Predicting Clinical Doses Based on Exposure-Response Modeling of Static Time-Kill Data

N. Mangal¹, J. Hoover², J. Wetherington³, M. Hossain⁴, N. Goyal⁴, D. Tenero⁴
¹Center for Pharmacometrics and Systems Pharmacology, University of Florida, Orlando, FL; ²Preclinical Biology, GlaxoSmithKline, Collegeville, PA; ³Clinical Statistics, GlaxoSmithKline, Collegeville, PA; ⁴Clinical Pharmacology Modeling and Simulation, GlaxoSmithKline, Philadelphia, PA

Background: Antimicrobial dose selection is guided by conventional pharmacokinetic/pharmacodynamic (PK/PD) indices/targets obtained in in vivo animal infection models. We tested whether in vitro static time-kill (TK) data could be used for prediction of clinical doses for gepotidacin (GSK2140944).

Methods: A population PK model for gepotidacin was previously developed using Phase I data. Static TK data were obtained against 6 isolates of Staphylococcus aureus at different gepotidacin concentrations and characterized by a PD model. Simulations were run for different dosing regimens and probabilities of target attainment (PTA) were obtained using the PK model and the:

a) in vivo PK/PD index/target (conventional method)

b) in vitro PD model-derived index/target (Δlog_{10} CFU/mL, change from baseline to 24 hours).

Correlation between PTA derived by the 2 methods were determined based on:

1) fAUC/MIC>13 (stasis in vivo) and Δlog_{10} CFU/mL≥0 (at least stasis in vitro)

2) fAUC/MIC>60 (1-log kill in vivo) and Δlog_{10} CFU/mL≥1 (at least 1-log kill in vitro)

Results: A 1-compartment PD model representing the bacterial population, growth saturation, and an E\text{max}-type bacterial kill function adequately characterized the in vitro TK data. Compelling concordance (r²=0.96) was found between the TK-derived endpoint (Δlog_{10} CFU/mL≥0) and the in vivo derived endpoint (fAUC/MIC>13) for stasis with weaker concordance (r²=0.88) between (Δlog_{10} CFU/mL≥1) and (fAUC/MIC>60), associated with 1-log kill in vivo.

Conclusions: The developed in vitro PD model reasonably predicted clinical doses for stasis, which is considered the predictive endpoint for less serious infections (e.g., skin). Reliably predicting bacterial killing (considered a more predictive endpoint for serious infections) requires further exploration to widen the model utility. This approach could allow selection of probable clinical doses early in drug development using in vitro time-kill data.