Pharmacokinetics-pharmacodynamics (PK-PD) of VNRX-5133, a broad-spectrum novel β-lactamase inhibitor (BS-BLI), in combination with cefepime in a one-compartment *in vitro* infection model

ECCMID 2018 | Paper Poster Session #76 | Paper Poster #P1537 | April 23, 2018 | 12:30pm – 13:30pm | Paper Poster Arena

Background

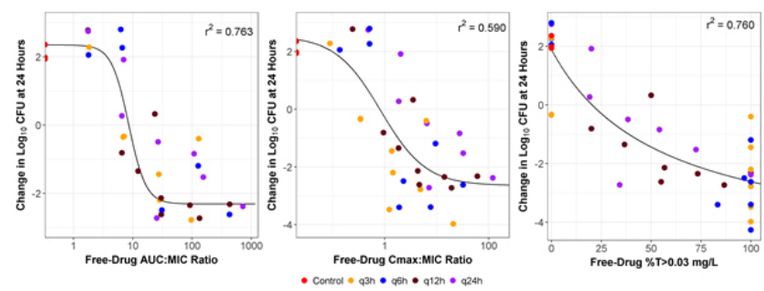
VNRX-5133 is a broad-spectrum, selective, non-β-lactam, BS-BLI with *in vitro* activity against all four Ambler class enzymes, including Class B metallo-β-lactamases. VNRX-5133 is being developed in combination with cefepime for the treatment of serious infections associated with β-lactamase producing bacteria. In order to optimize VNRX-5133 dosing, it is important to understand the PK-PD index associated with efficacy. To this end, a series of *in vitro* studies for VNRX-5133 in combination with cefepime were completed with the following objectives: 1) to identify the PK-PD index associated with VNRX-5133 efficacy; and 2) to determine the magnitude of the VNRX-5133 PK-PD index required for efficacy against cephalosporin and carbapenem-resistant Enterobacteriaceae (ENT) and *Pseudomonas aeruginosa* (PSA).

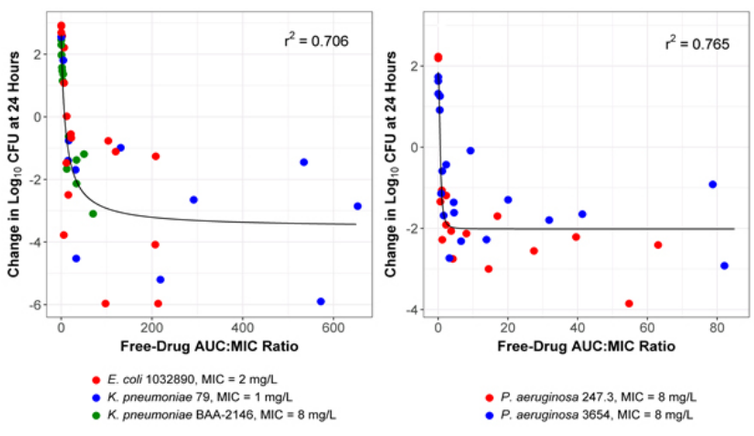
Methods

A 24 h one-compartment *in vitro* infection model was utilized in all studies. To identify the PK-PD index associated with VNRX-5133 efficacy, dose-fractionation studies were conducted using one isolate exposed to five VNRX-5133 exposures fractionated into regimens administered every 3, 6, 12, or 24 hours, in combination with a sub-clinical dose of cefepime administered q8h. In order to evaluate the inter-isolate variability in VNRX-5133 efficacy, dose-ranging studies were completed for five isolates (3 ENT and 2 PSA) producing a variety of serine- and/or metallo-β lactamase enzymes (NDM-1, VIM-2, CTX-M-15, KPC-3, TEM-1, and SHV-11) in combination with cefepime 2 g q8h. Hill-type models were used to describe relationships between change in $\log_{10}$ CFU from baseline at 24 hours and each of VNRX-5133 AUC:MIC ratio, C_{max}:MIC ratio and %T>threshold concentration, where the cefepime MIC was determined in the presence of 4 mg/L of VNRX-5133.

Results

AUC:MIC ratio and %T>0.03 mg/L described the efficacy of VNRX-5133 well (r^2 of 0.763 and 0.760, respectively. The magnitudes of AUC:MIC ratio associated with net bacterial stasis and 1- and 2-$\log_{10}$ CFU reductions from baseline were 7.42, 14.7, and 31.9 for ENT and 0.57, 0.93, and 6.41 for PSA, respectively.





Conclusions

These data, which demonstrated similar *in vitro* activity of VNRX-5133 against serine- and metallo-β–lactamases for both ENT and PSA, provide initial PK-PD targets for VNRX-5133 efficacy in combination with cefepime for the treatment of infections arising from carbapenem-resistant isolates.

Authors

Brian D. VanScoy[1]

Jennifer McCauley[1]

Elizabeth A. Lakota[1]

Haley Conde[1]

Sujata M. Bhavnani[1]

Tim Henkel[2]

Luigi Xerri[2]

Daniel C. Pevear[2]

Paul. G. Ambrose[1]

Affiliation

[1] Institute for Clinical Pharmacodynamics, Schenectady, New York, United States

[2] VenatoRx Pharmaceuticals, Malvern, Pennsylvania, United States

This project has been funded in whole or in part with Federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN272201300019C, and Wellcome Trust under Award No. 360G-Wellcome-101999/Z/13/Z.

VenatoRx PHARMACEUTICALS