Title: Detection of Immunogenicity and Unbiased Estimation of Model Parameters for Monoclonal Antibodies

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Objectives: To propose and evaluate methods for detection of immunogenic increase of elimination using concentration-time data and for unbiased estimation of model parameters in the presence of immunogenicity.

Methods: A large dataset (1000 subjects) was simulated with sampling scheme that included the rich data following the first and the last doses, and also trough and peak values for all other doses. Intravenous doses were administered on days 1, 8, 15, 28, and then every 4 weeks during the 24-weeks treatment period. A two-compartment model with parallel linear and Michaelis-Menten elimination, and pharmacokinetic parameters typical for the monoclonal antibodies with membrane-bound targets were used. Random effects with moderate (CV=20%) inter-subject variability were included for all parameters. The exponential residual error (CV=20%) was implemented as an additive error in the log-transformed variables. Immunogenicity was simulated in non-specific clearance in approximately 30% of subjects as (a) 5-fold increase following the doses at days 56, 84, 112, or 140 (with equal probability of each of these onset times), or (b) according to a steep Hill function of time with inter-individual variability in E_{max} and T_{50} parameters.

First, the model that did not account for immunogenicity was fitted to evaluate bias of the parameter estimates. Then, two methods of accounting for immunogenicity were tested.

The first method (called ETA-on-epsilon method) introduced the random effect on the magnitude of the residual error, hypothesizing that subjects with immunogenicity would have higher magnitude of this parameter. The same model was then fitted to the sequence of datasets where the increasing fractions of subjects with the highest residual error were commented out. Association of subjects with immunogenicity and subjects with high residual error was investigated. The obtained parameter estimates of each model were compared with the true parameters of non-immunogenic subjects.

The second method used the Nonmem mixture model routine. For the data set (a) it was assumed that the study population consisted of 5 subpopulations. Subpopulation 1 did not have immunogenicity while subpopulations 2, 3, 4, and 5 were allowed to have an increase in clearance following the doses at days 56, 84, 112 or 140 (to match the simulated pattern of immunogenic increase in clearance). For the data set (b) 2 subpopulations represented non-immunogenic and immunogenic subjects with increase in non-specific clearance modeled by the Hill function of time. The parameter estimates were compared with the true parameters, and the ability of the models to correctly identify presence and onset time of immunogenic response was investigated.

Results: The parameter estimates of the model that did not account for immunogenic increase of clearance were significantly biased and the estimate of the inter-individual variability in clearance was greatly inflated. Introduction of ETA-on-epsilon reduced, but not eliminated bias. High individual ETA-on-epsilon values identified immunogenic subjects. When subjects with high magnitude of the residual error were removed from the datasets, bias due to the unaccounted immunogenic increase of clearance was eliminated. At the same time, the variance of the ETA-on-epsilon random effect decreased to zero indicating that the ETA-on-epsilon random effect indeed accounted for immunogenicity.

The mixture models provided the unbiased estimates of the model parameters in both cases (a) and (b). The simulated immunogenic subjects were correctly assigned to the appropriate subpopulations. Thus, the estimates of the mixture model can be used to identify the onset of immunogenic increase of clearance.

The proposed methods allowed identification of subjects with immunogenic increase of clearance; they also reduced or completely eliminated bias of the parameter estimates in the simulated datasets.

Conclusions: For the simulated datasets with rich sampling, the proposed ETA-on-epsilon and mixture model methods identified subjects with immunogenic increase of clearance, provided unbiased individual estimates of the onset time and magnitude of immunogenicity, and unbiased estimates of population parameters. The proposed methods offer the approach to evaluate and describe influence of immunogenicity on the population PK parameters of monoclonal antibodies.

This work should be viewed as proof-of-concept investigation as it was applied in nearly perfect simulated conditions, with rich sampling before and after the onset of immunogenic reaction. Application to the real data will likely face more difficulties. However, the proposed methods provide useful tools for detection and evaluation of changes in the PK parameters related to immunogenicity.