Efficacy of cefepime / VNRX-5133, a novel β-lactamase inhibitor, against cephalosporin-resistant, ESBL-producing *K. pneumoniae* in a murine lung-infection model

ECCMID 2018 | Session OE112 | Oral Presentation #O0600 | April 22, 2018 | 16:00 – 16:05 | ePoster Arena 3

Background

Extended-spectrum β-lactamases (ESBLs) are a problematic resistance mechanism associated with cephalosporin-resistant *K. pneumoniae*, a pathogen responsible for both community and hospital acquired pneumonia. VNRX-5133 is a new broad-spectrum β-lactamase inhibitor with potent and selective direct inhibitory coverage for Class A, C, D Serine- and VIM/NDM class B metallo-β-lactamases. Combination with cefepime (FEP) achieves potent antibacterial activity against a significant proportion of carbapenem-resistant enterics (CRE). The current study was performed to evaluate the efficacy of this combination in the murine lung infection model with a cephalosporinase producing strain.

Methods

In vitro MICs of selected compounds were determined by broth microdilution in accordance with CLSI guidelines. Mice were anesthetized by IP injection of Ketamine HCl+Xylazine followed by intranasal inoculation with 6.5 $\log_{10}$ CFU of *K. pneumoniae* (CTX-M-14). Treatment was initiated 2 hours post-infection by subcutaneous administration of FEP alone, FEP/VNRX-5133 (2:1), FEP/tazobactam (2:1) or ceftazidime/avibactam (4:1). Mice were euthanized by CO2 inhalation 24 hrs post-infection, lungs aseptically removed, homogenized, serial diluted and plated for determination of bacterial burden in lung tissue.

Results

Mean bacterial lung titers for untreated controls were 6.21 and 9.84 $\log_{10}$ CFU at 2 and 24 hrs post-infection, respectively. FEP alone, at doses from 16 – 128 mg/kg exhibited minimal efficacy, with mean lung CFU values of 9.32 – 9.53 $\log_{10}$ CFU. FEP/VNRX-5133 exhibited excellent efficacy with mean bacterial lung titers of 4.59, 4.59, 5.69 and 6.82 $\log_{10}$ CFU at doses of 64:32, 32:16, 16:8 and 8:4 mg/kg, respectively (3 – 4+ $\log_{10}$ CFU reduction as compared to the corresponding doses of FEP alone). FEP/tazobactam was less efficacious with mean bacterial titers of 6.03, 6.49, 8.43 and 8.49 $\log_{10}$ CFU at the 64:32, 32:16, 16:8 and 8:4 mg/kg doses, respectively. Ceftazidime:avibactam (4:1) administration resulted in mean bacterial lung titers of 4.42, 5.51, 7.39 and 8.77 $\log_{10}$ CFU at 64:16, 32:8, 16:4 and 8:2 mg/kg, respectively.

Conclusions

VNRX-5133 provided an excellent protection of cefepime against this cephalosporin-resistant *K. pneumoniae*: cefepime/VNRX-5133 administration resulted in bacterial lung titers >4 $\log_{10}$ CFU inferior to animals receiving cefepime alone, demonstrating consistent rescue of cefepime in the neutropenic murine lung infection model of disease.

Authors

William J. Weiss[1]

Mark E. Pulse[1]

Phung Nguyen[1]

David Valtierra[1]

Kelly Peterson[1]

Kiahrae Carter[1]

Daniel C. Pevear[2]

Christopher J. Burns[2]

Luigi Xerri[2]

Affiliation

[1] PreClinical Services, University of North Texas College of Pharmacy, Fort Worth, Texas, 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.