Poster

[P25-8] P25-8: Immunosuppressive drugs (3): Biomarkers and pharmacokinetics

Chair: Hideyuki Motohashi, Japan

Mon. Sep 25, 2017 12:30 PM - 1:30 PM Annex Hall (1F)

(Mon. Sep 25, 2017 12:30 PM - 1:30 PM Annex Hall)

[P25-8-6] Additional value of CYP3A5 status in a tacrolimus population pharmacokinetic model used for therapeutic drug monitoring

Jean-Baptiste Woillard[1], Franck Saint-Marcoux[2], Caroline Monchaud[3], Christian Woloch[4], Pierre Marquet[5]
(1.CHU Limoges, Univ Limoges, 2.CHU Limoges, Univ Limoges, 3.CHU Limoges, Univ Limoges, 4.CHU Limoges, Univ Limoges, 5.CHU Limoges, Univ Limoges)

Keywords: non parametric, population pharmacokinetics, tacrolimus, CYP3A5, covariate

Background

In non-parametric (NP) population pharmacokinetics approaches, covariates (COV) may affect the number or size of support points. However their availability or relevance in a therapeutic drug monitoring context may be questionable. Our objective was to develop NP models with and without covariates (NP-0 and NP-COV) and to compare the estimated AUCs in an independent validation dataset.

Methods

Data collected from 20 patients on 2 occasions (days 7 and 90) were split into two datasets: one for development (15 patients, 29 PK profiles, 376 concentrations) and the other for validation (5 patients, 9 profiles, 115 concentrations). Population pharmacokinetics models were developed with Pmetrics. The investigated COV were CYP3A5 status, hemoglobin, weight, age, sex and occasion and their relevance was based on a decrease of AIC. Correlation coefficient r was calculated between observed and individual predicted concentrations. A limited sampling strategy (LSS) was developed using AUC weighted MMopt. In the validation set, biases between estimated AUCs using models with or without COV and trapezoidal AUC (NPtrap) were calculated. AUCs were also compared using a Friedman test for paired samples.

Results

An 8 parameters one-compartment model with 2 gamma laws to describe the absorption process was used to describe the PK profiles. Covariates retained were CYP3A5 status (1/0) and occasion on the C0 PK parameter using the following code: “C0=C01*C03**CYP3A5 &IF(occasion==90) C0=C01*C02*C03**CYP3A5”. Both of the final models described adequately the observed concentrations (r: NP-COV=0.96 and NP-0=0.97) while the model without COV had a lower AIC (NP-COV=-3477 and NP-0=-3496). In the validation dataset, AUC estimated using the best LSS (0, 1, 4h) showed only a slight difference between AUCs: relative bias (%) mean±SD[min;max], NP-0/NP-trap=2.57±10.9[-16.2;15.5]% and NP-COV/NP-trap=-0.04±6.2[-12.7;6.4]%. There was no significant difference between NP-0/NP-trap/NP-COV AUCs (p=0.485).

Conclusions

When models tightly fit the data, COV may not add value. Indeed, in a TDM context using LSS, most of the information is carried by the *a posteriori* data (i.e. concentrations) themselves if they are in sufficient number (i.e. a CYP3A5 expressor will have lower concentrations than a non-expressor).

©IATDMCT
Generated by Confit.

©IATDMCT
Generated by Confit.