P2738

Antimicrobial Activity of Cefepime in Combination with Taniborbactam (formerly VNRX-5133) Against Clinical Isolates of Enterobacterales from Europe Collected from 2018-2019 Surveillance

M. Hackel[1], D. Sahm[1]

[1]IHMA, Inc., Schaumburg, IL, USA

IHMA, Inc.
2122 Palmer Drive
Schaumburg, IL 60173 USA
www.ihma.com

INTRODUCTION

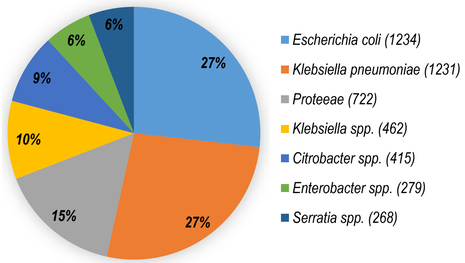
Taniborbactam, (formerly VNRX-5133), is a novel cyclic boronate-based broad-spectrum β-lactamase inhibitor with potent and selective direct inhibitory activity against both serine- and metallo-β-lactamases (Ambler Classes A, B, C and D). Taniborbactam greatly enhances the activity of cefepime against many difficult to treat organisms, including cephalosporin- and carbapenem-resistant Enterobacterales and *Pseudomonas aeruginosa*. In this study, we evaluated the *in vitro* activity of the investigational combination cefepime-taniborbactam and comparator agents against recent clinical isolates of Enterobacterales collected in Europe during 2018-2019 surveillance.

MATERIALS & METHODS

MICs of cefepime with taniborbactam fixed at 4 mg/L (FTB) and comparators were determined following CLSI M07-A11 guidelines [1] against 4,611 Enterobacterales (Figure 1). Quality control (QC) testing was performed each day of testing as specified by the CLSI [1, 2]. Isolates were from community and hospital infections collected from 113 sites in 24 European countries in 2018-2019 (Figure 2). Isolates were sourced from (n/percent of total): respiratory tract infections (1,727/37.5%), urinary tract infections (1,070/23.2%), intraabdominal infections (915/19.8%), bloodstream infections (639/13.9%), skin/soft tissue infections (259/5.6%), and unknown (1/<0.1%). Avibactam was tested at a fixed concentration of 4 mg/L in combination with ceftazidime, tazobactam was tested at a fixed concentration of 4 mg/L in combination with ceftolozane and piperacillin, and vaborbactam was tested at a fixed concentration of 8 mg/L in combination with meropenem. Resistant phenotypes were based on 2020 EUCAST breakpoints v10.0 [3]. As cefepime-taniborbactam breakpoints have not yet been established, the provisional non-resistant breakpoint of ≤8 mg/L was considered for comparative purposes. A set of 198 Enterobacterales with meropenem MIC ≥4 mg/L (n=95) or with cefepime/ceftazidime MIC ≥2 mg/L (n=103) was evaluated for the presence of MBL, KPC, ESBL, and OXA-48 group genes via PCR and sequencing. Three isolates with cefepime-taniborbactam MIC values of 16 mg/L were interrogated by whole genome sequencing (WGS).

RESULTS

Figure 1. Distribution of 4,611 Enterobacterales isolates by species



Klebsiella spp. consist of (n): *K. oxytoca* (321); *K. aerogenes* (139); *K. variicola* (2)
Proteeae consist of (n): *Morganella morganii* (154); *Proteus mirabilis* (268); *P. vulgaris* (163); *Providencia alcalifaciens* (1); *P. rettgeri* (53); *P. stuartii* (82); *Providencia* sp. (1)
Serratia spp. consist of (n): *S. fonticola* (1); *S. liquefaciens* (21); *S. marcescens* (235); *S. rubidaea* (2); *S. ureilytica* (9)
Citrobacter spp. consist of (n): *C. braakii* (27); *C. farmeri* (1); *C. freundii* (243); *C. koseri* (144)
Enterobacter spp. consist of (n): *E. asburiae* (17); *E. cloacae* (229); *E. cloacae* complex (22); *E. kobei* (7); *E. ludwigii* (4)

Figure 2. Distribution of 4,611 Enterobacterales isolates by country of isolation

