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In Vivo Pharmacokinetic/Pharmacodynamic (PK/PD) Evaluation of Cefepime-Taniborbactam Combination against Cefepime-Resistant Enterobacterales and *Pseudomonas aeruginosa* in a Murine Pneumonia Model

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ABSTRACT

Background: Cefepime-taniborbactam is a cephalosporin-cyclic boronate β-lactamase inhibitor combination in clinical development for nosocomial pneumonia due to multidrug-resistant Gram-negative bacteria. A murine pneumonia model was used to characterize cefepime-taniborbactam *in vivo* pharmacodynamics against cefepime-resistant Enterobacterales and *P. aeruginosa* strains.

Methods: Clinical cefepime-resistant Enterobacterales (n=13) and *P. aeruginosa* (n=5) strains expressing serine carbapenemases and/or other cefepime-hydrolyzing β-lactamases with cefepime-taniborbactam combination MICs 0.12–16 mg/L (taniborbactam fixed at 4 mg/L) were used. Pneumonia was induced via intranasal inoculation of neutropenic ICR mice with bacterial suspensions (10^7 cfu/mL). Cefepime and taniborbactam human-simulated regimens (HSRs) equivalent to clinical doses 2/0.5g q8h based on Phase I plasma exposures were established in the pneumonia model. The *in vivo* activity of cefepime HSR given alone or concomitantly with escalating taniborbactam exposures against 8 Enterobacterales and 4 *P. aeruginosa* strains was assessed. Efficacy was measured as change in $\log_{10}$ cfu/lungs at 24 h compared with 0 h controls. Taniborbactam pharmacokinetics were evaluated to determine systemic exposures of regimens used; magnitudes of the taniborbactam PK/PD index of activity ($fAUC_{0\text{-}24}$/MIC) required for efficacy were estimated using the Hill equation. In addition, the *in vivo* activity of cefepime-taniborbactam HSR was assessed against all 18 strains.

Results: Cefepime HSR alone produced no activity in all strains; average growth was 2.11 ± 0.80 $\log_{10}$ cfu/lungs. Among Enterobacterales, median (interquartile range [IQR]) taniborbactam $fAUC_{0\text{-}24}$/MIC values associated with stasis and 1 log kill were 0.96 (0.28–1.32) and 4.03 (0.94–7.87), respectively, while for *P. aeruginosa*, requirements were 1.35 (0.32–1.96) and 3.02 (0.85–3.74), for stasis and 1 log kill, respectively. Cefepime-taniborbactam HSR produced >2 log kill in 14/18 and >1 log kill in 18/18 strains.

Conclusions: Given the estimated taniborbactam $fAUC_{0\text{-}24}$ associated with a 0.5g q8h dose in healthy volunteers is ~205 mg*h/L, our data predict that this dose of taniborbactam, in combination with cefepime 2g q8h, will provide sufficient exposure to achieve bactericidal activity against cefepime-resistant Enterobacterales and *P. aeruginosa* isolates with cefepime-taniborbactam MICs up to and including 16 mg/L. These results were corroborated by marked bacterial kill observed in the pneumonia model upon administration of cefepime-taniborbactam HSR. Assessments of the probability of clinical attainment of the identified targets will be undertaken to support the selected cefepime-taniborbactam dose for treatment of pneumonia.

INTRODUCTION

- Taniborbactam is a cyclic boronate β-lactamase inhibitor with activity against Classes A, B, C and D β-lactamases.[1]
- Cefepime-taniborbactam met the primary noninferiority efficacy endpoint and demonstrated statistical superiority to meropenem in a Phase III study of adult patients with complicated urinary tract infections including those due to multi-drug resistant Enterobacterales and *Pseudomonas aeruginosa*.[2]
- We have previously demonstrated the potent *in vivo* activity of cefepime-taniborbactam combination against a range of Enterobacterales and *P. aeruginosa* clinical isolates expressing various serine-β-lactamases in the murine thigh infection model and in the murine complicated urinary tract infection model.[3,4]

OBJECTIVES

- The objective of the current study was to investigate the pharmacodynamics of cefepime-taniborbactam against cefepime-resistant Enterobacterales and *P. aeruginosa* clinical isolates expressing various serine β-lactamases (such as CTX-M, KPC, and OXA) as well as inducible AmpC-expressing *P. aeruginosa* in the murine pneumonia model to support cefepime-taniborbactam clinical dose selection for nosocomial pneumonia treatment.

MATERIALS & METHODS

Antimicrobial Test Agents

- Taniborbactam (batch numbers CA19-1355 and CA20-0265, Venatorx Pharmaceuticals, Inc.) was used for *in vivo* and *in vitro* testing.
- Cefepime vials (1 g, WG Critical Care, LLC) and cefepime HCl (batch number LRAB8503, Sigma-Aldrich) were used for *in vivo* and *in vitro* testing, respectively.

Bacteria and In vitro Susceptibility

- Eighteen clinical Enterobacterales and *P. aeruginosa* strains harboring genes for serine carbapenemases, extended-spectrum β-lactamases and/or inducible AmpC cephalosporinases.
- Cefepime and cefepime-taniborbactam MICs (at taniborbactam fixed concentration 4 mg/L) were determined in triplicate using broth microdilution as outlined by the CLSI (**Table 1**).

