1710

In Vitro Activity of Cefepime-Taniborbactam and Comparators Against a Global Collection of Carbapenem-Resistant Enterobacterales (CRE) and Carbapenem-Resistant *Pseudomonas aeruginosa* (CRPA) With and Without Carbapenemases

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

M. Wise[1], M. Hackel[1], D. Sahm[1] [1]IHMA, Inc., Schaumburg, IL, USA

INTRODUCTION

Carbapenem-resistant Enterobacterales (CRE) and *P. aeruginosa* (CRPA) present treatment difficulties owing to numerous possible resistance mechanisms, including the carriage of carbapenemases. Taniborbactam is a novel cyclic boronate-based broad-spectrum β-lactamase inhibitor with activity against serine-, and NDM & VIM metallo-β-lactamases (Ambler Classes A, B, C and D) [1]. The activity of the investigational combination cefepime-taniborbactam and comparator agents was evaluated against a recent global collection of carbapenemase and non-carbapenemase producing CRE and CRPA.

METHODS

17,827 Enterobacterales and 6,419 *P. aeruginosa* isolates collected from 59 countries in 2018-2021 were a part of this study. MICs of cefepime with taniborbactam fixed at 4 µg/mL and comparators were determined according to CLSI guidelines and interpreted using 2022 CLSI breakpoints [2,3]. Quality control (QC) testing was performed each day of testing as specified by the CLSI [2, 3]. CRE and CRPA were defined by resistance to meropenem. Organisms with cefepime-taniborbactam MIC values ≥16 µg/mL were characterized by whole genome sequencing, while those resistant to meropenem were screened for acquired β-lactamase carriage by multiplex PCR followed by Sanger sequencing [4].

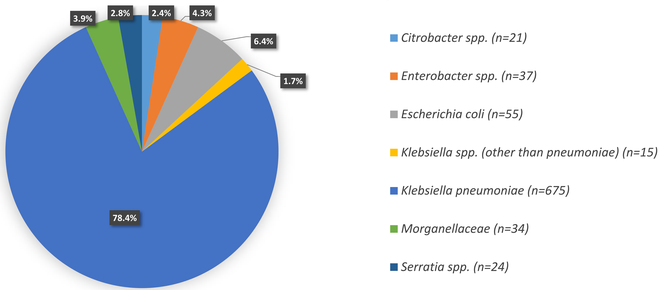
RESULTS

Table 1. *In vitro* susceptibility summary of cefepime-taniborbactam and comparators against CRE and CRPA genotypes

Organism group (n)	Drug[a]									
	FTB		CZA		C/T		MEV[b]		TZP	
	MIC_{50} (µg/ml)	% S[c]	MIC_{50} (µg/ml)	% S	MIC_{50} (µg/ml)	% S	MIC_{50} (µg/ml)	% S	MIC_{50} (µg/ml)	% S
CRE										
all (n=861)	16	90.2	>16	57.7	>8	1.2	>16	44.1	>128	0.3
carbapenemase positive (n=797)	16	90.2	>16	56.2	>8	1.0	>16	40.7	>128	0.0
NDM (n=291)[d]	32	75.3	>16	0.7	>8	0.3	>16	3.4	>128	0.0
VIM (n=33)	16	93.9	>16	0.0	>8	0.0	>16	30.3	>128	0.0
KPC (n=295)[e]	4	100	8	94.6	>8	0.0	4	91.9	>128	0.0
OXA-48-like (n=174)[f]	4	98.9	4	94.8	>8	3.4	>16	18.4	>128	0.0
carbapenemase negative (n=64)	16	90.6	>16	76.6	>8	3.1	8	87.5	>128	4.7
CRPA										
all (n=1397)	>32	85.5	>16	57.6	>16	52.6	>16	32.2	>128	20.7
carbapenemase positive (n=389)	>32	62.0	>16	13.6	>16	0.5	>16	4.9	>128	4.1
VIM (n=224)[d]	>32	82.6	>16	2.7	>16	0.9	>16	5.8	>128	2.2
carbapenemase negative (n=1008)	16	94.6	>16	74.5	>16	72.7	>16	42.8	>128	27.1

[a]FTB, cefepime with taniborbactam [taniborbactam fixed at 4 µg/mL]; CZA, ceftazidime-avibactam; C/T, ceftolozane-tazobactam; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam. S=susceptible.
[b]EUCAST breakpoints applied for meropenem-vaborbactam for *P. aeruginosa*.
[c]%S corresponds to cefepime-taniborbactam provisional susceptible breakpoint of ≤16 µg/ml for comparative purposes only.
[d]Excludes isolates co-carrying IMP metallo-β-lactamases
[e]Excludes isolates co-carrying MBLs
[f]Excludes isolates co-carrying MBLs or KPC

Figure 1. Taxonomic distribution of the 861 CRE identified in this study



Klebsiella spp. (other than *pneumoniae*) includes *K. aerogenes* (n=9) and *K. oxytoca* (n=6). *Morganellaceae* includes *Morganella morganii* (n=4), *Proteus mirabilis* (n=13), *Proteus vulgaris* (n=2), *Providencia rettgeri* (n=8), *Providencia* sp. (n=1), and *Providencia stuartii* (n=6).

