Dose sensitivity of pharmacokinetic difference between similar biologies with target-mediated drug disposition

Liang Li, Ping Ji*, Shamir Kalaria, Lei He, Jianmeng Chen, Anshu Marathe, Suresh Doddapaneni, Yaning Wang, Chandras Sahajwalla

Division of Clinical Pharmacology II, Food and Drug Administration, Silver Spring, MD, USA

Objectives: Target-mediated drug disposition (TMDD) indicates the high affinity binding of a therapeutic biologic to its pharmacological target site to such an extent that this affects its pharmacokinetic (PK) characteristics. The nonlinearity PK caused by TMDD has significant impact on clinical study design especially dose selection. The present work evaluated the sensitivity of dose in detecting PK difference between two similar biologies with nonlinear PK caused by TMDD.

Methods: Two similar therapeutic monoclonal antibodies exhibiting TMDD were compared in a randomized two-period crossover trial of 100 patients. Difference between the two biologies on binding affinity to the intended target and the binding affinity of the fragment crystallizable region (Fc) to the neonatal Fc receptor (FcRn) was assumed to lead to up to 10-fold difference in PK parameters such as linear clearance and TMDD. Inter-individual variability was assumed at 30% for these parameters. Random residual variability was applied using a proportional error model with a coefficient variation of 20%. Over a 100-fold dose range was tested in the simulation. Each scenario was simulated 1000 times using R software. The 90% confidence interval of geometric mean ratio C_{max} and AUC between products were calculated for power analysis.

Results: Higher dose is more sensitive with higher power to detect the difference due to FcRn binding. Lower dose is more sensitive with higher power to detect the difference in affinity binding involving TMDD. The doses in the middle are not as sensitive to detect the differences.

Conclusions: More than one dose, preferable high and low doses, appears necessary to evaluate the difference in receptor binding affinity in various regions of the protein structure between biologics exhibiting nonlinear PK caused by TMDD when conducting the PK comparability trials.

Disclaimer: The views expressed in this abstract are those of the authors and do not necessarily reflect the official views of the FDA.