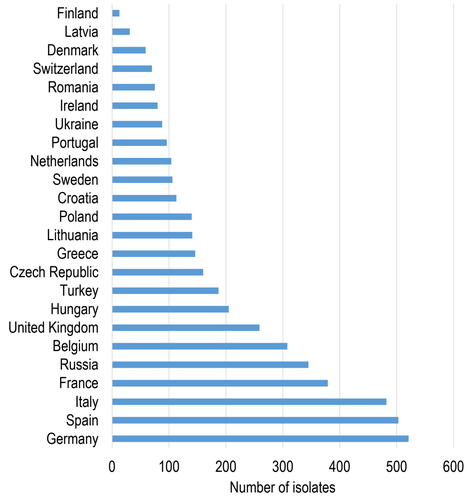


Table 1. *In vitro* activity of cefepime-taniborbactam and comparator agents against 4,611 Enterobacterales from Europe

Phenotype (n)	Antimicrobial	%S	%I	%R	MIC_{50}	MIC_{90}	Range
Enterobacterales (4,611)	Cefepime-taniborbactam	99.7[a]	--	0.3	0.06	0.25	≤0.008 - >16
	Cefepime	76.3	4.5	19.2	≤0.25	>16	≤0.25 - >16
	Ceftazidime	71.3	4.3	24.3	0.25	>16	≤0.03 - >16
	Ceftazidime-avibactam	98.3	--	1.7	≤0.12	0.5	≤0.12 - >16
	Ceftolozane-tazobactam	86.4	--	13.6	0.5	8	≤0.25 - >8
	Gentamicin	83.9	--	16.1	0.5	>16	≤0.12 - >16
	Levofloxacin	71.8	3.5	24.7	0.06	>8	≤0.004 - >8
	Meropenem	95.0	5.0	na	0.03	0.12	≤0.004 - >4
	Meropenem-vaborbactam	97.9	--	2.1	≤0.06	0.12	≤0.06 - >16
	Piperacillin Tazobactam	79.3	3.7	16.9	≤4	128	≤4 - >128
Cefepime-NS (1,092)	Cefepime-taniborbactam	98.6[a]	--	1.4	0.12	2	0.015 - >16
	Cefepime	0	18.9	81	>16	>16	2 - >16
	Ceftazidime	5.9	8.0	86.2	>16	>16	0.06 - >16
	Ceftazidime-avibactam	92.9	--	7.1	0.5	4	≤0.12 - >16
	Ceftolozane-tazobactam	52.0	--	48.0	2	>8	≤0.25 - >8
	Gentamicin	48.8	--	51.2	4	>16	≤0.12 - >16
	Levofloxacin	24.5	6.0	69.6	>8	>8	0.015 - >8
	Meropenem	79.5	20.5	na	0.06	>4	≤0.004 - >4
	Meropenem-vaborbactam	91.3	--	8.7	≤0.06	8	≤0.06 - >16
	Piperacillin Tazobactam	39.4	9.3	51.3	32	>128	≤4 - >128
Meropenem-NS (232)	Cefepime-taniborbactam	94.4[a]	--	5.6	1	4	0.03 - >16
	Cefepime	3.5	1.7	94.8	>16	>16	≤0.25 - >16
	Ceftazidime	4.3	0.4	95.3	>16	>16	0.06 - >16
	Ceftazidime-avibactam	70.7	--	29.3	2	>16	≤0.12 - >16
	Ceftolozane-tazobactam	2.2	--	97.8	>8	>8	0.5 - >8
	Gentamicin	30.6	--	69.4	>16	>16	≤0.12 - >16
	Levofloxacin	6.0	1.7	92.2	>8	>8	0.03 - >8
	Meropenem	0	100	na	>4	>4	4 - >4
	Meropenem-vaborbactam	58.6	--	41.4	4	>16	≤0.06 - >16
	Piperacillin-tazobactam	0.4	0.0	99.6	>128	>128	≤4 - >128
Piperacillin-tazobactam-NS (953)	Cefepime-taniborbactam	98.4[a]	--	1.6	0.25	2	0.015 - >16
	Cefepime	30.5	11.0	58.5	>16	>16	≤0.25 - >16
	Ceftazidime	19.7	6.0	74.3	>16	>16	0.06 - >16
	Ceftazidime-avibactam	91.7	--	8.3	0.5	4	≤0.12 - >16
	Ceftolozane-tazobactam	40.3	--	59.7	8	>8	≤0.25 - >8
	Gentamicin	56.6	--	43.4	1	>16	≤0.12 - >16
	Levofloxacin	36.1	6.3	57.6	4	>8	0.015 - >8
	Meropenem	75.8	24.2	na	0.06	>4	≤0.004 - >4
	Meropenem-vaborbactam	89.9	--	10.1	≤0.06	16	≤0.06 - >16
	Piperacillin-tazobactam	0	18.1	82	128	>128	16 - >128
ESBL-positive[b] (87)	Cefepime-taniborbactam	98.9[a]	--	1.2	0.12	1	0.03 - 16
	Cefepime	6.9	9.2	83.9	>16	>16	0.5 - >16
	Ceftazidime	1.2	9.2	89.7	>16	>16	1 - >16
