In-vitro activity of diverse β-lactam/AAI101 combinations vs. multidrug-resistant Gram-negative clinical strains

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Introduction
AAI101 is a novel extended-spectrum β-lactamase inhibitor (BLI), belonging to the penicillanic acid sulfone family, which is currently in Phase I clinical trials.

β-Lactam resistance in Gram-negative pathogens principally involves production of a wide diversity of β-lactamases, and may be exacerbated by auxiliary non-β-lactamase mechanisms such as porin mutations and upregulated efflux. Whilst BLIs like tazobactam (Tazo) have helped preserve the clinical value of β-lactams by inhibiting β-lactamases before they can inactivate the antibiotic, emergence of more aggressive β-lactamases, especially when complemented by auxiliary non-β-lactamase resistance mechanisms, have restricted treatment options for infections caused by multidrug-resistant (MDR) Enterobacteriaceae and non-fermentative bacilli.1

The purpose of this study was to assess the in-vitro activity of AAI101 in combination with different β-lactam antibiotics against 61 Gram-negative clinical isolates representing a variety of β-lactam resistance mechanisms.

Materials and Methods

- Agar dilution MICs were determined for 61 bacterial strains, each with a defined mechanism of β-lactam resistance (Table 1).

Table 1. Resistotypes of “challenge panel”*

<table>
<thead>
<tr>
<th>Species</th>
<th>Represented β-lactamases (and other resistance mechanism)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli (n = 22)</td>
<td>TEM-3, TEM-10, 3 CTX-M-2, 3 CTX-M-14, 3 CTX-M-15; 3 KPC, NMC-A; 5 pAmpCs (ACC, 2 CIT/CMyS, DHA, FOX); 2 OXA-48</td>
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<tr>
<td>K. pneumoniae (n = 15)</td>
<td>2 ESBL + porin loss; 11 KPC (including 6 ST258 phenotype); 2 OXA-48</td>
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<tr>
<td>Enterobacter spp. (n = 9)</td>
<td>TEM-24; 2 AmpC, 2 AmpC + porin loss, 3 KPC + cdAmpC; IMI</td>
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<tr>
<td>P. aeruginosa (n = 6)</td>
<td>PER-1; VEB; 2 AmpC, 2 upregulated Efflux</td>
</tr>
<tr>
<td>A. baumannii (n = 5)</td>
<td>OXA-51, OXA-58, OXA-23, OXA-24/40</td>
</tr>
<tr>
<td>Others (n = 4)</td>
<td>K1 hyperproducer (K. oxytoca), SME (S. marcescens), 2 cAmpC AmpCs (M. morganii, S. odorifera)</td>
</tr>
</tbody>
</table>

*AmpC prefixes: a, chromosome-encoded; cd, chromosome-encoded derepressed; c, chromosome-encoded inducible; p, plasmid-encoded

- Agents tested were piperacillin (Pip), ceftriaxone (Cro), cepfeme (Fep), and meropenem (Mem), alone or combined with AAI101 4, 8, or 16 mg/L; and Pip/Tazo 4 mg/L.
- Control strains E. coli ATCC25922 and P. aeruginosa ATCC27853 were tested in all assay runs.
- MICs were interpreted according to 2014 CLSI breakpoints (Cro breakpoints for P. aeruginosa not assigned, assumed identical to those for Acinetobacter spp.).2

Results

- AAI101 generally lacked intrinsic antibacterial activity (MICp > 128 mg/L).
- Increasing concentrations of AAI101 generally increased the activity of the partnered β-lactam antibiotics:

| KPC producers | 11. K. pneumoniae, 3 E. coli, 3 E. cloacae + cdAmpC |
| All KPC-producing E. coli and Enterobacter spp. were susceptible (+) to β-lactam/AAI101. |
| Generally, KPC-producing K. pneumoniae were β-lactam-/AAI101, but ST258 strains were not. |
| ESBL producers | 11. E. coli, 2 K. pneumoniae + porin loss, 1 K. oxytoca, 1 E. aerogenes, 2 P. aeruginosa |
| ESBL-producing Enterobacteriaceae were generally susceptible to Pip/BLI. The geometric mean MIC (GMM) for Pip/Tazo (15.4 mg/L) was reduced to 7.1 mg/L for Pip/AAI101 4 mg/L. |

- AAI101 increased Cro and Fep coverage of enterobacterial ESBL producers, and rendered the P. aeruginosa PER-1 producer Fep4 but not Cro4.
- AmpC producers: 5 pAmpC (E. coli), 8 cAmpC (2 E. cloacae, 2 E. cloacae + porin loss, 1 M. morganii, 1 S. odorifera, and 2 P. aeruginosa).
- AAI101 had little effect on the coverage of Pip, Cro, or Mem. |
- AAI101 increased substantially Fep coverage, from 44% susceptible for Fep alone (GMM, 1.3 mg/L) to 94% susceptible for Fep/AAI101 4 mg/L (GMM, 0.5 mg/L).
- OXA producers: 2 E. coli, 2 K. pneumoniae, 5 A. baumannii |
| No OXA-48 producers were Pip4 or Mem4, but + AAI101 8 mg/L 3/4 were Cro5, and 4/4 Fep5. |
| A. baumannii producing OXA-51 and OXA-58 were Pip4 (+ AAI101 16 mg/L) and Fep4 (+ AAI101 4 mg/L).
- Efflux: 2 P. aeruginosa |
| Both efflux isolates were Pip4 and Mem4; one became Fep4 with AAI101 8 mg/L. |

Conclusions

- Addition of AAI101 to Pip, Cro, Fep and/or Mem enhanced activity and generally restored susceptibility for a broad variety of MDR Gram-negative isolates, including:  
  - ESBL-producing Enterobacteriaceae and P. aeruginosa;  
  - K. pneumoniae, E. coli, and Enterobacter spp. with acquired class A or class D carbapenemases (KPC, IMI, OXA-48);  
  - chromosomally-encoded AmpC-producing Enterobacteriaceae and P. aeruginosa;  
  - A. baumannii with intrinsic or acquired class D carbapenemases; and  
  - P. aeruginosa strains with upregulated β-lactam efflux. |
- AAI101 has the potential to restore the clinical utility of well-established β-lactam for the treatment of infections caused by MDR Gram-negative pathogens.

References


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