Figure 2. MIC frequency distribution of cefepime-taniborbactam and comparator agents against 797 CRE carrying carbapenemases

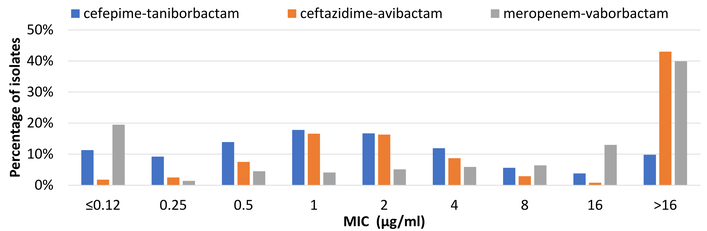


Figure 3. MIC frequency distribution of cefepime-taniborbactam and comparator agents against 64 carbapenemase-negative CRE

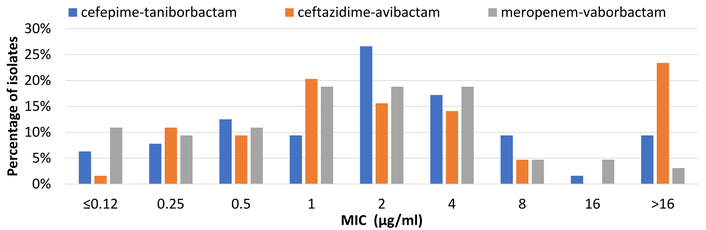


Figure 4. MIC frequency distribution of cefepime-taniborbactam and comparator agents against 224 CRPA carrying VIM-type carbapenemases

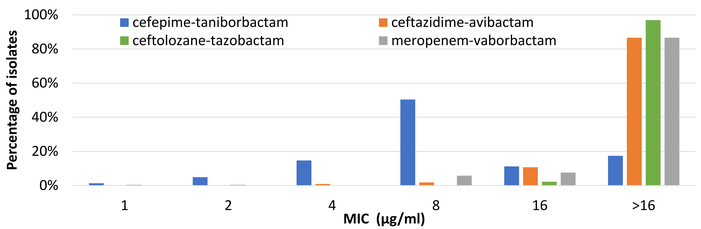
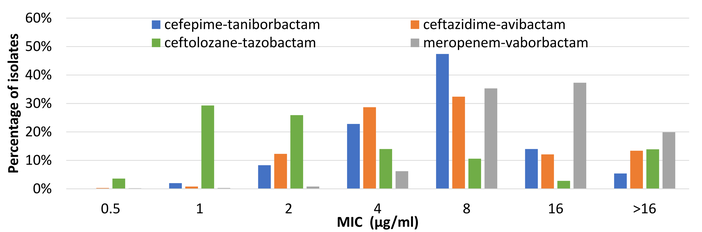


Figure 5. MIC frequency distribution of cefepime-taniborbactam and comparator agents against 1,008 carbapenemase-negative CRPA



RESULTS SUMMARY

CRE

- Among the 861 CRE identified (4.8% of total Enterobacterales examined; Fig. 1), 797 were found to carry a carbapenemase while the remaining 64 did not. Cefepime-taniborbactam inhibited the growth of 90.2% of the CRE at a concentration of ≤16 µg/mL (Table 1).
- For the carbapenemase-positive CRE, 90.2% of isolates were inhibited at ≤16 µg/mL cefepime-taniborbactam, a value considerably greater than the percentages susceptible to comparator agents at their respective CLSI breakpoints (Table 1, Fig. 2).
- At ≤16 µg/mL, cefepime-taniborbactam inhibited 75.3% and 93.9% of the NDM- and VIM-producing isolates, respectively. The most active comparator, meropenem-vaborbactam, inhibited 3.4% of NDM-producing and 30.3% of VIM-producing isolates (Table 1).
- For carbapenemase-negative CRE, 90.6% were inhibited at ≤16 µg/mL, again a higher percentage than comparators (Table 1, Fig. 3).

CRPA

- 21.8% (1,397/6,419) of *P. aeruginosa* examined were identified as CRPA, with 389 isolates carrying a carbapenemase and 1,008 isolates carbapenemase-negative. Cefepime-taniborbactam inhibited the growth of 85.5% of the CRPA at a concentration of ≤16 µg/mL (Table 1).
- Versus the CRPA carrying the most prevalent carbapenemase, VIM, 82.6% were inhibited at ≤16 µg/mL cefepime-taniborbactam. All comparators inhibited <10% of these isolates at their respective CLSI breakpoints (Table 1, Fig. 4).
- Against the carbapenemase-negative CRPA, cefepime-taniborbactam was the most active agent as 94.6% of this population was inhibited at ≤16 µg/mL (Table 1, Fig. 5).

CONCLUSIONS

Cefepime-taniborbactam displayed substantial *in vitro* activity against CRE and CRPA regardless of whether they harbored carbapenemases. More isolates of each group were inhibited by cefepime-taniborbactam at ≤16 µg/mL than were susceptible to all tested β-lactam/β-lactamase inhibitor combinations at their respective CLSI susceptible breakpoints. These data support the continued development of cefepime-taniborbactam as a potential new therapeutic antibacterial agent.

REFERENCES

1. Hamrick, et al. 2020. https://journals.asm.org/doi/epub/10.1128/AAC.01963-19.
2. Clinical and Laboratory Standards Institute. 2018. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards -- Eleventh Edition*. CLSI document M07-A11 Wayne, PA.
3. Clinical and Laboratory Standards Institute. 2022. *Performance Standards for Antimicrobial Susceptibility Testing*; Thirty-second Informational Supplement. CLSI Document M100S 2022. Wayne, PA.
4. Lob SH, Kazmierczak KM, Badal RE, et al. 2015. *Trends in susceptibility of Escherichia coli from intra-abdominal infections to ertapenem and comparators in the United States according to data from the SMART program, 2009 to 2013*. Antimicrob Agents Chemother 59:3606-3610.

DISCLOSURES

This project began 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 The Wellcome Trust under Award No. 360G-Wellcome-101999/Z/13/Z, and continues with federal funds from the Department of Health and Human Services; Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, under Contract No. HHSO100201900007C.