Title: ARGONAUT-III: Susceptibility of Carbapenem-resistant *Klebsiellae* to Cefepime-Taniborbactam

Authors

Mack, Andrew R [1,2]. Bethel, Christopher R [2]. Marshall, Steven [2]. Patel, Robin [3]. van Duin, David [4]. Fowler, Vance G [5]. Rhoads, Daniel D [6]. Jacobs, Michael R [6]. van den Akker, Focco [1]. Six, David A [7]. Moeck, Greg [7]. Papp-Wallace, Krisztina M [1,2]. Bonomo, Robert A [1,2,8].

[1] *Case Western Reserve University, Cleveland, Ohio, USA.*
[2] *Veterans Affairs Northeast Ohio Healthcare System, Cleveland, Ohio, USA.*
[3] *Mayo Clinic, Rochester, MN, USA.*
[4] *University of North Carolina, Chapel Hill, NC, USA.*
[5] *Duke University Medical Center, Durham, NC, USA*
[6] *University Hospitals Cleveland Medical Center, Cleveland, Ohio, USA.*
[7] *Venatorx Pharmaceuticals, Inc., Malvern, Pennsylvania, USA.*
[8] *CWRU-Cleveland VAMC Center for Antimicrobial Resistance and Epidemiology (CARES), Cleveland, Ohio, USA.*

Background

Klebsiellae are Gram-negative pathogens responsible for serious nosocomial and community-acquired infections. Carbapenem resistance, both intrinsic and acquired, complicates therapy. Taniborbactam (formerly VNRX-5133; Fig 1) is a bicyclic boronate β-lactamase inhibitor (BLI) that inhibits all four Ambler classes of β-lactamase enzymes, both serine- and metallo-, with the notable exception of class B IMP β-lactamases. Taniborbactam is currently undergoing phase 3 clinical trials in combination with cefepime (FEP; Fig 1) as part of the β-lactam-BLI (BL-BLI) combination FEP-taniborbactam (FTB).

Methods

We determined the activity of FTB against 200 carbapenem-resistant *Klebsiellae* (CRK) strains collected as part of the Antibiotic Resistance Leadership Group (ARLG) Consortium on Resistance against Carbapenems in *Klebsiella* (CRACKLE) study. Among these strains, 193 expressed class A KPCs, one expressed a class B NDM, and six expressed class D OXA-48 or variants. Broth microdilution minimum inhibitory concentrations (MIC)s were determined using the ThermoFisher Sensititre system with custom assay panels. American Type Culture Collection strains were used for quality control. The susceptible-dose-dependent breakpoint for FEP was provisionally used for FTB.

Results

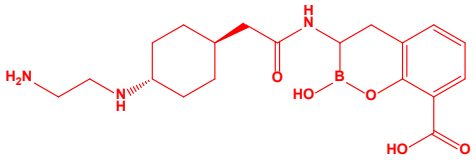
Among the 200 *Klebsiella* strains tested, susceptibility for β-lactams alone ranged from 1% for ceftazidime (CAZ), 2.5% for meropenem, and 13.5% for FEP (Table 1). The addition of BLIs increased % susceptibility compared to BL alone to: 98% for CAZ-avibactam (CZA); 95.5% for MEM-vaborbactam (MVB); and 99.0% for FTB. MIC_{50} and MIC_{90} were in the susceptible and provisionally susceptible range for CZA and MVB, and in the provisionally susceptible range for FTB. Analyzing the CZA and MVB non-susceptible strains, 7 of 9 MVB non-susceptible strains and 2 of 4 CZA-resistant strains were provisionally susceptible to FTB.

Title: ARGONAUT-III: Susceptibility of Carbapenem-resistant *Klebsiellae* to Cefepime-Taniborbactam

Conclusions

The addition of taniborbactam restored susceptibility to FEP in 99.0% of CRACKLE isolates studied, comparable to CZA and MVB. Taniborbactam also restored FEP activity against some MVB- and CZA-resistant strains. FTB may provide a promising therapy for CRK infections.

Taniborbactam (VNRX-5133)



Cefepime

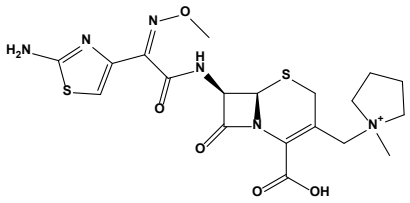


Figure 1: Structures of taniborbactam and cefepime. The β-lactamase inhibitor is in red and the β-lactam antibiotic is in black.

	AMK	CST	CAZ	CZA	FEP	FTB	MEM	MVB	TGC
CLSI Susceptible Breakpoint	≤16	≤2*	≤4	≤8/4	≤8	≤8**	≤1	≤4/8	≤2
MIC_{50}	16	0.5	>16	1	>32	0.25	>4	≤ 0.03	1
MIC_{90}	32	>4	>16	2	>32	2	>4	1	4
%S	60	77	1	98	13.5	99**	2.5	95.5	88.5

Table 1: MIC_{50} and MIC_{90} values (µg/mL) and percent susceptibility for *Klebsiella pneumoniae* strains (n=200). AMK, amikacin; CST, colistin; CAZ, ceftazidime; CZA, ceftazidime-avibactam; FEP, cefepime; FTB, cefepime-taniborbactam; MEM, meropenem; MVB, meropenem-vaborbactam; TGC, tigecycline. * The breakpoint for CST is intermediate, as no susceptible breakpoint is available. ** The susceptible-dose-dependent breakpoint for FEP alone was provisionally applied to FTB. Breakpoints from CLSI M100, 31st ed, 2021.