	Ceftazidime-avibactam	100	--	0	0.25	1	≤0.12 - 4
	Ceftolozane-tazobactam	78.2	--	21.8	1	8	≤0.25 - >8
	Gentamicin	56.3	--	43.7	2	>16	0.25 - >16
	Levofloxacin	18.4	14.9	66.7	8	>8	0.03 - >8
	Meropenem	100	0	na	0.03	0.12	0.015 - 2
	Meropenem-vaborbactam	100	--	0	≤0.06	0.12	≤0.06 - 0.25
	Piperacillin-tazobactam	62.1	11.5	26.4	8	128	≤4 - >128
KPC-positive[c] (36)	Cefepime-taniborbactam	100[a]	--	0	1	2	0.03 - 8
	Cefepime	0	0	100	>16	>16	8 - >16
	Ceftazidime	0	0	100	>16	>16	8 - >16
	Ceftazidime-avibactam	94.4	--	5.6	2	4	≤0.12 - >16
	Ceftolozane-tazobactam	0	--	100	>8	>8	8 - >8
	Gentamicin	36.1	--	63.9	>16	>16	≤0.12 - >16
	Levofloxacin	5.6	0.0	94.4	>8	>8	0.06 - >8
	Meropenem	0	100	na	>4	>4	4 - >4
	Meropenem-vaborbactam	97.2	--	2.8	0.12	2	≤0.06 - 16
	Piperacillin-tazobactam	0	0	100	>128	>128	>128 - >128
MBL-positive[d] (30)	Cefepime-taniborbactam	93.3[a]	--	6.7	0.5	8	0.03 - 16
	Cefepime	0.0	3.3	96.7	>16	>16	2 - >16
	Ceftazidime	0	0	100	>16	>16	16 - >16
	Ceftazidime-avibactam	0	--	100	>16	>16	16 - >16
	Ceftolozane-tazobactam	0	--	100	>8	>8	>8 - >8
	Gentamicin	20.0	--	80.0	>16	>16	0.5 - >16
	Levofloxacin	6.7	3.3	90.0	>8	>8	0.03 - >8
	Meropenem	3.3	96.7	na	>4	>4	1 - >4
	Meropenem-vaborbactam	6.7	--	93.3	>16	>16	1 - >16
	Piperacillin-tazobactam	0	0	100	>128	>128	32 - >128
OXA-48-positive[e] (34)	Cefepime-taniborbactam	100[a]	--	0	1	4	0.12 - 4
	Cefepime	14.7	5.9	79.4	>16	>16	0.5 - >16
	Ceftazidime	17.7	2.9	79.4	>16	>16	0.5 - >16
	Ceftazidime-avibactam	100	--	0	1	1	0.25 - 2
	Ceftolozane-tazobactam	5.9	--	94.1	>8	>8	1 - >8
	Gentamicin	38.2	--	61.8	>16	>16	≤0.12 - >16
	Levofloxacin	5.9	5.9	88.2	>8	>8	0.12 - >8
	Meropenem	11.8	88.2	na	>4	>4	1 - >4
	Meropenem-vaborbactam	50.0	--	50.0	8	>16	0.12 - >16
	Piperacillin-tazobactam	0	0	100	>128	>128	64 - >128

Cefepime-taniborbactam, cefepime with taniborbactam fixed at 4 mg/L; ceftazidime-avibactam, ceftazidime with avibactam fixed at 4 mg/L; ceftolozane-tazobactam, ceftolozane with tazobactam fixed at 4 mg/L; meropenem-vaborbactam, meropenem with vaborbactam fixed at 8 mg/L; piperacillin-tazobactam, piperacillin with tazobactam fixed at 4 mg/L; NS, nonsusceptible based on 2020 EUCAST breakpoints v10.0
[a]corresponds to Enterobacterales provisional susceptible breakpoint of ≤8 mg/L
[b]Note organisms could also possess AmpC-type enzymes, or OSBLs
[c]Note organisms could also possess ESBLs, AmpC-type enzymes, or OSBLs
[d]Note organisms could also possess serine carbapenemases, ESBLs, AmpC-type enzymes, or OSBLs