Neutropenic Murine Pneumonia Model

- Female ICR mice were rendered neutropenic by cyclophosphamide; uranyl nitrate was given to induce renal impairment.
- Mice were inoculated intranasally with 50 µLof 10^7 cfu/ml bacterial suspensions in 3% mucin.

Pharmacokinetic Studies

- Plasma and bronchopulmonary pharmacokinetics of taniborbactam in combination with cefepime were assessed in the infection model.
- Cefepime human-simulated regimen (HSR, 2 g q8h as a 4 h infusion) alone and in combination with taniborbactam HSR (0.5 g q8h as a 4 h infusion) were established in the infection model based on plasma exposures determined in Phase I studies.[5]
- Pharmacokinetic studies of the established cefepime HSR in combination with escalating proportions of the doses of taniborbactam HSR were examined to determine the exposures of the regimens utilized in “taniborbactam dose-ranging studies”.
- Plasma and bronchoalveolar (BAL) fluid samples were assayed for cefepime, taniborbactam and urea using LC-MS/MS.
- Cefepime and taniborbactam exposures in plasma and epithelial lining fluid (ELF) were estimated and the ELF penetration ratios were calculated as the ratio of the ELF area under the curve over 24 h ($AUC_{0\text{-}24}$) to unbound (free) plasma $AUC_{0\text{-}24}$ (**Tables 2-3**).
- Protein binding percentages applied for cefepime were 20% in humans and 0% in mice, while for taniborbactam they were 0% in humans and 19.4% in mice.[3]

Taniborbactam Dose-Ranging Studies

- Efficacy of cefepime HSR in combination with escalating taniborbactam exposures was assessed against 12 clinical cefepime-resistant Enterobacterales and *P. aeruginosa* isolates.
- Efficacy was measured as the change in $\log_{10}$ cfu/lungs at 24 h compared with 0 h controls (**Figure 1**).
- Plasma taniborbactam $fAUC_{0\text{-}24}$/MIC thresholds required to achieve efficacy endpoints were estimated using the Hill-equation (**Figure 2**).

In Vivo Activities of Cefepime/Taniborbactam HSRs

- *In vivo* activities of cefepime HSR as monotherapy and in combination with taniborbactam HSR were assessed against 18 clinical cefepime-resistant Enterobacterales and *P. aeruginosa* isolates.
- Efficacy was measured as the change in $\log_{10}$ cfu/lungs at 24 h compared with 0 h controls (**Figure 3**).

RESULTS

Table 1. MICs of examined Enterobacterales and *P. aeruginosa* isolates. EC: *Escherichia coli,* ECL: *Enterobacter cloacae,* KP: *Klebsiella pneumoniae,* PSA: *Pseudomonas aeruginosa*

Isolate ID	MIC (mg/L)		β-lactamase encoded
	Cefepime	Cefepime +Taniborbactam (4 mg/L)	
EC 720	>512	16	CTX-M-15, OXA-1
EC 747	512	2	KPC
EC 748	512	2	ESC-35, OXA-1, KPC-3
EC 753	>512	2	CTX-M-15
EC 755	>512	16	CTX-M-15, EC-TYPE, OXA-1, TEM-1
ECL 108	>512	2	KPC-2, ACT-7, CTX-M-15, OXA-1, TEM-1B
ECL 124	>512	8	CTX-M-15
KP 579	>512	16	OXA-48, CTX-M-15
KP 647	>512	0.12	KPC-3
KP 679	>512	4	OXA-232, OXA-9, TEM-1A, CTX-M-15, OXA-1
KP 681	>512	1	CTX-M-15, OXA-1, OXA-232, SHV-1
KP 731	>512	1	KPC-3
KP 744	>512	4	OXA-48, CTX-M-15
PSA 1681	>512	8	OXA-486, PDC-8, OXA-10, CTX-M-2
PSA 1711	128	16	PDC-103, KPC-2
PSA 1714	32	4	PDC-1
PSA 1715	16	4	PDC-5
PSA 1844	>512	2	KPC-2, PDC-42

Table 2. Cefepime exposures achieved in humans receiving 2 g every 8 h as a 4 h infusion vs. infected mice receiving cefepime HSR

Matrix	Regimen	Species	%fT>MIC for a MIC (mg/L) of:							$fAUC_{0\text{-}24}$ (mg·h/L)	fC_{max} (mg/L)	ELF:Plasma Penetration
			2	4	8	16	32	64	128			
Plasma		Human	100%	100%	99%	73%	45%	0%	0%	700.9	52.0	
	Monotherapy	Mouse	100%	100%	93%	77%	35%	0%	0%	656.8	54.0	
	In combination with taniborbactam 1.56% HSR	Mouse	100%	100%	100%	97%	52%	0%	0%	821.0	60.6	
	In combination with taniborbactam 12.5% HSR	Mouse	100%	100%	98%	80%	37%	0%	0%	668.2	48.9	
	In combination with taniborbactam 100% HSR	Mouse	100%	99%	95%	88%	59%	3%	0%	858.4	76.9	
ELF	Monotherapy	Mouse	100%	100%	90%	50%	0%	0%	0%	428.4	31.0	0.65
	In combination with taniborbactam 1.56% HSR	Mouse	100%	100%	98%	70%	14%	0%	0%	516.7	35.8	0.63
	In combination with taniborbactam 12.5% HSR	Mouse	100%	100%	93%	51%	2%	0%	0%	406.1	34.2	0.61
	In combination with taniborbactam 100% HSR	Mouse	100%	100%	95%	74%	17%	0%	0%	545.2	39.0	0.64

