**The Arenicin-3 Derived Clinical Candidate AA139 Shows Potent Activity Against Gram-Negative Pathogens**


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Revised Abstract

Background

Arenicin-3 is an antimicrobial peptide isolated from Arenicola marina living on sediments in the tidal water of the North Sea. Extensive lead optimization of Arenicin-3 produced the clinical candidate AA139. This current study investigated the activity of AA139 against a recent worldwide collection of isolates of Gram-negative bacteria.

Methods

Minimal inhibitory concentrations were determined by broth microdilution following CLSI guidelines (M7-A6). Recent clinical isolates of Gram-negative bacteria including multi-resistant K. pneumoniae (n=116), P. aeruginosa (n=111), E. coli (n=110) and A. baumannii (n=105) were investigated.

Results

Summary MIC results are given in the Table. These results showed that AA139 exhibited powerful antimicrobial activity against Gram-negative bacteria. Resistance to other agents did not appear to affect the activity of AA139.

Susceptibility Testing

MIC tests were performed by broth microdilution against all isolates in line with Clinical and Laboratory Standards Institute (CLSI) susceptibility testing standards (1,2). AA139 and polymyxin B were tested in the presence of 0.002% polysorbate 80 (present in test wells and during all dilution steps). Concurrent quality control testing using Escherichia coli ATCC 35218, Pseudomonas aeruginosa ATCC 27853 and Escherichia coli ATCC 25922 was performed as per CLSI M07-A9 [1]. CLSI breakpoints were used to determine susceptibility to comparator antimicrobials where available [2]. For the Enterobacteriaceae, polymyxin B susceptibility breakpoints for P. aeruginosa were used [2].

Strain Statistics

Geographic distribution was well-balanced with strains being equally distributed among Asia, North America, Europe and the rest of the world.

Background

The Arenicin family consists of three members: Arenicin-1 and -2, which were characterized by a Russian research group (Ovchinnikova et al., 2004), and Arenicin-3 which is a novel member of the family. Arenicin-3 was isolated from the marine lugworm Arenicola marina; it contains 21 natural amino acid residues constrained in an amphipathic beta hairpin structure by two disulfide bridges between Cys3, Cys20 and Cys7, Cys16. Four positively charged arginines, and 9 hydrophobic residues contribute to the amphipathic characteristics of the peptide.

In this study we present the Minimal Inhibitory Concentration of AA139 and comparators against a panel of world-wide recently collected Gram-negative clinical isolates.

References


Results

**Antimicrobial abbreviations:**

| TDF = piperacillin/tazobactam; MPM = memearable; LVX = levofloxacin; GEN = gentamicin; CAZ = ceftazidime; MBL = polymyxin B |
|---|---|---|---|---|---|---|---|---|
| **A. baumannii** | **E. coli** |
| MIC (µg/mL) | MIC (µg/mL) | MIC (µg/mL) | MIC (µg/mL) | MIC (µg/mL) | MIC (µg/mL) | MIC (µg/mL) | MIC (µg/mL) |
| **AA139** | **AA139** | **AA139** | **AA139** | **AA139** | **AA139** | **AA139** | **AA139** |
| HtR | HtR | HtR | HtR | HtR | HtR | HtR | HtR |
| 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| S | S | S | S | S | S | S | S |
| 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| R | R | R | R | R | R | R | R |
| 65 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

**Conclusions**

- **Percent of multidrug-resistant strains (resistance to ≥3 comparators) was particularly high for A. baumannii (82.4%), followed by K. pneumoniae, P. aeruginosa and E. coli with 31.0, 24.3 and 7.3%, respectively.**

- **Activity of AA139 was uniform among strains tested and there was no correlation with the geographical location or the source of isolation.**

- **Importantly, activity of AA139 was independent from strains’ resistance profile.**