Impact of Age on Population Parameter Estimates and Pediatric Prediction Performances of Monoclonal Antibody Clearance: A Simulation Study

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Objectives: To explore the impact of the contribution of age to analysis datasets and estimation models on population parameter estimates (PPE) and pediatric prediction performances (PPP) of monoclonal antibody clearance (mAb CL) by a stochastic simulation and estimation approach.

Methods: Individual mAb CL data were simulated using a log-normal distribution model into which an allometric exponent (ALM) of 0.75 on body weight (BW) and an age-dependent maturation (MAT) submodel were incorporated according to Robbie et al. [1]. No target-mediated CL was assumed. Several datasets of CL were generated with different combination of subject’s age categories (neonates/infants, children, adolescents and adults), and then analyzed by the true model and an alternative model without MAT. PPE were compared in terms of the analyzed dataset and applied model. PPP were evaluated by visual predictive checks. All analyses were conducted using NONMEM 7.2.0.

Results: When a dataset included all four age categories, all parameters of the true model were accurately estimated. The alternative model estimated ALM as approximately 0.94. Involving children’s data in datasets enabled an accurate estimation of all parameters of the true model. With only adult data, the population mean, between-subject variability and ALM were comparable to the true values in both cases where estimated by the true and alternative models.

Conclusions: PPE of mAb CL are affected by the contribution of age to analysis datasets and estimation models. Children are a highly informative population to characterize mAb CL over age and BW. For pediatric predictions based on adult data, a simple approach assuming BW-proportional CL regardless of age (fixing ALM to 1 without MAT) may be useful. To be more accurate, it is recommended to fix ALM to 0.75 without MAT in adult population pharmacokinetic modeling, and then add the MAT submodel to the CL in pediatric simulations.

References: