Susceptibility to cefepime / VNRX-5133 in 298 carbapenem-resistant Enterobacteriaceae producing serine- and metallo-β-lactamases

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Background

VNRX-5133 is a new β-lactamase inhibitor with direct-acting broad-spectrum inhibitory coverage for Class A, C, D Serine- and VIM/NDM class B metallo-β-lactamases. Combination with cefepime achieves potent antibacterial activity against a relevant proportion of carbapenem-resistant enterics (CRE). Although the production of inactivating enzymes is the most efficient and epidemiologically relevant mechanism of resistance to β-lactams, select enterics (e.g., *E. coli*, *K. pneumoniae*) can, in rare cases, exploit additional non-transmissible resistance mechanisms to restrict antibiotic access to the target. This study sought to examine the distribution of these two different mechanisms of resistance in a large collection of CRE clinical isolates.

Methods

Susceptibility testing was performed according to CLSI methods with cefepime, meropenem, ceftazidime and cefepime combined with VNRX-5133 fixed at 4mg/L, relative to ceftazidime combined with avibactam fixed at 4 mg/L. The study examined 298 CRE isolates consisting of 156 NDM-, 44 OXA-48, 39 VIM- and 59 KPC-producing Enterobacteriaceae. Cellular extracts generated from isolates with MIC values above the breakpoint of 8 mg/L were used to assess inhibitory activity of VNRX-5133 by IC_{50} relative to purified enzymes. Quantitative real-time RT-PCR examined expression levels of OmpK35/36 in *K. pneumoniae* and OmpF/C in *E. coli*.

Results

Changes in susceptibility to cefepime/VNRX-5133 in a sub-population of CRE isolates with cefepime MIC≥512 mg/L were not due to resistant enzyme variants as extracts generated from all resistant isolates proved equally sensitive to VNRX-5133 (IC_{50}<0.1 μM) as both susceptible extracts and purified enzymes. CRE isolates within this sub-group were found to be downregulated in OmpK35/36 and OmpF/C in *K. pneumoniae* and *E. coli* respectively, confirming that severely decreased cefepime/VNRX-5133 permeability are responsible for this level of resistance. Against the remaining 245 CRE isolates with cefepime MIC≤256 mg/L, VNRX-5133 was highly active in restoring cefepime activity, achieving a proposed susceptibility breakpoint of 8 mg/L in 93.1% of isolates, relative to ceftazidime/avibactam at 53.5%.

Conclusions

As expected, downregulation of porin channel expression, a non-transmissible resistance mechanism, can decrease susceptibility to β-lactams. Where β-lactamase production is the primary mechanism of resistance, cefepime/VNRX-5133 has unprecedented activity against KPC-,OXA-,VIM- and NDM-producing Enterobacteriaceae with no less sensitive enzyme variants detected.

Authors

Jonathan M. Tyrrell[1]

Mohammed Wali[2]

Denis M. Daigle[2]

Ali Farag Aboklaish[1]

Natalia Kurepina[3]

Barry Kreiswirth[3]

Timothy R. Walsh[1]

Daniel C. Pevear[2]

Luigi Xerri[2]

Affiliation

[1] School of Medicine, Institute of Infection and Immunity, Cardiff University, Heath Park, Wales, United Kingdom

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

[3] New Jersey Medical School, Public Health Research Institute, Rutgers University, Newark, New Jersey, United States

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