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Assessment of Cefepime-Taniborbactam Human Exposures to Suppress the Emergence of Resistance among Serine- and Metallo-β-Lactamase-Producing Gram-Negative Bacteria in a Hollow Fiber Infection Model

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Abstract

Background Cefepime-taniborbactam (FTB) efficacy and safety are currently being evaluated in a Phase 3 trial (NCT03840148). Taniborbactam (TAN), a boronic acid-based β-lactamase inhibitor, restores susceptibility to cefepime (FEP) when resistance is driven by serine- or metallo-β-lactamases (ie, NDM, VIM). This in vitro study assessed whether clinical FTB exposures suppress treatment-emergent resistance in pathogenic Enterobacterales and *Pseudomonas aeruginosa*.

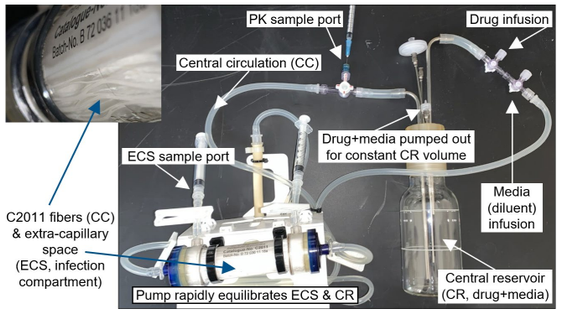
Methods Bioreactors (C2011, FiberCell) were inoculated with clinical strains (N=6) using highly concentrated log phase cultures (>10^8 CFU). Syringe pumps supplied humanized exposures of FEP (2 g), FTB (2 g/0.5 g), ceftazidime-avibactam (CZA, 2 g/0.5 g), each as 2 h infusions q8h, or meropenem-vaborbactam (MEV, 2 g/2 g q8h, 3 h infusion) for 7 days. Exposures were confirmed by UPLC-MS/MS for all agents. Subpopulations with elevated FTB MICs (4x) were monitored with drug-supplemented agar. CZA or MEV served as positive or negative controls for selected strains. Samples, serially removed from bioreactors, were washed prior to quantitative culture to prevent drug carryover.

Results All strains grew rapidly in the presence of FEP, consistent with resistance by broth microdilution (BMD). With the addition of TAN, there was extensive killing of the total bacterial populations by FTB, and subpopulations with elevated FTB MICs were never recovered. Like FTB against *Klebsiella pneumoniae* (KP) BAA-1705, CZA initially decreased the inoculum to the lower limit of detection, but unlike FTB, allowed regrowth to 3.7 $\log_{10}$ CFU/mL by day 7. The first dose of FTB was bactericidal against VIM+ and NDM+ KP strains while regrowth occurred prior to 8 h of MEV and CZA challenge, respectively. Notably, early failure of MEV is discordant with susceptibility by BMD (MIC= 4 µg/mL). By day 7, FTB sterilized an OXA-48+ KP strain that when challenged by MEV, grew to 9.8 $\log_{10}$ CFU/mL at 24 h.

Conclusions In a 7-day HFIM with humanized exposures and high initial inoculums, FTB provided sustained bactericidal activity against multidrug-resistant Enterobacterales and *P. aeruginosa* strains harboring a diversity of β-lactamases and suppressed growth of resistant subpopulations. These data are crucial to inform understanding of the potential role for FTB in gram-negative bacterial infections and future clinical studies.

Introduction

- Taniborbactam (TAN, formerly VNRX-5133) is a novel cyclic boronate β-lactamase inhibitor (BLI) that lacks intrinsic antibacterial activity.[1]
- TAN potentiates cefepime's in vitro activity against Enterobacterales and *P. aeruginosa* strains harboring serine (SBL)- and metallo (MBL)-β-lactamases (e.g., CTX-M, SHV, NDM, VIM, AmpC, OXA-48),[1] which translates to in vivo bactericidal activity observed with human exposures of cefepime-taniborbactam (FTB).[2]
- Hollow fiber infection models (HFIM, schematic below) are dynamic in vitro systems preferred for assessments of antimicrobial resistance prevention.[3]



Methods

Bacterial strains, antimicrobial agents, & susceptibility testing

- Strains (N=6) were acquired from the CDC & FDA Antibiotic Resistance (AR) Isolate Bank, American Type Culture Collection (ATCC), or the International Health Management Associates (Schaumburg, IL).
- Commercially available vials of cefepime (FEP), ceftazidime (CAZ), and meropenem (MEM) were used in the HFIM, while analytical powders (Sigma-Aldrich) were used in susceptibility tests.
- Taniborbactam (Carbogen Amcis AG, Aarau, Switzerland, batches CA18-0790 and CA19-1355), avibactam (Venatorx, lot no. RT00097-130), and vaborbactam (MedChemExpress, Monmouth Junction, NJ, batch 29328) were used throughout the study.
- Minimum inhibitory concentration (MIC) modal values were determined by broth microdilution according to CLSI (M07) methods; recommended quality control (QC) strains were included for each agent.[4]