Table 3. Taniborbactam exposures achieved in humans receiving 0.5 g every 8 h as a 4 h infusion vs. infected mice receiving taniborbactam

Matrix	Regimen	Species	$fAUC_{0\text{-}24}$ (mg·h/L)	ELF:Plasma Penetration
Plasma		Human	205.2	
	Taniborbactam 1.56% HSR	Mouse	3.2	
	Taniborbactam 12.5% HSR	Mouse	22.1	
	Taniborbactam 100% HSR	Mouse	229.9	
ELF	Taniborbactam 1.56% HSR	Mouse	3.5	1.11
	Taniborbactam 12.5% HSR	Mouse	21.0	0.95
	Taniborbactam 100% HSR	Mouse	195.2	0.85

Figure 1. Taniborbactam dose-ranging efficacy in combination with cefepime HSR against Enterobacterales (n = 8) and *P. aeruginosa* isolates (n = 4). Each open circle represents the mean $\log_{10}$ cfu/lungs for one bacterial strain per regimen

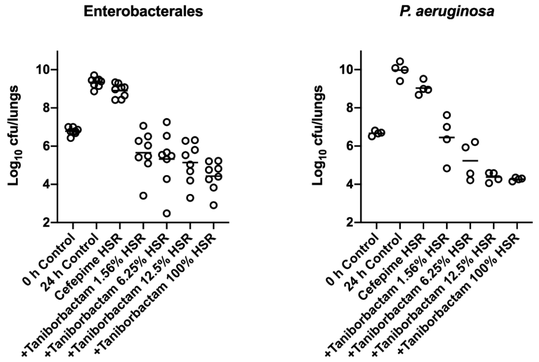
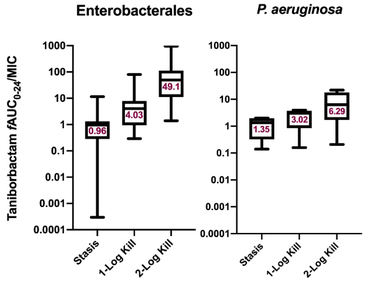
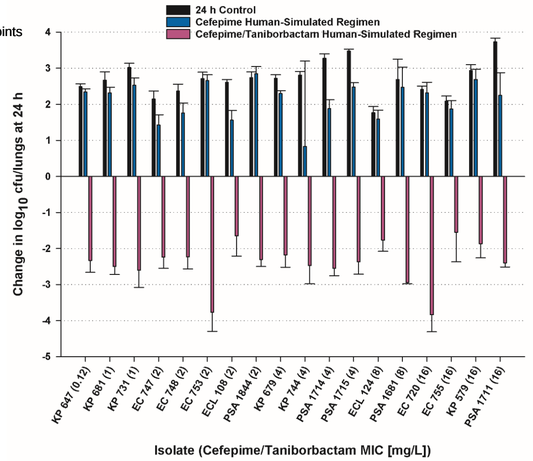


Figure 2. Taniborbactam $fAUC_{0\text{-}24}$/MIC required to achieve efficacy endpoints against Enterobacterales (n = 8) and *P. aeruginosa* (n = 4) when co-administered with the cefepime HSR



Median values are displayed on the plots
Hinges: 25th and 75th percentiles
Whiskers: 10th and 90th percentiles

Figure 3. Comparative efficacy of cefepime HSR alone and in combination with taniborbactam HSR against 13 Enterobacterales and 5 *P. aeruginosa* clinical isolates expressing serine β-lactamases



CONCLUSIONS

- The co-administration of taniborbactam with cefepime restored the *in vivo* efficacy of cefepime against clinical cefepime-resistant Enterobacterales and *P. aeruginosa* isolates expressing a broad range of serine β-lactamases in the neutropenic pneumonia model with cefepime-taniborbactam MICs up to and including 16 mg/L.
- The taniborbactam $fAUC_{0\text{-}24}$/MIC targets required for various efficacy endpoints were identified for each species. Assessments of the probability of the clinical attainment of these PK/PD targets should be undertaken to support the selected cefepime-taniborbactam dose (2 g-0.5 g every 8 h as a 4 h infusion) for treatment of pneumonia.
- The administration of human-simulated exposures of cefepime-taniborbactam combination (2 g-0.5 g every 8 h as a 4 h infusion) resulted in >2 log kill in 14/18 and >1 log kill in 18/18 strains. These data further support the consideration of cefepime-taniborbactam combination for the treatment of nosocomial pneumonia due to these organisms.

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