In Vitro Activity of Cefepime-Taniborbactam Against Molecularly Characterized Enterobacterales and *P. aeruginosa* Collected Worldwide from 2018-2020

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

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

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

DISCLOSURES

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INTRODUCTION

Taniborbactam is a novel cyclic boronate-based broad-spectrum β-lactamase inhibitor that displays activity against serine-β-lactamases and most metallo-β-lactamases (Ambler Classes A, B, C and D) [1]. Taniborbactam restores the activity of cefepime against cephalosporin- and carbapenem-resistant Enterobacterales and *Pseudomonas aeruginosa*. The activity of the investigational combination cefepime-taniborbactam and comparator agents was evaluated against a global collection of clinical isolates of Enterobacterales and *P. aeruginosa* with defined β-lactamase carriage.

MATERIALS & METHODS

- 13,731 Enterobacterales and 4,619 *P. aeruginosa* isolates collected from 56 countries in 2018-2020 were a part of this study.
- MICs of cefepime with taniborbactam fixed at 4 mg/L and comparators were determined by the ISO 20776-1:2019 reference method [2] and interpreted using 2021 EUCAST breakpoints [3]. The provisional breakpoint of 8 mg/L was used for cefepime-taniborbactam.
- Organisms with cefepime-taniborbactam MIC ≥16 mg/L were characterized by whole genome sequencing, while those resistant to meropenem were screened for acquired β-lactamase genes by PCR followed by Sanger sequencing [4]. Additionally, 614 randomly selected Enterobacterales with cefepime and/or ceftazidime MIC values of ≥2 mg/L and 92 randomly selected *P. aeruginosa* with ceftazidime and/or cefepime MIC values of ≥16 mg/L were examined by PCR/Sanger.

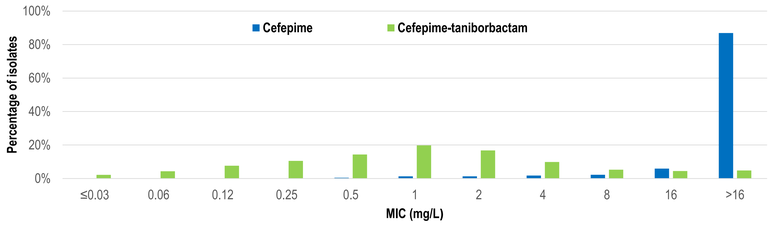
RESULTS

Table 1. *In vitro* activity of cefepime-taniborbactam and comparator agents against molecularly characterized sets of isolates

Organism / Genotype	N(%)[a]		MIC$_{90}$ (mg/L)/Percent susceptible					
		FTB[b]	FEP	CZA	CT	MEM	MEV	TZP
Enterobacterales								
Carbapenemase[c,h]	627 (49.6%)	8/90.7	>16/1.9	>16/60.1	>8/1.0	>64/5.4	>16/51.8	>128/0.0
MBL[d]	229 (18.1%)	>16/76.0	>16/0.0	>16/0.9	>8/0.0	>64/0.9	>16/15.3	>128/0.0
KPC[e]	230 (18.2%)	4/100	>16/0.9	8/93.9	>8/0.4	>64/3.5	2/98.3	>128/0.0
OXA-48 group[e]	168 (13.3%)	4/98.2	>16/6.0	2/94.6	>8/3.0	64/14.3	>16/38.1	>128/0.0
ESBL[f]	534 (42.2%)	1/98.7	>16/3.6	1/98.5	>8/77.3	0.12/95.9	0.12/99.8	>128/60.3
AmpC[g]	34 (2.7%)	2/100	16/64.7	2/94.1	>8/58.8	0.5/94.1	0.25/100	>128/64.7
P. aeruginosa								
Carbapenemase[c,i]	216 (19.5%)	>32/69.9	>32/12.0	>16/16.7	>16/0.9	>8/0.0	>16/6.0	>128/3.2
MBL[d]	176 (15.9%)	>32/68.2	>32/4.0	>16/3.4	>16/1.1	>8/0.0	>16/6.3	>128/2.3

