In vitro activity of cefepime in combination with VNRX-5133 against meropenem and/or cefepime resistant clinical isolates of *Pseudomonas aeruginosa*

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Background

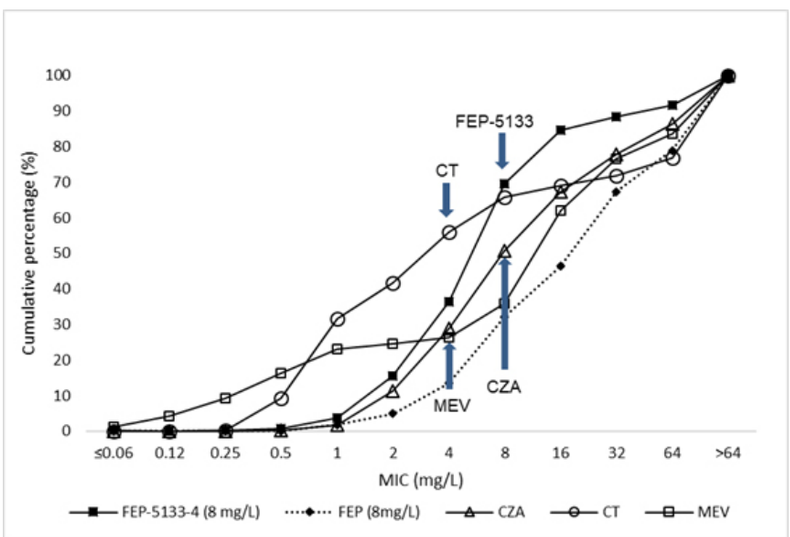
VNRX-5133 is a novel cyclic boronate-based broad-spectrum β-lactamase inhibitor with potent and selective direct inhibitory activity against both serine- and metallo-β-lactamases (Ambler Classes A, B, C and D). VNRX-5133 greatly enhances the activity of cefepime against many difficult to treat organisms, including cephalosporin and carbapenem resistant Enterobacteriaceae and *Pseudomonas aeruginosa*, regardless of the type of beta-lactamase produced. In this study we report on the *in vitro* activity of cefepime tested in combination with VNRX-5133 (FEP/VNRX-5133) and comparator agents against 817 *P. aeruginosa* isolates non-susceptible to cefepime, meropenem, or both.

Methods

All study organisms were clinical isolates previously collected and frozen at -70°C. A total of 817 *P. aeruginosa* were selected from among 7,626 isolates collected in 2013-2015, based on previous MIC results for non-susceptibility to cefepime (MIC>8 mg/L), meropenem (MIC >2 mg/L), or both. MICs of cefepime with VNRX-5133 at a fixed concentration of 4 mg/L (FEP/VNRX-5133) and comparator agents were determined applying CLSI (2017) guidelines and breakpoints where available. The FDA breakpoint was applied for ceftazidime/avibactam and meropenem/vaborbactam. For comparison purposes, the cefepime high dose breakpoint of ≤8 mg/L was used for FEP/VNRX-5133.

Results

Results are presented in the cumulative MIC susceptibility curves below, with arrows indicating the current CLSI or FDA breakpoints. FEP/VNRX-5133 was the most active compound against 817 highly resistant isolates of *P. aeruginosa*. 70% of isolates were inhibited at the concentration of 8 mg/L, and a total 85% inhibited at 16 mg/L. This compares with 56% for ceftolozane/tazobactam, 51% for ceftazidime/avibactam and 26% for meropenem/vaborbactam at their respective susceptible breakpoints.



FEP-5133-4, cefepime tested in combination with VNRX-5133 at 4 mg/l; FEP, cefepime; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEV, meropenem-vaborbactam; arrows indicate current CLSI or FDA breakpoints

Conclusions

The combination of cefepime and VNRX-5133 demonstrated the most potent *in vitro* activity among all comparators against 817 cefepime and/or meropenem resistant *P. aeruginosa*. Because this drug combination exhibited substantial potential for the treatment of infections caused by resistant *P. aeruginosa*, further development is warranted.

Authors

Mark Estabrook[1]

Meredith Hackel[1]

Dan Sahm[1]

Affiliation

[1] International Health Management Associates, Schaumburg, Illinois, United States

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