Identification of Time-Varying CL in Population Pharmacokinetic Analysis: CWRES plot vs. Bayesian information criterion (BIC)

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Objectives: Graphic assessment has been widely used as diagnostics approach in population pharmacokinetic analysis (PPK). Diagnostic plot of weighted residual (CWRESi) vs. time is generally used to detect signal of time varying PK. We conducted model-based simulation analysis to evaluate whether CWRESi is sensitive for signal of time varying PK with clearance (CL) over time.

Methods: Concentration-time profiles in 500 virtual subjects were simulated by using a literature reported linear two-compartment PPK model with zero-order IV infusion and time-varying first-order elimination, for an IV administered monoclonal antibody. An E\textsubscript{max} model was used to describe time varying CL. Simulation investigated CL change over time with different rate (slow to fast) and extent (mild to strong). The simulation scenarios in this analysis include: (1) Varying maximal CL decreased from 20% to 80% at a given rate of CL change (fix time of 50\% of maximal effect (ET\textsubscript{50}) to 60 days); (2) Varying rate of CL changes (ET\textsubscript{50} = 10-600 day) and fix the maximal decrease of CL to 80\%; (3) Varying rate of CL changes (ET\textsubscript{50} = 10-600 day) and fix the maximal decrease of CL to 20\%. BIC were calculated for model comparison.

Results: No time associated trend was observed in diagnostic plots (CWRESi vs. time) of PPK models with and without including time varying CL. BIC values in all simulations were lower in models with time varying CL than that in models without that, except the model with 20\% maximal change of CL and ET\textsubscript{50} = 10 day. Difference of BIC values between models with and without accounting for time-varying CL increased when varying rate decrease.

Conclusions: Model evaluation using BIC or likelihood ratio test approach may be better choices for assessment of time-varying PK, as diagnostic assessment might not be sensitive to detect signal of CL change over time.

Reference: