Antimicrobial activity of cefepime in combination with VNRX-5133 against a global collection of clinical 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 many difficult to treat organisms, including cephalosporin and carbapenem resistant Enterobacteriaceae and *Pseudomonas aeruginosa*. The activity of cefepime in combination with VNRX-5133 and comparator agents was evaluated against recent clinical isolates.

Methods

Tested strains included drug-resistant and molecularly characterized isolates. MICs of cefepime/VNRX-5133 fixed at 4 mg/L (FEP/VNRX-5133), and comparator agents were determined against 1,385 gram-negatives and 405 gram-positives applying CLSI (2017) guidelines and breakpoints. For FEP/VNRX-5133 (dosed at 2g tid), cefepime dose dependent breakpoint of 8 mg/L was applied to Enterobacteriaceae and *P. aeruginosa*.

Results

FEP/VNRX-5133 showed potent *in vitro* activity against all Enterobacteriaceae, with an MIC_{90} of 0.5 mg/L, compared to cefepime, levofloxacin, meropenem, and piperacillin-tazobactam (MIC_{90} values >128, >4, 4, >64 mg/L, respectively). FEP/VNRX-5133 inhibited 99% of all Enterobacteriaceae at the cefepime dose dependent breakpoint of ≤8 mg/L, including 99% of ESBL-producers and 93% of meropenem-nonsusceptible isolates. FEP/VNRX-5133 was active against *P. aeruginosa*, with an MIC_{90} of 8 mg/L and 90% susceptible. There was little or no potentiation of cefepime activity against the gram-positive isolates and *H. influenzae*, 100% sensitive to 2 mcg/ml.

Organism (n)	% Susceptible/MIC_{90} (mg/L)				
	FEP/VNRX-5133	FEP	LVX	MEM	TZP
Enterobacteriaceae (1,120)	99 (0.5)	71 (>128)	64 (>4)	88 (4)	60/>64
Enterobacteriaceae, ESBL + (307)	99 (0.5)	40 (>128)	37 (>4)	98 (0.12)	27/>64
Enterobacteriaceae, MEM NS (134)	93 (8)	8 (>128)	19 (>4)	0 (128)	6/>64
Pseudomonas aeruginosa (153)	90 (8)	68 (64)	64 (>4)	69 (128)	60/>64
Pseudomonas aeruginosa, MEM NS (48)	65 (16)	8 (>128)	6 (>4)	0 (>4)	0 (>64)
Haemophilus influenzae (112)	100 (0.12)	100 (0.12)	99 (0.03)	100 (0.06)	nt
Staphylococcus aureus , MSSA (114)	na (2)	na (4)	94 (0.5)	na (0.5)	nt
Staphylococcus epidermidis (100)	na (0.25)	na (0.5)	88 (>4)	na (0.12)	nt
β-haemolytic streptococci (201)	100 (0.06)	100 (0.06)	98 (1)	100 (0.03)	nt

FEP/VNRX-5133-4, FEP+VNRX-5133 at 4 mg/L; FEP, cefepime; LVX, levofloxacin; MEM, meropenem; TZP, piperacillin-tazobactam; ESBL+, extended-spectrum β-lactamase producer; NS, non-susceptible; ESBL+, extended-spectrum β-lactamase producer; MSSA, methicillin-susceptible *S. aureus* ; na, no breakpoint; nt, not tested

Conclusions

Cefepime in combination with VNRX-5133 demonstrated excellent *in vitro* activity and was the most potent drug tested against recent gram-negative clinical isolates, including difficult to treat cephalosporin and carbapenem-resistant Enterobacteriaceae and *Pseudomonas aeruginosa*. 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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