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Abstract (poster session)

Pharmacokinetic-pharmacodynamics (PK-PD) predict a high probability of efficacy for plazomicin against serious infections caused by carbapenem-resistant Enterobacteriaceae (CRE)

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Objectives: Plazomicin, a novel aminoglycoside (AG) under development to treat serious Gram-negative infections, is active against clinical isolates that possess a broad range of resistance mechanisms including AG-modifying enzymes, carbapenemases and fluoroquinolone target-site mutations that limit the utility of other antibiotics. Using Monte Carlo simulation (MCS), population PK (PPK), and PK-PD targets from murine infection models, the efficacy of plazomicin against infections caused by CRE was predicted. Methods: Plazomicin plasma and epithelial lining fluid (ELF) PK from neutropenic infected mice and data from a neutropenic murine lung Klebsiella pneumoniae (Kp) infection model [ICAAC 2012, Abstract A-042] were used to determine plasma and ELF area under the concentration-time curve to MIC ratio (AUC:MIC) targets for efficacy. A plazomicin PPK model was built using clinical data from subjects and patients with varying renal function. Using this model, an individualized plazomicin dosing regimen approach was derived. Using MCS, the probability of target attainment (PTA) in simulated patients with varying renal function was evaluated by MIC and overall PTA was evaluated in the context of plazomicin's MIC distribution against multidrug-resistant (MDR) Kp. Results: Median (range) plasma and ELF AUC:MIC targets associated with a 2-log10 CFU reduction in Kp in murine lung were 39 (17-137) and 32 (14-112), respectively. MCS was performed using the PPK model (3-compartment model including significant covariate relationships for weight and creatinine clearance [CLcr]) and PTA was assessed for patients receiving a plazomicin dose (mg/kg) of 0.14 + 0.17 x CLcr once daily or twice this dose every 48 hours for patients with CLcr of 15-30 mL/min/1.73 m2 (see Table 1). Using median plasma and ELF AUC:MIC targets, PTA across renal function groups was >= 97.7% for MIC=2 mg/L. Overall PTA for both targets across renal function groups based on the plazomicin MIC distribution vs. MDR Kp [Galani I et al. J. Chemother. 2012;24:191-194] was >= 97.2%. Conclusions: The predicted percentage of patients achieving plasma and ELF AUC:MIC targets against MDR Kp is high (>= 97.2%), suggesting that the proposed approach to plazomicin dosing will provide plasma exposures consistent with efficacy in the majority of patients with CRE bacteremia and ELF exposures consistent with efficacy in the majority of patients with CRE bacterial pneumonia.

Table 1. Percent probability of patients achieving plasma or ELF AUC:MIC targets across renal function groups for MIC = 2 and over a MIC distribution for plazomicin against MDR *K. pneumoniae*

Renal Function Group (CLcr range)	Percent probability of patients achieving the plasma or ELF AUC:MIC ratio target associated with a 2-$\log_{10}$ CFU reduction in *K. pneumoniae* from baseline			
	Plasma AUC:MIC target = 39[a]		ELF AUC:MIC target = 32[b]	
	MIC = 2 mg/L	Overall[c]	MIC = 2 mg/L	Overall[c]
Normal (CLcr 90 to 150 mL/min/1.73 m^2)	99.6	99.0	97.7	97.2
Mild impairment (CLcr of 60 to <90 mL/min/1.73 m^2)	99.9	99.5	99.2	98.1
Moderate impairment (CLcr of 30 to <60 mL/min/1.73 m^2)	99.9	99.4	99.4	98.5
Severe impairment (CLcr of 15 to <30 mL/min/1.73 m^2)	100	99.6	99.2	98.5

a. Using PK-PD target attainment results based on Day 1 plasma AUC_{0-24} values and the median plasma AUC:MIC target of 39.
b. Using PK-PD target attainment results based on Day 2 ELF AUC_{0-24} values (which assumed ELF to plasma equilibration by this time point) and the median ELF AUC:MIC target of 32.
c. Based on PK-PD target attainment by MIC results over the MIC distribution for MDR *K pneumoniae* (Galani I *et al.* J. Chemother. 2012;24:191-194).