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P2418 Activity of a novel extended-spectrum beta-lactamase inhibitor, AAI101, combined with cefepime against beta-lactamase-producing Enterobacteriaceae in a neutropenic murine pneumonia model

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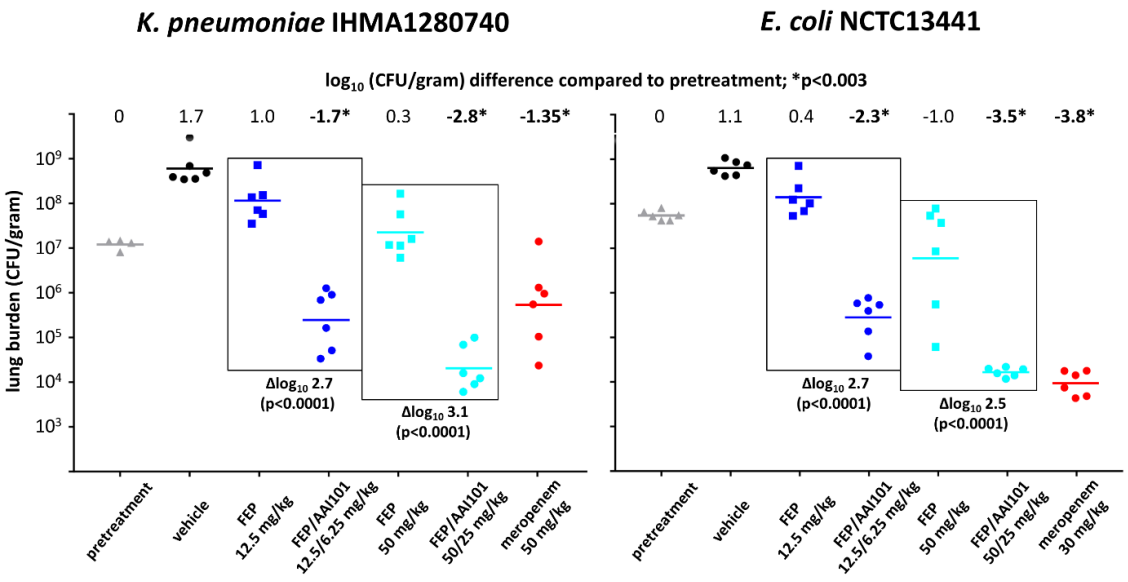
Background: AAI101 is a novel β-lactamase inhibitor with potent activity against ESBLs and other β-lactamases. AAI101 combined with cefepime is in Phase 2 clinical trials. The ability of AAI101 to restore cefepime activity towards cefepime-resistant Enterobacteriaceae with defined constellations of β-lactamases was examined in a neutropenic mouse pneumonia model.
Materials/methods: MICs of test isolates were determined according to CLSI guidelines. Pharmacokinetic profiles in male ICR mice were obtained following intravenous administration of single doses of cefepime/AAI101 (60/30 mg/kg). Immunosuppressed male mice were infected by nasal instillation with lethal doses of *K. pneumoniae* IHMA1280740 co-producing SHV-OSBL (original-spectrum β-lactamase), TEM-OSBL, CTX-M-15 (ESBL), and DHA-1 (AmpC) β-lactamases, or *E. coli* NCTC13441 co-producing TEM-OSBL, CTX-M-15, and OXA-1 (class D) β-lactamases. Vehicle, cefepime, cefepime/AAI101 (2/1 w/w), or meropenem was administered intravenously q4h beginning 2 hours post-infection. At 26 hours post-infection lungs were excised and pulmonary bioburdens determined by quantitative culture. Data were analyzed using the Kruskal-Wallis test, with the Conover-Inman *post-hoc* test for all pairwise comparisons between groups.
Results: MICs (µg/mL) for the test strains were as follows:

Strain	Cefepime	Cefepime + 4 µg/mL AAI101	Meropenem
K. pneumoniae IHMA1280740	>128	0.06	0.125
E. coli NCTC13441	32	0.25	0.06

In both plasma and epithelial lining fluid the elimination half-life for cefepime was *ca.* 11 minutes, and for AAI101 *ca.* 14 minutes; lung penetration relative to plasma of cefepime and of AAI101 was *ca.* 36% and *ca.* 76%, respectively. *K. pneumoniae* IHMA1280740 and *E. coli* NCTC13441 each demonstrated robust post-infection growth in mouse lungs. A dose-response effect for cefepime/AAI101 was observed over the range 6.25/3.125-100/50 mg/kg for both test strains. For the same concentration of cefepime (FEP), cefepime/AAI101 combination treatment showed significantly superior efficacy to cefepime monotherapy ($p < 0.0001$) against both strains, and equivalent or superior efficacy to meropenem (Figure).
Conclusions: The experimental extended-spectrum β-lactamase inhibitor AAI101 restores efficacy of cefepime in a neutropenic murine model of pneumonia caused by cefepime-resistant Enterobacteriaceae co-producing ESBL and OSBL-type β-lactamases plus an AmpC or a OXA-1 β-lactamase. AAI101 in combination with cefepime represents a promising new therapeutic modality for treatment of infections caused by drug-resistant Enterobacteriaceae.


K. pneumoniae IHMA1280740
E. coli NCTC13441
log10 (CFU/gram) difference compared to pretreatment; *p<0.003
lung burden (CFU/gram)
0
1.7
1.0
-1.7*
0.3
-2.8*
-1.35*
Δlog10 2.7 (p<0.0001)
Δlog10 3.1 (p<0.0001)
0
1.1
0.4
-2.3*
-1.0
-3.5*
-3.8*
Δlog10 2.7 (p<0.0001)
Δlog10 2.5 (p<0.0001)
pretreatment
vehicle
FEP 12.5 mg/kg
FEP/AAI101 12.5/6.25 mg/kg
FEP 50 mg/kg
FEP/AAI101 50/25 mg/kg
meropenem 50 mg/kg
meropenem 30 mg/kg