Introduction

β-Lactam antibiotics are the primary treatments for a broad spectrum of bacterial infections. Production of β-lactamases (e.g. ESBLs, serine carbapenemases, AmpCs) by multidrug-resistant (MDR) Gram-negative bacteria reduces the clinical efficacy of these drugs by deactivating the β-lactam. MDR is an increasingly common problem associated with longer hospital stays, higher treatment costs, and in some cases increased mortality.1-3 Development of β-lactamase inhibitors (BLIs) such as tazobactam (Tazo) has helped preserve the clinical value of various β-lactam antibiotics by protecting them against hydrolysis. However, new, more aggressive β-lactamases are emerging that are not susceptible to existing BLIs.4 New BLIs therefore are required.

AAI101 is an extended-spectrum BLI belonging to the penicillanic acid sulfone class. The purpose of this study was to characterize the spectrum of AAI101 activity against epidemiologically important serine β-lactamases when combined with different classes of β-lactam antibiotics.

Materials and Methods

• 57 isogenic strains, each expressing a unique β-lactamase were prepared from Escherichia coli K-12 derivative TOP10/DH10B and DH5α (Table 1).

Table 1. Isogenic strain characteristics

<table>
<thead>
<tr>
<th>β-Lactam class</th>
<th>n</th>
<th>Expressed β-lactamase</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESBLs</td>
<td>31</td>
<td>Clavulanate-susceptible: 6 TEMs, SHV-12, 8 CTX-Ms, 5 GESs, 4 PERs, VEB-1, BEL-1, BES-1, TLA-2</td>
</tr>
<tr>
<td>Carbapenemases</td>
<td>14</td>
<td>Clavulanate-resistant: TEM-68, TEM-121, SHV-49 (penicillinase)</td>
</tr>
<tr>
<td>Non-carbapenemase OXAs</td>
<td>8</td>
<td>OXA-1, OXA-10, OXA-18, OXA-35, OXA-47, OXA-143, OXA-145, OXA-163</td>
</tr>
<tr>
<td>pAmpCs</td>
<td>4</td>
<td>CMY-2, DHA-1, FOX-5, ACC-1</td>
</tr>
</tbody>
</table>

• Broth microdilution minimum inhibitory concentrations (MICs) for each strain were obtained for piperacillin (Pip), ceftriaxone (Cro), cefepime (Fep), and meropenem (Mem) at AAI101 at a fixed concentration of 4, 8, or 16 mg/L; Pip + Tazo 4 mg/L (Pip/Tazo) also was tested.

• Quality control strain E. coli ATCC25922 was included in all assay runs.
• Antibiotic susceptibilities were assigned according to 2014 CLSI breakpoints (mg/L) :
  - Pip: S ≤ 16, I = 32-64, R ≥ 128
  - Fep: S ≤ 2, I = 4-8, R ≥ 16
  - Mem: S ≤ 1, I = 2, R ≥ 4
  - Cro: S ≤ 1, I = 2, R ≥ 4

Results

• AAI101 alone lacked intrinsic antibacterial activity against all strains (MIC50 >128 mg/L).

   ESBL producers
   • 6% of strains were susceptible to Pip (Pip5); up to 97% were Pip5 with AAI101 4-16 mg/L.
   • Geometric mean MICs (GMMs) for ESBLs with Pip/Tazo and Pip/AAI101 4 mg/L were 3.42 mg/L and 2.67 mg/L, respectively.
   • AAI101 4 mg/L rendered all strains Cro5 or Fep5 (GMMs, 0.06-0.09 mg/L).
   • All strains were Mem5; in some cases addition of AAI101 lowered MICs further.

Class A carbapenemase-producers
• No strains were Pip5; up to 89% were Pip5 with Pip/AAI101 4-16 mg/L.
• 22% were Cro5 (GMM, 6.9 mg/L); up to 67% were Cro5 with Cro/AAI101 4-8 mg/L.
• All but one strain (GES-2) was Fep5 (GMM, 0.73 mg/L); all were susceptible to Fep/AAI101 (GMMs, 0.21 mg/L and 0.06 mg/L for AAI101 4 and 8 mg/L, respectively).
• 56% of strains were Mem5; up to 89% were susceptible to Mem/AAI101 4-8mg/L.

OXA producers
• 77% of strains (including the OXA-48 producer) were susceptible to Pip/AAI101 16 mg/L.
• 62% were Cro5 (GMM, 0.58mg/L) and 69% were Fep5 (GMM, 2.38 mg/L); 100% were Cro5 and Fep5 with AAI101 8 mg/L (GMMs, 0.06 mg/L and 0.11 mg/L, respectively).
• All strains were Mem5; in some cases MICs were further reduced with AAI101.

Figure 1. Percentage of strains susceptible to different β-lactam antibiotics ± BLIs (*Only tested with Pip)

• AAI101 in combination with diverse β-lactams, can treat infections caused by MDR Gram-negative pathogens that produce β-lactamases not susceptible to other BLIs.

Conclusions

• By inhibiting many aggressive β-lactamases of epidemiological concern (e.g. ESBLs, Class A carbapenemases, and OXAs), AAI101 functioned as an extended-spectrum BLI, substantially improving the coverage of Pip, Cro, and Fep towards diverse β-lactamase producers.
• Across the isogenic strain panel the coverage of Pip/AAI101 was comparable to that of Mem and superior to that of Pip/Tazo; coverage of Fep/AAI101 was superior to that of Mem.
• β-Lactam/AAI101 combinations have the potential to replace carbapenems as first-line agents.
• AAI101, in combination with diverse β-lactams, can treat infections caused by MDR Gram-negative pathogens that produce β-lactamases not susceptible to other BLIs.

References


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