Figure 3. MIC distribution of cefepime-taniborbactam and select comparator agents against 4,611 Enterobacterales

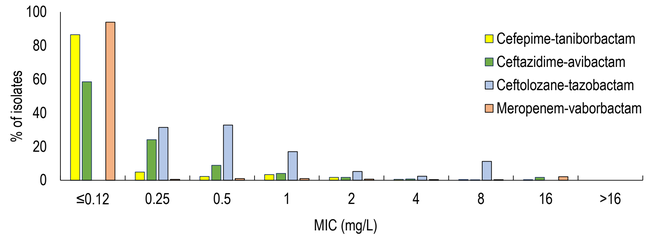
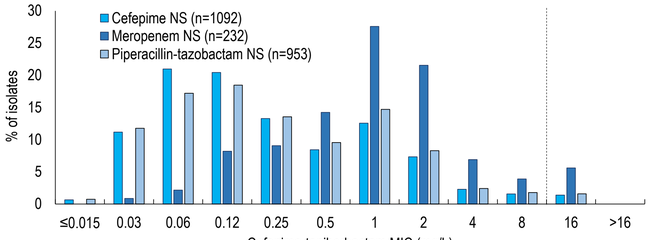
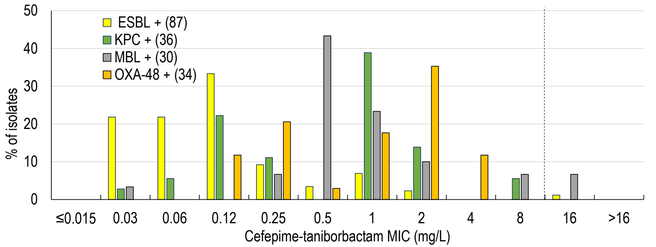


Figure 4. MIC distribution of cefepime-taniborbactam against resistant Enterobacterales



NS, non-susceptible based on 2020 EUCAST breakpoints; dashed line indicates the cefepime-taniborbactam provisional non-resistant breakpoint of ≤8 mg/L

Figure 5. MIC distribution of cefepime-taniborbactam against molecularly characterized Enterobacterales



Dashed line indicates the cefepime-taniborbactam provisional non-resistant breakpoint of ≤8 mg/L; MBLs consist of (n): NDM (27), VIM (3)

RESULTS SUMMARY

- Cefepime-taniborbactam showed potent *in vitro* activity against all Enterobacterales, with $MIC_{50/90}$ values of 0.06/0.25 mg/L and >99% inhibited at the provisional susceptible breakpoint of ≤8 mg/L (Table 1, Figure 3).
- Cefepime-taniborbactam activity was maintained against resistant subsets of Enterobacterales, with MIC_{90} values of 2 mg/L against cefepime- non-susceptible, 4 mg/L against meropenem-non-susceptible and 2 mg/L against piperacillin-tazobactam-non-susceptible isolates (Table 1, Figure 4).
- Cefepime-taniborbactam maintained activity against MBL- (NDM=27, VIM=3) , KPC-, OXA-48 group, and ESBL-positive isolates (MIC_{90} range, 1 to 8 mg/L; 93.3% to 100% of MIC values of ≤8 mg/L) (Table 1, Figure 5).
- Whole genome sequence analysis suggested likely explanations for most of the isolates exhibiting cefepime-taniborbactam MIC values ≥16 mg/L, including penicillin-binding protein 3 variation (*E. coli*), permeability defects (*K. pneumoniae*), and possible efflux pump up-regulation (*K. pneumoniae*).

CONCLUSIONS

Taniborbactam significantly restored the *in vitro* activity of cefepime against Enterobacterales, including isolates nonsusceptible to protected β-lactam/β-lactamase inhibitor combinations and those expressing serine and metallo-β-lactamases. These findings support the continued development of cefepime-taniborbactam as a potential new treatment option for challenging infections due to resistant Gram negative pathogens.

REFERENCES

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