Population pharmacokinetic model and Bayesian estimation of mycophenolic acid AUC in patients on enteric-coated mycophenolate sodium

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Background. Mycophenolic acid (MPA), the active moiety of enteric-coated mycophenolate sodium (EC-MPS), is characterized by highly variable pharmacokinetics. To our knowledge, only two population pharmacokinetic (POPPK) models and one Bayesian estimator (MAP-BE) have been published to estimate the AUC of MPA for EC-MPS, in renal transplantation specifically. Our objective was to develop a POPPK model and a MAP-BE allowing the estimation of MPA AUC with a limited sampling strategy in solid organ transplant (SOT) recipients and patients with auto-immune diseases (AID) on EC-MPS.

Methods. Full and sparse MPA pharmacokinetics profiles were extracted from our expert system ISBA and split into a training and a validation set (respectively 75% and 25% of the profiles). Pharmacokinetic parameters were estimated in Monolix® with the stochastic approximation expectation-maximization (SAEM) algorithm. First order, transit, simple and double gamma absorption models were compared. The selection criteria of the model were a minimized -2 log likelihood and relative standard error of PK parameters estimation <40%. The evaluation of the model included visual inspection of goodness-of-fit plots and prediction-corrected visual predictive check. The AUC estimated by MAP-BE and LSS was compared to the reference trapezoidal $AUC_{0\text{-}12h}$ estimated with Simulx®. The prediction error and root mean square error had to be respectively <10% and <25%.

Results. We included 153 PK profiles (863 concentration values) collected from 129 patients (116 SOT, 13 AID), aged (median [IQR]) 47 year-old [22-63]. The EC-MPS dose per intake was 360 mg [360-720] and the reference $AUC_{0\text{-}12h}$ was 51.6 h.mg/L [39.8-67.1]. The best POPPK model was a two-compartment model with double-gamma absorption and first-order elimination. The only covariate kept in the final model was the indication of EC-MPS. The final model included inter-occasion variability on the rate constants of the gamma distribution. The main PK parameters (mean±SD) were: MAT_1=4.3±3.4 h; MAT_2=7.4±5.5 h; Cl/F=9.3±4.3 L/h; Vd/F=10.2±1.3 L. The optimal LSS is under investigation.

Conclusions. The double absorption gamma model showed accurate fit and reduced computation time. The MAP-BE will provide clinicians a convenient and robust tool for EC-MPS dose individualization in SOT and AID patients.

Key Words. Mycophenolate sodium, population pharmacokinetic, Bayesian estimator, solid organ transplantation.