Pharmacokinetic Indices Driving Antibacterial Efficacy of CF-301 - a Novel First-In-Class Lysin

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Introduction: CF-301 is being developed for treatment of S. aureus bacteremia, exhibits rapid S. aureus-specific bacteriolysis, anti-biofilm activity, has low propensity for resistance and pronounced synergy with other antibiotics.

Objectives: To determine the PK indices driving the antibacterial effect of CF-301.

Methods: Mice infected with $10^6$ CFU (colony forming units) S. aureus were administered CF-301 divided into 1, 2, 3, or 4 doses over 24-h. Change in log₁₀ CFU at 24-h post infection was used as the dependent variable in a regression analysis to examine the predictive value of PKPD indices (AUC/MIC, Cmax/MIC, percent time concentration stays above MIC over a 24-h period (%T>MIC), or a combination of these indices), in more than 20 different models ranging from linear to nonlinear. The model fits were assessed by comparing the Residual Standard Errors. Also, efficacy of CF-301 (1 to 60 mg/kg in 4 divided doses), alone or in the presence of sub-therapeutic doses of daptomycin (0.5-5 mg/kg), was evaluated in a separate experiment against 10 clinical S. aureus isolates (MIC range: 4-64 μg/mL), and various models were fit to the data.

Results: While all indices and index combinations displayed a degree of relationship with CF-301 efficacy, the AUC/MIC alone had the best predictive value and followed a sigmoidal Emax model. %T>MIC was numerically as strong a predictor of efficacy, but AUC/MIC had a larger shape parameter (Hill power 4 vs. 2) with a smaller EC₅₀ (Figure), which indicates antibacterial effect of CF-301 is more sensitive to changes in AUC/MIC compared to %T>MIC.

Conclusions: AUC/MIC is the PKPD index most predictive of CF-301 efficacy against S. aureus. Based on estimated AUCs from a Phase 1 study in humans (separate abstract), AUC/MIC targets of approximately 1.5 and 0.5 are expected to be achieved in humans at CF-301 doses in the ranges of 0.1-0.2 mg/kg (as a single agent) and 0.03-0.1 mg/kg (in combination with daptomycin).