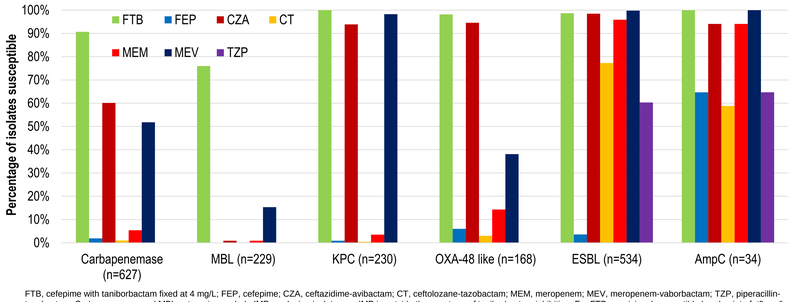
FTB, cefepime with taniborbactam fixed at 4 mg/L; FEP, cefepime; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEM, meropenem; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam. For *P. aeruginosa*, "Susceptible, increased exposure" is given for FEP and TZP.
[a]Percentage is based on total molecularly characterized (Enterobacterales, n=1265; *P. aeruginosa*, n=1110)
[b]"Percent susceptible" corresponds to percentage of isolates inhibited by ≤8 mg/L FTB.
[c]Excluding IMP-producing isolates, as IMP is outside the spectrum of taniborbactam inhibition.
[d]Excluding IMP-producing isolates. Organisms could also possess serine-β-lactamases
[e]Organisms could also possess OSBLs (original-spectrum β-lactamases, e.g., TEM-1, SHV-1, etc.), ESBLs and/or AmpC-type enzymes, but no carbapenemases other than those noted
[f]Organisms could also possess OSBLs and AmpC-type enzymes
[g]Organisms could also possess OSBLs
[h]207 isolates carried NDM; 212 isolates carried OXA-48 group; 240 isolates carried KPC; 22 isolated carried VIM. Note, several isolates carried multiple carbapenemases.
[i]17 isolates carried NDM; 13 isolates carried KPC; 159 isolates carried VIM; 1 isolate carried DIM; 34 isolates carried GES with reported carbapenemase activity. Note, several isolates carried multiple carbapenemases.

Figure 1. Cefepime and cefepime-taniborbactam MIC value frequency distribution against carbapenemase-carrying Enterobacterales (n=627)



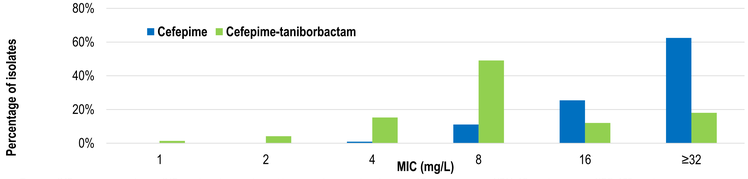
Excludes IMP-producing isolates, as IMP is outside the spectrum of taniborbactam inhibition. Includes, 207 isolates carrying NDM; 212 isolates carrying OXA-48 group; 240 isolates carrying KPC and 22 isolates carrying VIM. Note, several isolates carried multiple carbapenemases.

Figure 2. Percentage of isolates from various Enterobacterales genotypes susceptible to cefepime-taniborbactam and comparator agents



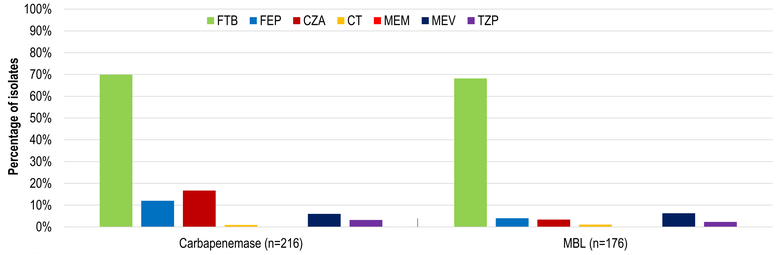
FTB, cefepime with taniborbactam fixed at 4 mg/L; FEP, cefepime; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEM, meropenem; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam. Carbapenemase and MBL categories exclude IMP-producing isolates, as IMP is outside the spectrum of taniborbactam inhibition. For FTB, provisional susceptible breakpoint of ≤8 mg/L employed.

