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P2423 In vitro activities of AAI101, a novel extended-spectrum beta-lactamase inhibitor, and tazobactam, in combination with cefepime, against extended-spectrum beta-lactamase producing Klebsiella pneumoniae clinical isolates

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Background: AAI101, a novel penicillanic acid sulfone β-lactamase inhibitor (BLI) active against ESBLs and other β-lactamase types, is in Phase 2 clinical development in combination with cefepime. Emergence and spread of aggressive β-lactamases amongst *Enterobacteriaceae* has compromised the clinical utility of marketed BLIs such as tazobactam. This study sought to compare *in vitro* efficacies of AAI101 with those of tazobactam against ESBL-producing *Klebsiella pneumoniae*, amongst the most clinically challenging *Enterobacteriaceae.*

Materials/methods: The efficacies of AAI101 and tazobactam were compared for a geographically diverse panel of *K. pneumoniae* (n = 120, 94.2% cefepime-resistant; MIC_{90} >128 mg/L), using cefepime as a β-lactam partner. Each isolate tested produced one or more ESBL ± an OXA-48 carbapenemase or a plasmid-encoded AmpC cephalosporinase. CTX-M-type ESBLs were identified in 87.5% of isolates, SHV-type ESBLs in 15.8%, an OXA-48 in 8.3%, and an AmpC in 6.7%. Most isolates also encoded OSBL (original-spectrum β-lactamase)-TEMs and/or OSBL-SHVs. The ability of AAI101 or tazobactam, each at a fixed concentration of 4 or 8 mg/L, to restore cefepime activity towards the isolates was determined by broth microdilution. Imipenem and ertapenem were included as comparators.

Results: MIC_{90} data are presented in the Table. Against ESBL-only-producing *K. pneumoniae* cefepime-AAI101 was 16-fold more potent than cefepime-tazobactam at BLI concentrations of 4 or 8 mg/L. Towards ESBL-producing isolates co-producing an OXA-48 or an AmpC, cefepime-AAI101 was >8-fold more potent than cefepime-tazobactam. In the presence of 8 mg/L of AAI101, cefepime was as potent as imipenem against ESBL-only producers, and more potent than imipenem towards isolates co-producing an OXA-48 or an AmpC. The MIC_{90} for ertapenem was >8 mg/L.

K. pneumoniae	MIC_{90} (mg/L)						
	Comparators			FEP combined with BLI fixed at			
				4 mg/L		8 mg/L	
	FEP	ETP	IPM	AAI101	TZB	AAI101	TZB
ESBL-only (n = 102)	>128	>8	1	2	32	1	16
ESBL + OXA-48 or AmpC (n = 18)	>128	>8	>8	8	>64	8	>64
all (n = 120)	>128	>8	2	4	64	1	32

FEP, cefepime; TZP tazobactam; IPM imipenem; ETP ertapenem

Conclusions: AAI101 is a much more effective β-lactamase inhibitor than tazobactam. Against a challenge panel of ESBL-producing *K. pneumoniae* ± an OXA-48 or a plasmid-encoded AmpC, AAI101 at a fixed concentration of 4 mg/L restores cefepime activity to the CLSI susceptibility breakpoint for ESBL-only producers, at least comparable to imipenem and superior to tazobactam. These data support further clinical investigation of AAI101 in combination with a β-lactam partner for treatment of infections by *K. pneumoniae* producing ESBLs with or without an OXA-48 carbapenemase or an AmpC cephalosporinase.