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ePoster Viewing
New and old beta-lactamase inhibitors

IN-VITRO ACTIVITY OF AAI101, A NEW BETA-LACTAMASE INHIBITOR, COMBINED WITH BETA-LACTAM ANTIBIOTICS AGAINST A CHALLENGE PANEL OF BETA-LACTAM-RESISTANT GRAM-NEGATIVE CLINICAL ISOLATES

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Objectives: AAI101 is an extended-spectrum beta-lactamase inhibitor currently in clinical development. This study sought to determine MICs of various beta-lactam antibiotics in the presence of fixed concentrations of AAI101 using a 'challenge panel' of Gram-negative clinical isolates selected for their variety of medically-important beta-lactam resistance mechanisms.

Methods: MICs were determined (agar dilution) for 61 isolates of Enterobacteriaceae, *P. aeruginosa*, and *A. baumannii*, each with a defined mechanism of beta-lactam resistance. The panel included 29 isolates with carbapenemases (KPCs in 11 *Klebsiella pneumoniae,* 3 *Escherichia coli*, and 3 *Enterobacter* spp. additionally derepressed for AmpC; 3 non-KPC class A carbapenemases in Enterobacteriaceae; OXA carbapenemases in 4 Enterobacteriaceae and 5 *Acinetobacter baumannii*) and 17 isolates with ESBLs or K1 enzyme (including 2 *K. pneumoniae* strains with accompanying porin loss), 13 AmpC producers and 2 *Pseudomonas* with efflux. Agents tested were piperacillin (Pip), ceftriaxone (Cro), cefepime (Fep), and meropenem (Mem), alone or combined with AAI101 at different fixed concentrations; Pip + 4 mg/L tazobactam (Pip/Tazo) served as a control. *E. coli* ATCC25922 and *P. aeruginosa* ATCC27853 were included in all assay runs. Antibiotic susceptibilities were interpreted using 2013 CLSI breakpoints.

Results: Numbers of isolates susceptible to the beta-lactam +/- inhibitor combinations are presented in the table, arranged broadly according to beta-lactam resistance mechanism. AAI101 lacked intrinsic antibacterial activity against most strains surveyed (MIC_{50} >128 mg/L; range = 16->128 mg/L). Addition of 4-16 mg/L of AAI101 generally reduced Pip and cephalosporin MICs for KPC and ESBL producers by >=4 log_2 dilution steps. None of the 17 KPC-producing Enterobacteriaceae were susceptible to Pip, Pip/Tazo, Cro, or Mem, and only 1 isolate was susceptible to Fep. When combined with AAI101 at 8 mg/L, 12 (71%) KPC producers became susceptible to Fep, 11 (65%) to Mem, 8 (47%) to Cro, and 6 (35%) to Pip; raising the AAI101 concentration to 16 mg/L restored susceptibility to Pip in 11 KPC producers (65%). Similarly, none of the 4 OXA-48 producers was susceptible to Pip (+/- Tazo,+/- AAI101), Mem (+/- AAI101), Cro, or Fep; whereas in the presence of 8 mg/L AAI101 3/4 OXA-48 producers became susceptible to Cro, and all 4 to Fep.

Conclusion: Addition of the extended-spectrum beta-lactamase inhibitor AAI101 to piperacillin, ceftriaxone, cefepime, or meropenem enhanced antibiotics activity and restored susceptibility for a broad variety of multidrug-resistant Gram-negative isolates, including ESBL-producing *P. aeruginosa*, OXA-producing *A. baumannii*, carbapenemase-producing *K. pneumoniae,* and *Enterobacter* spp. AAI101 has the potential, in combination with established beta-lactam antibiotics, to treat infections caused by multidrug-resistant Gram-negative pathogens.

Drug	Class A	Class A + Porin Loss	Class C	Class C + Porin Loss	Classes A + C	Class D	Efflux	% Overall (n=61)
Pip	2/32	0/2	1/11	0/2	0/3	0/9	2/2	8
Pip/Tazo	14/32	0/2	4/11	1/2	0/3	0/9	2/2	34
Pip/AAI101 (4)	21/32	0/2	3/11	0/2	1/3	0/9	2/2	44
Pip/AAI101 (8)	20/32	1/2	8/11	0/2	2/3	0/9	2/2	54
Pip/AAI101 (16)	26/32	2/2	9/11	0/2	2/3	2/9	2/2	70
Fep	11/32	0/2	9/11	1/2	0/3	0/9	1/2	36
Fep/AAI101 (4)	25/32	1/2	11/11	2/2	3/3	6/9	1/2	80
Fep/AAI101 (8)	26/32	2/2	11/11	2/2	3/3	6/9	2/2	85
Cro	3/32	0/2	1/11	0/2	0/3	0/9	0/2	7
Cro/AAI101 (4)	18/32	0/2	2/11	0/2	0/3	2/9	0/2	36
Cro/AAI101 (8)	21/32	2/2	2/11	0/2	1/3	3/9	0/2	48
Mem	15/32	0/2	11/11	0/2	0/3	0/9	2/2	46
Mem/AAI101 (4)	23/32	0/2	11/11	0/2	2/3	0/9	2/2	62
Mem/AAI101 (8)	25/32	1/2	11/11	0/2	3/3	0/9	2/2	69