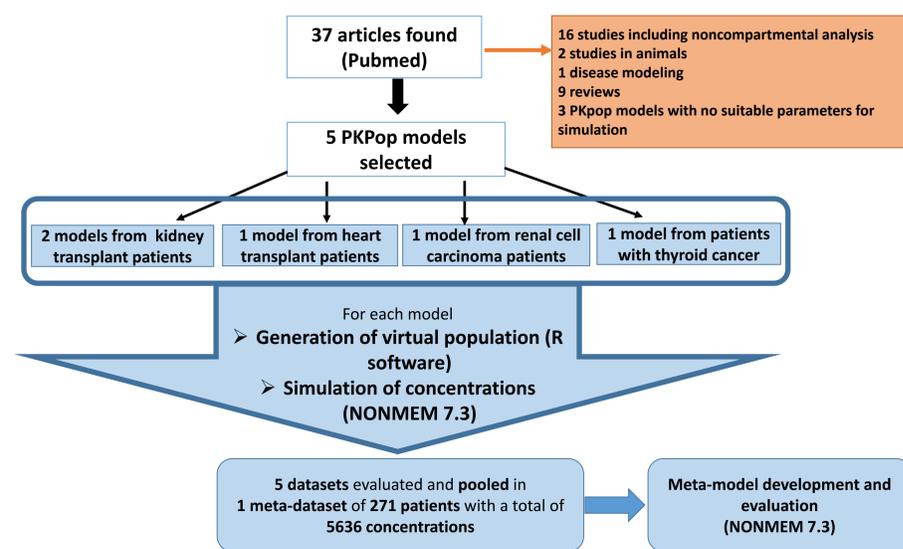Fig.1 : Selection of published model and simulation of dataset

Figure 2 : Goodness-of-fit plots of the final Pkpop model (A) observed versus individual predicted concentrations and (B) individual weighted residuals (IWRES) versus time after treatment initiation
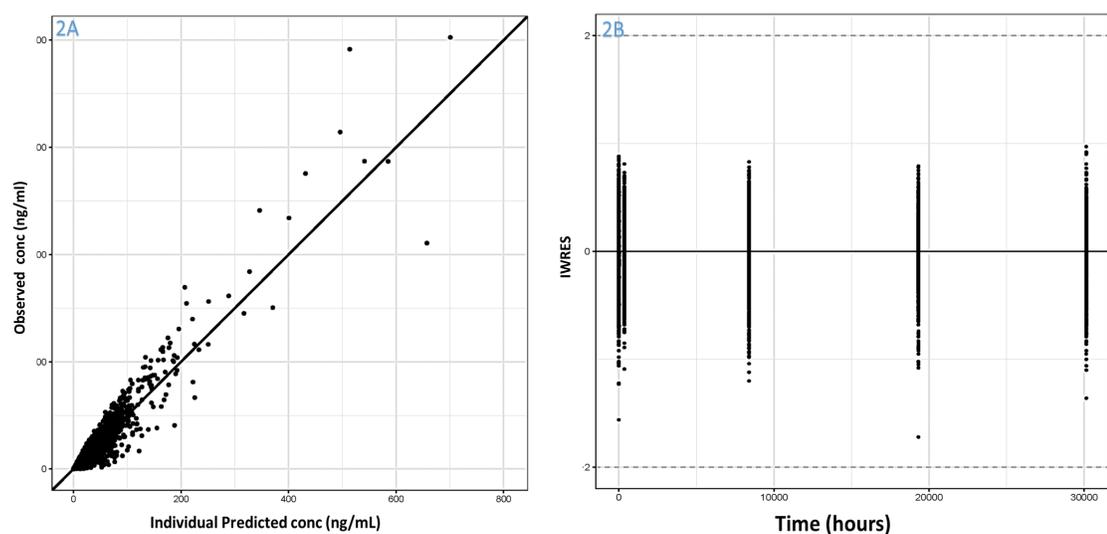

