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ePoster Viewing
New and old beta-lactamase inhibitors

CHARACTERIZATION OF BETA-LACTAMASE INHIBITION BY AAI101, AN EXTENDED SPECTRUM BETA-LACTAMASE INHIBITOR

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Objectives: AAI101 is an extended spectrum beta-lactamase inhibitor (BLI) currently in clinical development. This study sought to profile the spectrum of activity of AAI101 towards specific serine beta-lactamases of epidemiological importance by identifying susceptibilities of isogenic *Escherichia coli* strains towards beta-lactam antibiotics combined with AAI101.

Methods: MICs towards 57 isogenic *E. coli* K-12 strains, each expressing a unique beta-lactamase, were determined for 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) was included as a control. Antibiotic susceptibilities were assigned according to 2013 CLSI breakpoints.

Results: AAI101 was highly effective at inhibiting extended spectrum beta-lactamases (ESBLs). Whilst 6% of 31 ESBL producers surveyed were susceptible to Pip (PipS) alone, addition of 4-16 mg/L AAI101 rendered up to 97% of these strains PipS. In the presence of 4 mg/L AAI101, 100% of ESBL producers became CroS and FepS (geometric mean MIC, 0.06-0.09 mg/L). AAI101 likewise proved highly effective at inhibiting class A carbapenemases (cACPases). Of 9 cACPase producers examined (including KPC-2 and KPC-3 producers), none was PipS, whereas adding 4-16 mg/L AAI101 progressively increased the proportion of PipS strains, up to 89%. Seven of 9 cACPase producers were resistant to Cro (CroR) (geomean MIC, 6.9 mg/L), but addition of 4 mg/L and 8 mg/L AAI101 rendered 5 and 6 of these CroR strains CroS (geomean MICs, 0.3 mg/L and 0.1 mg/L, respectively). Only 5/9 cACPase producers were susceptible to Mem, but addition of 4 mg/L and 8 mg/L AAI101 improved coverage of Mem towards this panel to 7/9 and 8/9, respectively. AAI101 was less effective at enhancing AmpC producer susceptibilities to Pip, although 75% of AmpC producers surveyed were PipS at 16 mg/L AAI101. AAI101 did not increase the number of AmpC producers susceptible to Cro, but it lowered their MICs towards this cephalosporin. AAI101 had very good activity towards OXA beta-lactamases; the presence of 16 mg/L AAI101 rendered 77% of 13 OXA producers PipS (including an OXA-48 producer). Most OXA producers were CroS and FepS, but addition of 4-8 mg/L AAI101 expanded OXA coverage and lowered MICs.

Conclusion: At clinically achievable concentrations AAI101 inhibited many beta-lactamases of epidemiological concern, namely ESBLs, class A carbapenemases (including KPC-2 and KPC-3), OXAs (including OXA-48), and, to a lesser extent, AmpCs. Furthermore, AAI101 proved a better inhibitor of ESBLs, class A carbapenemases, and OXAs than tazobactam. AAI101 has the potential, in combination with established beta-lactam antibiotics, to treat infections caused by multidrug-resistant Gram-negative pathogens, including producers of beta-lactamases not sensitive to other BLIs.

Numbers of isogenic *E. coli* strains susceptible to Pip, Cro, Fep, or Mem in the absence and presence of BLI (mg/L)

BL/BLI combination	ESBLs[a]	Class A carbapenemases[b]	AmpC[c]	OXAs[d]
Pip	2/31	0/9	0/4	1/13
Pip + Tazo (4)	28/31	3/9	2/4	3/13
Pip + AAI101 (4)	30/31	5/9	1/4	8/13
Pip + AAI101 (8)	29/31	5/9	2/4	9/13
Pip + AAI101 (16)	30/31	8/9	3/4	10/13
Cro	5/31	2/9	1/4	8/13
Cro + AAI101 (4)	31/31	7/9	1/4	11/13
Cro + AAI101 (8)	31/31	8/9	1/4	13/13
Fep	23/31	8/9	4/4	10/13
Fep + AAI101 (4)	31/31	9/9	4/4	11/13
Fep + AAI101 (8)	31/31	9/9	4/4	13/13
Mem	31/31	5/9	4/4	13/13
Mem + AAI101 (4)	31/31	7/9	4/4	13/13
Mem + AAI101 (8)	31/31	8/9	4/4	13/13

[a]includes 2 clavulanate-resistant ESBLs + 1 clavulanate-resistant penicillinase
[b]including KPC-2 and KPC-3
[c]CMY-2, DHA-1, ACC-1, FOX-5
[d]includes 5 carbapenemases