Cefepime-taniborbactam (formerly cefepime/VNRX-5133) demonstrates potent activity vs. Enterobacterales with *bla*$_{OXA-48}$

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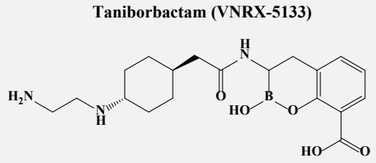
Abstract

Background: Infections caused by OXA-48 carbapenemase-producing Enterobacterales are difficult to treat due to limited therapeutic options. To combat these problematic pathogens, β-lactam-β-lactamase inhibitor combinations are an effective strategy. Taniborbactam (formerly VNRX-5133) is a novel, investigational boronic-acid β-lactamase inhibitor. The combination of cefepime with taniborbactam possesses antimicrobial activity against Enterobacterales carrying class A, B, C, and/or D enzymes. Herein, we assessed the activity of cefepime-taniborbactam against a panel of (N=50) Enterobacterales carrying *bla*$_{OXA-48}$.
Methods: CLSI-based agar dilution susceptibility testing was conducted using cefepime-taniborbactam and comparators cefepime, meropenem-vaborbactam, and ceftazidime-avibactam against *Escherichia coli*, *Escherichia hermannii*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* carrying *bla*$_{OXA-48}$. Most strains were isolated between 2007-2012 from France, Lebanon, Morocco, Algeria, Switzerland, Sultanate of Oman, Egypt, Libya, the Netherlands, and Turkey. Host sources included sputum, urine, rectal swab, pus, blood, placenta, and bronchoalveolar lavage fluid. Time-kill assays with cefepime, cefepime-taniborbactam, and ceftazidime-avibactam were performed at MIC multiples of 1×, 2×, and 4× using *E. coli* DOV (*bla*$_{OXA-48}$, *bla*$_{CTX-M-15}$, *bla*$_{TEM-1}$, *bla*$_{OXA-1}$) and *E. coli* MLI (*bla*$_{OXA-48}$, *bla*$_{VEB}$, *bla*$_{TEM-1}$, *bla*$_{CMY-2}$).
Results: The addition of taniborbactam to cefepime shifted the MICs to the provisionally susceptible range; the MIC_{90} value decreased from >32 µg/mL for cefepime to 4 µg/mL for cefepime-taniborbactam. Cefepime-taniborbactam MIC_{50}/MIC_{90} values (0.5/4 µg/mL, respectively) were lower than those for meropenem-vaborbactam (1/16 µg/mL, respectively) and comparable to those for ceftazidime-avibactam (0.5/1 µg/mL). Time-kill assays revealed time-dependent reductions in the number of CFU/mL from 0 to 6 h for *E. coli* DOV with cefepime-taniborbactam and ceftazidime-avibactam at 1×, 2×, and 4× MIC multiples. Moreover, 4× MIC multiples for cefepime-taniborbactam and ceftazidime-avibactam were bactericidal up to 24 h against this same strain. Conversely, only cefepime-taniborbactam at 1×, 2×, and 4× MIC displayed time-dependent reductions in the number of CFU/mL from 0 to 6 h for *E. coli* MLI. Bactericidal activity was maintained up to 24 h at 2× and 4× MIC of cefepime-taniborbactam against *E. coli* MLI.
Conclusions: Taniborbactam in combination with cefepime was highly active against this diverse panel of Enterobacterales with *bla*$_{OXA-48}$ and represents a potential addition to our antibiotic arsenal.

Background

- Based on structural characteristics, β-lactamases are grouped in four different Ambler classes: A, B, C, or D.
- Class A, C, and D β-lactamases use serine as a nucleophile, while class B enzymes are Zn^{2+}-dependent metallo-enzymes.
- The most problematic and difficult-to-treat β-lactamase-producing Gram-negative pathogens include carbapenem-resistant Enterobacterales (CRE) that produce class D OXA-48-like carbapenemases.
- The boronic acid β-lactamase inhibitor, taniborbactam (formerly VNRX-5133) is being developed in combination with cefepime.
- Taniborbactam is unique compared to all other clinically available β-lactamase inhibitors as it inhibits class A, B, C, and D β-lactamases (except class B IMP enzymes) (1-3).

Taniborbactam (VNRX-5133)



Goal: Assess the antimicrobial activity of cefepime-taniborbactam against CRE carrying *bla*$_{OXA-48}$.

Results

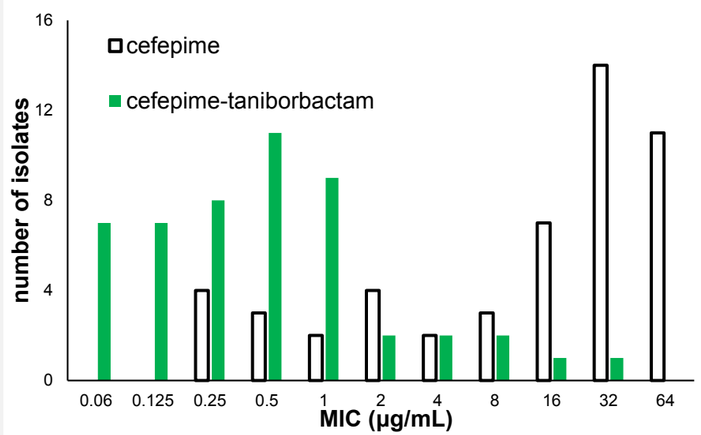


Figure 1. Agar dilution susceptibility testing results (MIC) for cefepime alone (white bars) compared to cefepime combined with taniborbactam (green bars) against a panel of 50 CRE carrying *bla*$_{OXA-48}$. The addition of taniborbactam to cefepime reduced the MIC_{90} values from 32 µg/mL to 4 µg/mL.