Hollow fiber infection model

- The HFIM employed was constructed as described previously by others.[5]
- Log phase bacterial suspensions (>10^7 CFU/mL, >10^8 total CFU) were used to inoculate the extracapillary space of hollow fiber cartridges (C2011, FiberCell Systems, Frederick MD).
- Programmable syringe pumps infused all drugs (q8h for 7 days) to recapitulate human plasma exposures.
- FEP monotherapy (2 g q8h, 2 h infusion) arms served as growth controls in all experiments.
- Positive controls were run with ceftazidime-avibactam (CZA, 2 g/0.5 g q8h, 2 h infusion) and meropenem-vaborbactam (MEV, 2 g/2 g q8h, 3 h infusion) against KP ATCC BAA-1705 and KP AR 0135, respectively.

Hollow fiber infection model (continued)

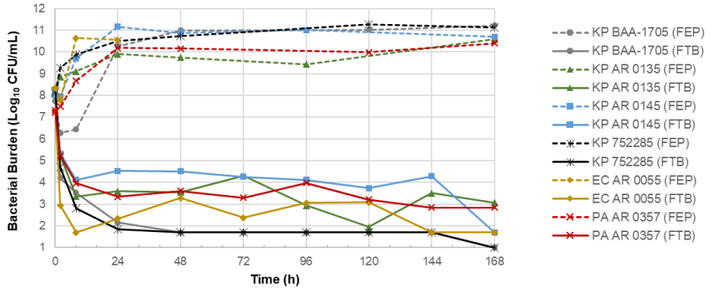
- Negative controls were CZA and MEV against KP AR 0145 and KP 752285, respectively. Except for growth controls, sampling ceased when regrowth to 10 $\log_{10}$ CFU/mL was observed.
- Efficacy outcomes of FTB, CZA, and MEV human exposures were monitored by quantitative culture (Figures 1 and 2) with a lower limit of detection of 1.7 $\log_{10}$ CFU/mL except at 168 h (1 $\log_{10}$ CFU/mL).
- Resistant subpopulations were monitored using drug-supplemented (4x MIC) agar plates prepared daily.

Pharmacokinetic (PK) analysis

- Target free (unbound) drug PK profiles for FTB (2 g/0.5 g q8h, 2 h infusion) were based on population parameters (unpublished data on file) derived from healthy volunteers.[6] Free CZA and MEV plasma profiles were informed by Prescribing Information[7] and published data,[8] respectively (Figures 3–5).
- Prior to efficacy studies, the FTB PK profile was confirmed in the central and extracapillary compartments of a sterile C2011 (Figure 3). In efficacy studies, PK samples were collected from the central circulation to confirm BLI concentrations and monitor β-lactamase-induced degradation of the β-lactams; acceptable observed BLI exposure was defined as >80% of the $AUC_{0\text{-}tau}$ (last dose) target.
- Drug concentrations were determined by LC-MS/MS with Acquity I-Class UPLC (Waters). Standard curves were prepared in the HFIM matrix (FEP, TAN, 0.05–10 µg/mL; CAZ, MEM, VAB, 0.05–50 µg/mL; AVI, 0.1–50 µg/mL). QC acceptance criteria were set to ±20% and dilution QCs were performed as needed.
- Samples were stored at -80°C prior to assay; MEV samples were stabilized in an equal volume of 1 M MOPS buffer (pH 7) prior to freezing.

Results

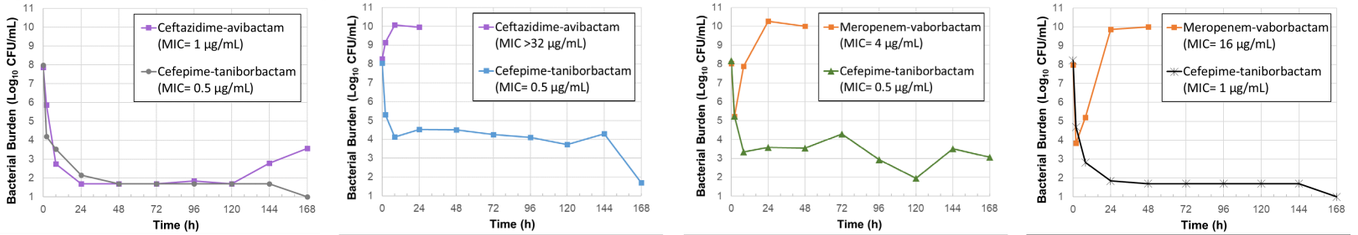
Figure 1. Efficacy of cefepime (FEP) alone and FEP-taniborbactam (FTB) human exposures in the HFIM.