Figure 3. Cefepime and cefepime-taniborbactam MIC value frequency distribution against carbapenemase-carrying *P. aeruginosa* (n=216)



Excludes IMP-producing isolates, as IMP is outside the spectrum of taniborbactam inhibition. Includes, 17 isolates carrying NDM; 13 isolates carrying KPC; 159 isolates carrying VIM; 1 isolate carrying DIM (Dutch imipenemase) and 34 isolates carrying GES with reported carbapenemase activity. Note, several isolates carried multiple carbapenemases.

Figure 4. Percentage of carbapenemase- and MBL-positive *P. aeruginosa* genotypes susceptible to cefepime-taniborbactam and comparator agents



FTB, cefepime with taniborbactam fixed at 4 mg/L; FEP, cefepime; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEM, meropenem; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam. Excludes IMP-producing isolates, as IMP is outside the spectrum of taniborbactam inhibition. For FTB, provisional susceptible breakpoint of ≤8 mg/L employed.

RESULTS SUMMARY

- Against Enterobacterales carrying carbapenemases (n=627), cefepime-taniborbactam was the most active agent tested, with 90.7% of isolates inhibited at ≤8 mg/L (95.2% inhibited at ≤16 mg/L) and an MIC$_{90}$ value of 8 mg/L (Table 1 and Figure 1).
- The ability of taniborbactam to inhibit MBLs was clearly evident when this set was limited to non-IMP MBL-producers (n=229), as 76.0% of the population was inhibited at the provisional breakpoint of 8 mg/L (87.8% inhibited at ≤16 mg/L), a far greater proportion that the nearest comparator, meropenem-vaborbactam (15.3% susceptible).
- Cefepime-taniborbactam was also the most active agent examined versus Enterobacterales harboring the serine-carbapenemases KPC (n=230) and OXA-48-like (n=168) with 100% (MIC$_{90}$, 4 mg/L) and 98.2 % (MIC$_{90}$, 4 mg/L) of the organisms inhibited at ≤8 mg/L, respectively (Table 1 and Figure 2). For OXA-48 group, the % inhibited at ≤16 mg/L was 98.8%.
- Versus ESBL- (n=534) and AmpC- (n=34) possessing Enterobacterales, cefepime-taniborbactam exhibited potent activity, with 98.7% (MIC$_{90}$, 1 µg/mL), and 100% (MIC$_{90}$, 0.25 µg/mL) of each population inhibited at ≤8 µg/mL, respectively (Table 1 and Figure 2). For the ESBLs, the % inhibited at ≤16 mg/L was 99.3%
- The addition on taniborbactam to cefepime shifted the mode of the MIC distribution against non-IMP carbapenemase-carrying *P. aeruginosa* to 8 mg/L from a value of ≥32 mg/L for cefepime alone (Figure 3).
- Against non-IMP carbapenemase-carrying (n=216) and MBL-carrying *P. aeruginosa* (n=176), cefepime-taniborbactam was the most active antimicrobial agent tested, with 69.9% and 68.2% of the isolates inhibited at ≤8 µg/mL, respectively (Table 1 and Figure 4). At an inhibitory threshold of ≤16 mg/L, these percentages increased to 81.9% and 79.0%, respectively,

CONCLUSIONS

The addition of taniborbactam to cefepime greatly enhances its *in vitro* activity against both Enterobacterales and *P. aeruginosa* carrying serine- and metallo-β-lactamases. These findings support the continued development of cefepime-taniborbactam as a potential new therapeutic agent for use against β-lactamase-harboring Gram-negative pathogens resistant to currently available antimicrobial agents.

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