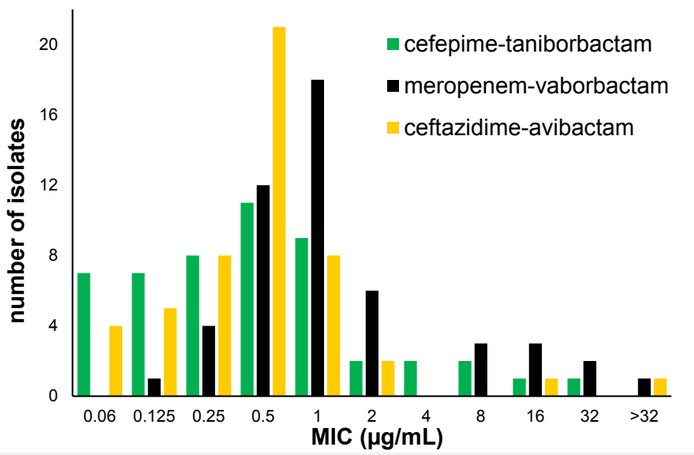


Figure 2. Agar dilution susceptibility results for cefepime-taniborbactam (green bars) compared to meropenem-vaborbactam (black bars), and ceftazidime-avibactam (yellow bars) against 50 CRE carrying *bla*$_{OXA-48}$. The MIC_{50}/MIC_{90} values for cefepime-taniborbactam (0.5/4 µg/mL, respectively) are lower than those for meropenem-vaborbactam (1/16 µg/mL, respectively), and comparable to those for ceftazidime-avibactam (0.5/1 µg/mL, respectively).

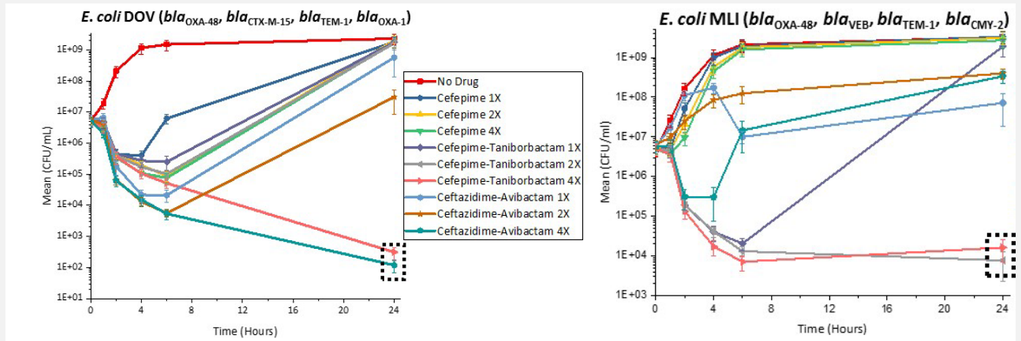


Figure 3. Time-kill assays for *E. coli* DOV (left) and *E. coli* MLI (right) against cefepime, cefepime-taniborbactam, and ceftazidime-avibactam. For *E. coli* DOV at 1×, 2×, and 4× the MIC of cefepime-taniborbactam and ceftazidime-avibactam, time-dependent reductions in CFU/mL were observed between 0 and 6 h; and at 4× the MIC both drug combinations were bactericidal up to 24 h. For *E. coli* MLI only cefepime-taniborbactam displayed time-dependent reductions in CFU/mL from 0 to 6 h at 1×, 2×, and 4× the MIC; 2× and 4× the MIC remained bactericidal up to 24 h. Values with ≥ 3 log reduction are annotated by a dashed black rectangle. Each strain possessed the following MIC: *E. coli* DOV, cefepime 16 µg/mL, cefepime-taniborbactam 0.25 µg/mL, and ceftazidime-avibactam 0.25 µg/mL; *E. coli* MLI, cefepime 128 µg/mL, cefepime-taniborbactam 2 µg/mL, and ceftazidime-avibactam 16 µg/mL.

Conclusions

- The addition of taniborbactam lowered cefepime MIC against CRE carrying *bla*$_{OXA-48}$.
- The antimicrobial activity of cefepime-taniborbactam was comparable to that of ceftazidime-avibactam against this panel of CRE.
- Time-kill assays with cefepime-taniborbactam vs ceftazidime-avibactam revealed time-dependent reduction in CFU/mL by cefepime-taniborbactam, which was bactericidal for the two strains (*E. coli* DOV and *E. coli* MLI)
- Cefepime-taniborbactam possesses the potential to be a promising addition to our antibiotic arsenal.

References

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