Strain	Known Encoded β-Lactamases	Broth microdilution MIC (µg/mL) FEP	FTB	CZA	MEV
K. pneumoniae ATCC BAA-1705	KPC-2, TEM, SHV	32	0.5	1	0.06
K. pneumoniae AR 0135	VIM-1, OXA-9, SHV-12, TEM-1A	>32	0.5	>32	4
K. pneumoniae AR 0145	NDM-1, CTX-M-15, OXA-1, OXA-9, SHV-11, TEM-1A	>32	0.5	>32	>32
K. pneumoniae 752285	OXA-48, CTX-M-15	>32	1	0.5	16
Escherichia coli AR 0055	NDM-1, CMY-6, OXA-1	>32	4	>32	>32
P. aeruginosa AR 0357	VEB-1, OXA-10	>32	8	8	4

FEP, cefepime; FTB, cefepime-taniborbactam; CZA, ceftazidime-avibactam; MEV, meropenem-vaborbactam

Figure 2. Efficacy of FTB and various positive and negative control arms in the HFIM.



***K. pneumoniae* ATCC BAA-1705** (KPC-2)

Despite early bactericidal activity of CZA, the strain began to regrow at day 6 while the FTB culture was sterile at day 7; resistant CZA colonies (4x MIC) were not identified among the total population on days 6–7 and thus cannot explain the observed regrowth.

***K. pneumoniae* AR 0145** (NDM-1)

Concordant with CZA resistance attributable to NDM-1 hydrolysis, rapid regrowth occurred, and ceftazidime troughs were undetectable. TAN protected FEP from NDM-1 and CTX-M-15.

***K. pneumoniae* AR 0135** (VIM-1)

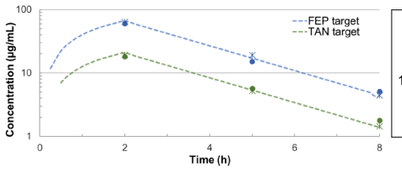
Regrowth in the MEV arm is discordant with a susceptible MIC result,[4] implicating VIM-1 hydrolysis of meropenem (troughs undetectable); a MEV resistant subpopulation was detected by 8 h. TAN adequately protected FEP exposures.

***K. pneumoniae* 752285** (OXA-48)

MEV allowed regrowth consistent with meropenem degradation by uninhibited OXA-48 activity (troughs undetectable). The FTB culture was sterile at day 7 with FEP protected from enzymatic hydrolysis by TAN.

Target pharmacokinetic profiles

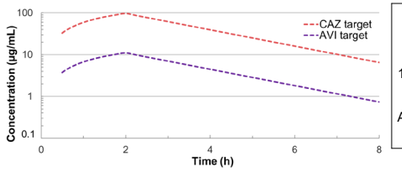
Figure 3. Cefepime-taniborbactam target plasma exposure (2 g/0.5 g q8h, 2 h infusion). *Dots and asterisks represent observed drug concentrations in the central circulation and extracapillary space, respectively.*



FEP %Time Above:
4 µg/mL = 100%
8 µg/mL = 81%
16 µg/mL = 59%

TAN $AUC_{0\text{-}24}$
206 µg*h/mL

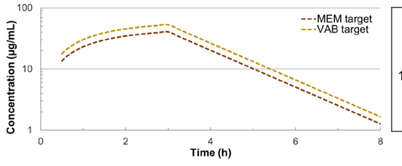
Figure 4. Ceftazidime-avibactam (2 g/0.5 g q8h, 2 h infusion) target plasma exposure.



CAZ %Time Above:
4 µg/mL = 100%
8 µg/mL = 94%
16 µg/mL = 72%

AVI
$AUC_{0\text{-}24}$ = 110 µg*h/mL
%T> 1 µg/mL =91%

Figure 5. Meropenem-vaborbactam (2 g/2 g q8h, 3 h infusion) target plasma exposure.



MEM %Time Above:
4 µg/mL = 78%
8 µg/mL = 63%
16 µg/mL = 47%

VAB $AUC_{0\text{-}24}$
546 µg*h/mL

Conclusions

- **In a rigorous 7-day HFIM, humanized exposures of cefepime-taniborbactam (FTB) maintained bactericidal activity against challenging clinical strains that produce SBLs and/or MBLs.**
- **Resistant subpopulations did not emerge from FTB-treated models.**
- **These results support the clinical development of FTB and inform understanding of its potential role in SBL+ and/or MBL+ gram-negative bacterial infections.**

References

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