P908

Abstract (poster session)

Efficacy of BAL30072 in murine thigh infection models of multi-resistant Gram-negative bacteria

J.K. Gould, A. Sattar, P. Thommes, L.J. Payne, W. Stubbings, J. Spickermann, G. Daws, P. Warn* (Manchester, UK; Basel, CH)

Objectives: New antibiotics active against multidrug-resistant (MDR) Enterobacteriaceae, P. aeruginosa, and A. baumannii are urgently needed. BAL30072 (SFM) is a monocyclic beta-lactam antibiotic belonging to the sulfactams with potent activity against resistant isolates, including those harbouring AmpC B-lactamases, metallo- (class B) or OXA- (class D) carbapenemases and is currently in phase 1 of clinical development. In these studies we used a neutropenic murine thigh burden model to study the pharmacokinetic and pharmacodynamic relationships of SFM against a range of multi-resistant Gram negative bacteria. Methods: MICs were determined by CLSI M07 A9 modified by the addition of 16ug/ml bipyridyl. ICR mice were rendered neutropenic with 2 doses of cyclophosphamide then infected IM into both thighs with E. coli, K. pneumoniae or P. aeruginosa including isolates expressing blaNDM-1. In PK studies mice were immunosuppressed and infected and blood samples collected 10 minutes -8 hours post infection following 1-8 doses of SFM. In the efficacy studies treatment was started 1h post-infection and administered at 12.5-400mg/kg/dose IV every two hours. Mice were euthanized at 9h post-infection and burdens quantified. A PK/PD mathematical model was used to link drug concentrations with the effect, and to define the drug exposure producing near maximal activity. Results: MICs of SFM ranged from <0.03->16ug/ml. SFM was well tolerated at all doses used. The PK of SFM was approximately linear with T1/2 ranging from 20-40 minutes following multiple and single dosing respectively. Untreated mice demonstrated >1 log10cfu/g increase in burden. SFM was highly effective against all isolates with MICs <=4.0µg/ml reducing the thigh burdens by >2 log10 cfu/g at optimized doses. Maximum efficacy was observed then the free drug T>MIC (fT>MIC) approached 100% but achieved stasis when fT>MIC was over 50%. Conclusions: SFM is highly active against MDR bacteria including those expressing blaNDM-1. Efficacy of SFM is time dependent and rapid in vivo bactericidal activity can be induced when fT>MIC is greater than 50%.