In vitro activity of cefepime in combination with VNRX-5133 when tested against cephalosporin and carbapenem resistant β-lactamase producing gram-negative isolates

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Background

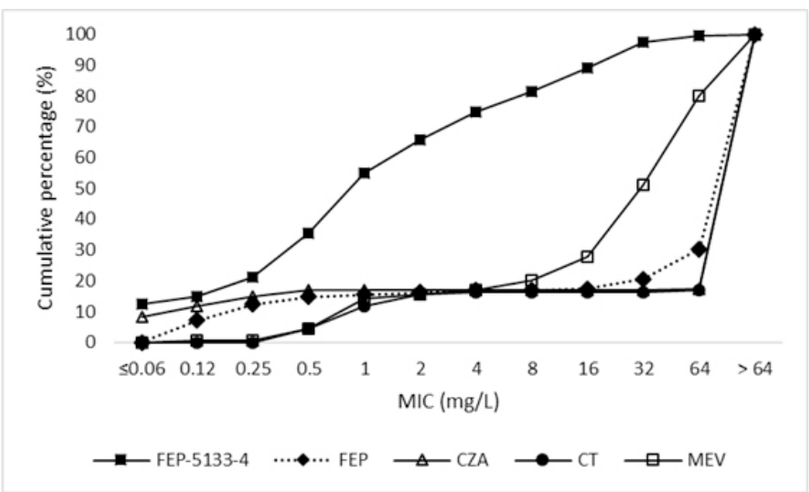
VNRX-5133 is a novel cyclic boronate-based broad-spectrum β-lactamase inhibitor with potent and selective direct inhibitory activity against both serine- and metallo-β-lactamases (Ambler Classes A, B, C and D). VNRX-5133 greatly enhances the activity of cefepime against difficult to treat organisms, including cephalosporin and carbapenem resistant Enterobacteriaceae and *Pseudomonas aeruginosa* producing serine and metallo- β-lactamases from all classes. The *in vitro* activity of cefepime in combination with VNRX-5133 (FEP/VNRX-5133) and comparators was evaluated against recent clinical isolates harboring NDM, OXA-48, and VIM carbapenemases.

Methods

155 Enterobacteriaceae (130 NDM-producers and 25 OXA-producers), and 50 VIM-producing *P. aeruginosa* from 2013-2015 were included in this analysis. 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. The FDA breakpoint was applied for ceftazidime-avibactam and meropenem-vaborbactam. Based on a cefepime dose of 2g tid, the CLSI dose dependent breakpoint of 8 mg/L was applied to cefepime and FEP/5133 for Enterobacteriaceae. The presence of carbapenemase genes (NDM, OXA-48, and VIM) was assessed via multiplex PCR, followed by amplification of the full-length genes and sequencing.

Results

Results for 155 NDM- or OXA-48-producing Enterobacteriaceae are shown in the cumulative MIC susceptibility curves. The combination of cefepime and VNRX-5133 demonstrated potent *in vitro* activity against these highly resistant Enterobacteriaceae, and was the most active antimicrobial tested. 81% of isolates were inhibited at the cefepime susceptible breakpoint of 8 mg/L, and a total of 89% were inhibited at 16 mg/L. In comparison, susceptibility was 17% for ceftazidime-avibactam, 16% for ceftolozane-tazobactam, and 17% for meropenem-vaborbactam. FEP/VNRX-5133 was also the most active antimicrobial against 50 VIM-producing *P. aeruginosa*, with 60% susceptible, compared to 0% for ceftazidime-avibactam, ceftolozane-tazobactam, and meropenem-vaborbactam.



N=155 Enterobacteriaceae (130 NDM, 25 OXA-48); 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

Conclusions

Cefepime demonstrated excellent in vitro activity in combination with VNRX-5133 against recent gram-negative carbapenemase-producing clinical isolates, regardless of enzyme class. Because this drug combination exhibited substantial potential for the treatment of infections caused by isolates often resistant to the first line of therapy, further development is warranted.

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