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Paper Poster Session
Discovery of more new antibacterial drugs

In vitro activity of cefepime-AAI101 vs. drug-resistant Klebsiella pneumoniae clinical isolates

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Background: AAI101 is an extended-spectrum beta-lactamase inhibitor in clinical development as a combination product with cefepime and with piperacillin. This study explored the antibacterial activity of cefepime in the presence of AAI101 towards *Klebsiella pneumoniae* strains expressing carbapenemases or extended-spectrum beta-lactamases (ESBLs) and belonging to diverse sequence types.

Material/methods: A largely cefepime-resistant challenge panel of 106 *K. pneumoniae* clinical isolates selected for expression of carbepenemases and ESBLs were obtained from the Sourasky Medical Center. The strains were collected from the USA, Columbia, Italy, Greece, and the Middle East. OXA-48, KPC isozymes, and CTX-M isozymes were identified by PCR and gene sequencing. Sequence type was established by multilocus sequence typing or pulsed-field gel electrophoresis; ST258 clones also were identified by detection of the *pilv-l* allele. Antibiotic susceptibility testing was performed by broth microdilution according to CLSI guidelines, with *E. coli* ATCC 25922 as a quality control strain. Cefepime was examined over the concentration range 0.5-32 ug/mL, alone or combined with a fixed concentration of tazobactam (4 ug/mL) or AAI101 (4 and 8 ug/mL). Drug-dependent susceptibility (S-DD; MIC =/< 8 ug/mL) or resistance (R; MIC >/= 16 ug/mL) were assigned according to CLSI 2015 cefepime breakpoints; geometric mean (GM) MICs were calculated for subsets according to the beta-lactamase produced.

Results: The *K. pneumoniae* panel comprised 21 KPC-2 producers, 61 KPC-3 producers, 9 CTX-M producers (1 CTX-M-1, 5 CTX-M-2, 3 CTX-M-25), 5 uncharacterized ESBL producers, and 10 OXA-48 producers. Cefepime alone up to 8 ug/ml inhibited growth of 5/106 strains. AAI101 alone up to 128 ug/mL did not inhibit growth of any strain. Addition of 8 ug/ml of AAI101 to cefepime up to 8 ug/ml inhibited growth of 95% of KPC-2, 80% of OXA-48, and 100% of ESBL producers, but only 18% of KPC-3 producers. AAI101 was a more potent beta-lactamase inhibitor than tazobactam of KPCs, CTX-Ms, and OXA-48 (see Table). Most KPC-2 producers (clinically, the most prevalent KPC worldwide) belonged to non-CC258 sequence types and were more susceptible to cefepime-AAI101 than KPC-3 producers, which were predominantly ST258/CC258s. However, CTX-M producers, all of which were ST258s, were susceptible to cefepime-AAI101 (see Table), indicating that susceptibility to cefepime-AAI101 is a function of beta-lactamase rather than sequence type. A dosage effect for AAI101 was noted, broader coverage and lower cefepime MICs being achieved with a fixed AAI101 concentration of 8 ug/mL than with a fixed AAI101 concentration of 4 ug/mL.

Conclusions: AAI101, an extended-spectrum beta-lactamase inhibitor, proved highly effective at bolstering the activity of cefepime against a challenge panel of *Klebsiella pneumoniae* representing the high end of the enterobacterial resistance spectrum (carbapenemase and ESBL producers). The combination of AAI101 and cefepime warrants clinical investigation as a treatment for infections caused by cefepime-resistant klebsiellae.

Table. Cefepime susceptibility*: numbers of strains susceptible (S-DD) and *geometric mean MICs* (ug/mL) according to β-lactamase and sequence type

	n	Cefepime alone	Cefepime-tazobactam (4)	Cefepime-AAI101 (4)	Cefepime-AAI101 (8)	
KPC-2	21	S-DD, 0/21 *GM MIC, 50.80*	S-DD, 12/21 *GM MIC, 10.08*	S-DD, 16/21 *GM MIC, 3.07*	S-DD, 20/21 *GM MIC, 1.75*	
KPC-3	61	S-DD, 0/61 *GM MIC, 61.16*	S-DD, 4/61 *GM MIC, 44.49*	S-DD, 8/61 *GM MIC, 36.67*	S-DD, 11/61 *GM MIC, 30.23*	
CTX-M	9	S-DD, 2/9 *GM MIC, 32.00*	S-DD, 3/9 *GM MIC, 18.66*	S-DD, 7/9 *GM MIC, 1.85*	S-DD, 9/9 *GM MIC, 0.73*	
OXA-48	10	S-DD, 1/10 *GM MIC, 39.40*	S-DD, 4/10 *GM MIC, 16.00*	S-DD, 9/10 *GM MIC, 2.30*	S-DD, 8/10 *GM MIC, 2.14*	
Unclassified ESBL pro-ducers	5	S-DD, 2/5 *GM MIC, 12.13*	S-DD, 5/5 *GM MIC, 0.57*	S-DD, 5/5 *GM MIC, 0.57*	S-DD, 5/5 *GM MIC, 0.50*	

*2015 CLSI breakpoints (ug/mL): S-DD ≤ 8, R ≥ 16