Fig.3 : NPDE Plots. (A) Distribution of NPDE and (B) NPDE versus predicted concentrations
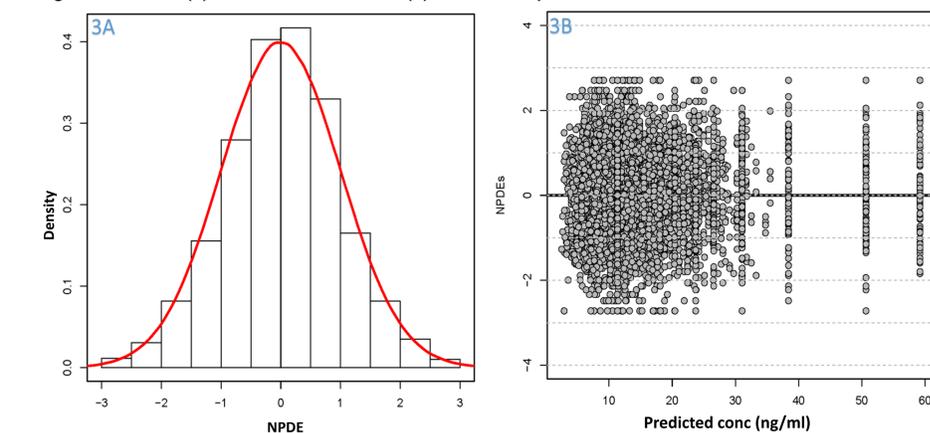

Figure 4 : Prediction-corrected visual predictive check (pcVPC) of model's description of the data
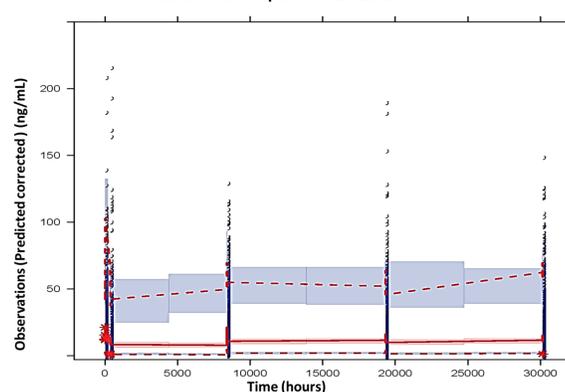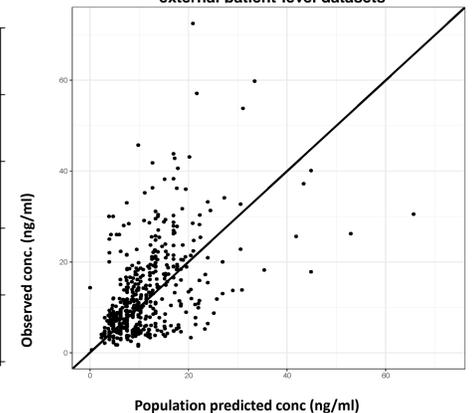

Figure 5 : Goodness-of-fit plots of the final PKpop model in the external patient-level datasets

Results

The meta-model developed using simulated everolimus concentrations was structurally a two-compartment model with first order absorption and a lag time and first order elimination. The type of indications (transplantation or oncology) were found to influence the drug apparent clearance (CL/F) (1.3 higher in transplant patients). A dose-dependent clearance has been described according to the following relationship : $CL/F = (DOSE/2.5)^{0.27}$.

Apparent clearance, central compartmental volume, intercompartmental clearance, first-order absorption rate and absorption lag-time were 23.42 L.h^{-1}, 46.01 L.h^{-1}, 183.5 L, 5.434 h^{-1} and 0.6329 h, respectively for a 60kg patient taking 2mg twice daily. The model parameters were estimated with acceptable imprecision (i.e. relative standard error of <20%, except for the absorption rate).

The individual predictions were evenly distributed around the line of unity (Figure 2). Normalized prediction distribution error (NPDE) analysis showed adequate predictive ability, with the distribution of the NPDEs showing acceptable deviation from a normal distribution (Figure 3). Prediction-corrected visual predictive checks (pcVPC) (Figure 4) showed how well the average trend of the observations (solid red line) and how well the variability of the observed data (dashed red lines) fall within the model simulated (n=1000) average trend (red shaded area) and the model simulated variability (blue shaded areas) represented as 95% confidence interval. The model displayed acceptable results with regards to external validation as shown by an adequate correlation between observed and predicted everolimus concentrations for the external datasets (Figure 5).

Conclusion

A PKpop meta-model was developed using simulated data from kidney or heart transplant patients, and cancer patients and validated using observed data from transplant patients. Our study have some limitations. We assumed normal distribution for the parameters generated using mean and standard deviation published. However, the performances of this meta-model are similar to those of existing models for both types of indications. Further validation in oncology is needed.

References

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