AAI101 is a novel zwiptenil extended-spectrum β-lactamase inhibitor (BLI) belonging to the penillicacid sulfonamide family. In vitro studies using Gram-negative clinical isolates with defined mechanisms of β-lactam resistance and isogenic strains of E. coli each expressing a single defined class A, C, or D β-lactamase established that AAI101 synergizes the antibacterial activity of diverse β-lactam classes.1,2 Mouse models have demonstrated the superior potency of AAI101 to tazobactam (Tazo) when one or the other BLI is coadministered with a β-lactam to animals with a systemic or localized tissue (thigh) infection.3,4 A combination of AAI101 and tazobactam (Fep) is in Phase II trials for infections caused by multidrug-resistant Gram-negative pathogens.

As producers of extended-spectrum β-lactamases (ESBLs) and KPC carbapenemases, Klebsiella pneumoniae represents a particularly therapeutic challenge. KPC-2 is the most common KPC isoform, though outbreaks of Klebsiella expressing KPC-3 have occurred in some locales.5 Spread of KPC-producing K. pneumoniae reportedly is associated with multilocus sequence type 258 (ST258) and single locus variants thereof, which jointly comprise K. pneumoniae clonal cluster 258 (CC258).

This study compared the activity of AAI101 with that of tazobactam on K. pneumoniae strains representing a challenge panel of predominantly Klebsiella pneumoniae strains expressing ESBLs or carbapenemases, and belonging to diverse sequence types.

Materials and Methods

- AAI101, weight-purity 97%, was supplied by Allecra Therapeutics SAS (Stuart Shapiro, Allecra Therapeutics SAS, 13, rue de Village Neuf, F-68300 St. Louis, France). Ertapenem was obtained from commercial suppliers. Both microdilution MICs were obtained according to CLSI protocols.6 Cefepime was examined as doubling dilutions of 1-64 µg/mL, whereas AAI101 was tested at fixed concentrations of 4 µg/mL and 8 µg/mL. MIC testing with a fixed concentration of 8 µg/mL of AAI101 correlated best with in-vivo efficacy using humanized-dosing of cefepime-AAI101, reflecting the greater exposure achievable for a given dose of AAI101 compared to an equimolar dose of tazobactam.
- Geometric means (geometric MICs) were calculated as described by Caspers et al.6
- Breakpoints for cephalosporins were not assigned; therefore, CLSI breakpoint assignments (1-2×MIC) followed those for ceftazidime.
- A large-scale epidemiologically-relevant challenge panel of 106 β-lactamase clinical strains, from patients hospitalized in the Middle East, Europe, and the USA during 2007-2013, was recruited from the culture collection
- of the Tel Aviv Sourasky Medical Center.
- β-Lactamase in strains comprising the challenge panel were identified by gene and sequence. Sequence type was established by MLST or PFGE. ST258 isolates also were identified by detection of the pilE allele. Quality control strains (E. coli ATCC25922, P. aeruginosa ATCC27853) were included in all assays run.
- The β-lactamase and sequence type distributions for the 106 K. pneumoniae clinical isolates were surveyed as at:

<table>
<thead>
<tr>
<th>β-Lactam</th>
<th>Cefepime</th>
<th>Fep</th>
<th>Fep/Tazo (4)</th>
<th>Fep/AAI101 (8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPC-2 (n=21)</td>
<td>0.04 µg/mL</td>
<td>0.08 µg/mL</td>
<td>0.08 µg/mL</td>
<td>0.08 µg/mL</td>
</tr>
<tr>
<td>KPC-3 (n=16)</td>
<td>0.04 µg/mL</td>
<td>0.08 µg/mL</td>
<td>0.08 µg/mL</td>
<td>0.08 µg/mL</td>
</tr>
<tr>
<td>CTX-M (n=11)</td>
<td>0.04 µg/mL</td>
<td>0.08 µg/mL</td>
<td>0.08 µg/mL</td>
<td>0.08 µg/mL</td>
</tr>
<tr>
<td>Other ESBL (n=15)</td>
<td>0.04 µg/mL</td>
<td>0.08 µg/mL</td>
<td>0.08 µg/mL</td>
<td>0.08 µg/mL</td>
</tr>
<tr>
<td>OXA-48-like (n=10)</td>
<td>0.04 µg/mL</td>
<td>0.08 µg/mL</td>
<td>0.08 µg/mL</td>
<td>0.08 µg/mL</td>
</tr>
</tbody>
</table>

In vitro activity of cefepime-AAI101 vs. drug-resistant Klebsiella pneumoniae clinical isolates

Y. Carmeli,1 A. Adams,2 E. Eleonor Rashin,3 R. Pypstra,4 and S. Shapiro5

1Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; 2Allecra Therapeutics SAS, St. Louis, France

References


Figure: Effect of tazobactam and AAI101 on cephalosporin susceptibility* and geometric mean MICs (µg/mL)