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Abstract (oral session)

In vivo efficacy of aztreonam-avibactam against multidrug-resistant Enterobacteriaceae harbouring New Delhi metallo beta-lactamase-1 (NDM-1) and other beta-lactamases

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Objectives: Aztreonam-avibactam (ATM-AVI) is a combination of an established monobactam and a novel beta-lactamase inhibitor, with potent activity against Enterobacteriaceae expressing serine beta-lactamases (Classes A and C) and metallo-beta-lactamases (Class B) such as NDM-1. This study aimed to describe the in vivo efficacy and preliminary pharmacokinetic/pharmacodynamic (PK/PD) relationship of ATM-AVI against beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae. Methods: ATM-AVI was evaluated in the neutropenic mouse thigh infection model using E. coli ARC3600 (NDM-1, OXA-1, CMY-6) and K. pneumoniae ARC3802 (NDM-1, TEM-1, CTX-M-15, SHV-2a, DHA-1). Strains were multi-drug resistant with ATM alone MIC of 16 and 128 mg/L, respectively, versus ATM-AVI MIC of 0.125 mg/L for both. ATM-AVI was dosed subcutaneously at a fixed 4:1 ratio of 50/12.5 to 400/100 mg/kg every 4 hours, and efficacy was expressed as the change in bacterial density after 24 hours of therapy. ATM-AVI pharmacokinetics were determined with single doses of 50/12.5, 100/25, and 200/50 mg/kg, and were corrected for plasma protein binding to obtain free drug exposures. PK/PD indices of interest were ATM free time above the ATM-AVI MIC (fT>MIC) and AVI free time above critical threshold concentration of 2-2.5 mg/L (fT>2-2.5 mg/L), as determined by PK/PD studies in the in vitro hollow-fiber infection model (HFIM). Results: ATM-AVI demonstrated efficacy against beta-lactamase producing Enterobacteriaceae, with >2-log kill against E. coli ARC3600 and 0.5-log kill for K. pneumoniae ARC3802. ATM exposures were 70-100% fT>MIC for both strains at studied doses, while AVI exposures ranged 19% to 48% fT>2-2.5 mg/L. With ATM exposure maximized (i.e., >50% fT>MIC), efficacy of the combination was correlated with AVI fT>2-2.5 mg/L (R^2=0.823, 0.935). For E. coli ARC3600, AVI fT>2.5 mg/L of 22%, 29%, and 41% was associated with stasis, 1-log kill, and 2-log kill, respectively. For K. pneumoniae ARC3802, stasis was observed at a similar AVI magnitude of 25% fT>2 mg/L. In contrast, ATM alone showed 2-log regrowth at equivalent doses for both strains. Conclusion: ATM-AVI was efficacious against beta lactamase producing Enterobacteriaceae in the neutropenic mouse thigh model. In the presence of maximized ATM exposure, in vivo efficacy was correlated with AVI fT>2 2.5 mg/L. Requisite AVI exposures for stasis and maximum kill in vivo were comparable to those observed in the in vitro HFIM.