The Robust Response of a Physiological Model of Granulopoiesis to PK Variability

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Objectives: The increasing use of mechanistic models in pharmacometrics raises numerous questions about their sensitivity to pharmacokinetic (PK) variability and the reliability of their predictions when considering patient populations as opposed to individual patients. We investigated the robustness of the predictions of a physiological model for neutrophil development with regards to PK variability.

Methods: We have previously determined optimal filgrastim dosing during 14-day cyclical chemotherapy treatment using our physiological model of granulopoiesis. This model was constructed using first principles and parameters were estimated from the literature. To investigate the sensitivity of the model's predictions, we incorporated previously published PopPK (both interindividual and interoccasion variability—IOV) models for both PM00104 and filgrastim. A variety of variability scenarios were simulated for respective cohorts of 500 in silico patients and several statistical measures were performed with reference to three crucial clinical endpoints, namely the time to the neutrophil nadir, the nadir value, and the area under the concentration-effect curve.

Results: In all five test scenarios, no statistically significant deviations from the reference case were found using three different statistical measures. The inclusion of IOV did not impact the predictions over three successive chemotherapy cycles.

Conclusions: Our results suggest that physiological models inherently incorporate variability by means of their rational construction. Accordingly, mechanistic models demonstrate robust predictions, which situates their utility in systems pharmacology and lends credence to efforts incorporating physiological accuracy into mathematical models for use in pharmacometrics.

References: