Poster 590

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Activities of Cefepime-Taniborbactam and Ceftazidime-Avibactam against Cefepime-Resistant Respiratory Gram-Negative Pathogens in a Hollow Fiber Infection Model

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Abstract

Background Cefepime-taniborbactam (FTB) combines cefepime (FEP), a fourth generation cephalosporin with taniborbactam, a novel inhibitor of metallo (MBL)- and serine-β-lactamases (SBL). FTB 2.5g IV q8h was safe and effective in adults with complicated urinary tract infections in a Phase 3 trial (NCT03840148). FTB is also under development for hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP).

Methods An in vitro hollow fiber infection model (HFM) was used to assess resistance emergence in MBL- and/or SBL-producing *Klebsiella pneumoniae* (KP, n=5) and *Pseudomonas aeruginosa* (PA, n=3) treated with humanized exposures of FTB or ceftazidime-avibactam (CZA). Dense (≥ 7 log CFU/mL) log-phase cultures were inoculated into HFM cartridges and treated with human equivalent doses of FEP (2g q8h), FTB (2.5g q8h), or CZA (2.5g q8h) for 4 days. KP strains collectively harbored NDM (n=2), VIM (n=1), CTX-M (n=4), SHV-ESBL (n=1), CMY (n=1), KPC (n=1), and/or OXA-48 (n=1). PA strains produced VIM (n=1), CTX-M (n=1), or KPC (n=1). Pharmacokinetic profiles of FTB and CZA in HFMs, based on free drug exposures in plasma of healthy volunteers, were confirmed by LC-MS/MS. For CZA HFMs with MBL-producing strains, EDTA was added to sequester zinc to restore CZA susceptibility (MIC ≤ 8 μg/mL). Viable bacteria were quantified by serial dilution plating; subpopulations with elevated MICs (≥ 4x) were monitored on FTB- or CZA-supplemented agar.

Results FEP, FTB, and CZA MICs ranged from 16 to > 128 μg/mL, 0.5–8 μg/mL, and 2 to > 128 μg/mL, respectively. In the HFM, FEP was inactive (n=7) or bacteriostatic (n=1, FEP MIC=16 μg/mL). FTB was bactericidal (≥ 3-log kill) against all 8 strains; subpopulations with elevated FTB MICs were not detected. Against MBL producers, CZA was inactive without EDTA and was bacteriostatic (n=2) or bactericidal (n=2) only when EDTA was added to disable MBLs. Against non-MBL producers, all of which were CZA-susceptible, CZA was either bactericidal (n=1) or bacteriostatic (n=2) or allowed growth due to emergence of resistance (n=1).

Conclusion Humanized exposures of FTB in a HFM were bactericidal against high inocula of MBL- and/or SBL-producing, multidrug-resistant respiratory pathogens and prevented emergence of resistance for 4 days. The results support development of FTB for HABP/VABP.

Introduction

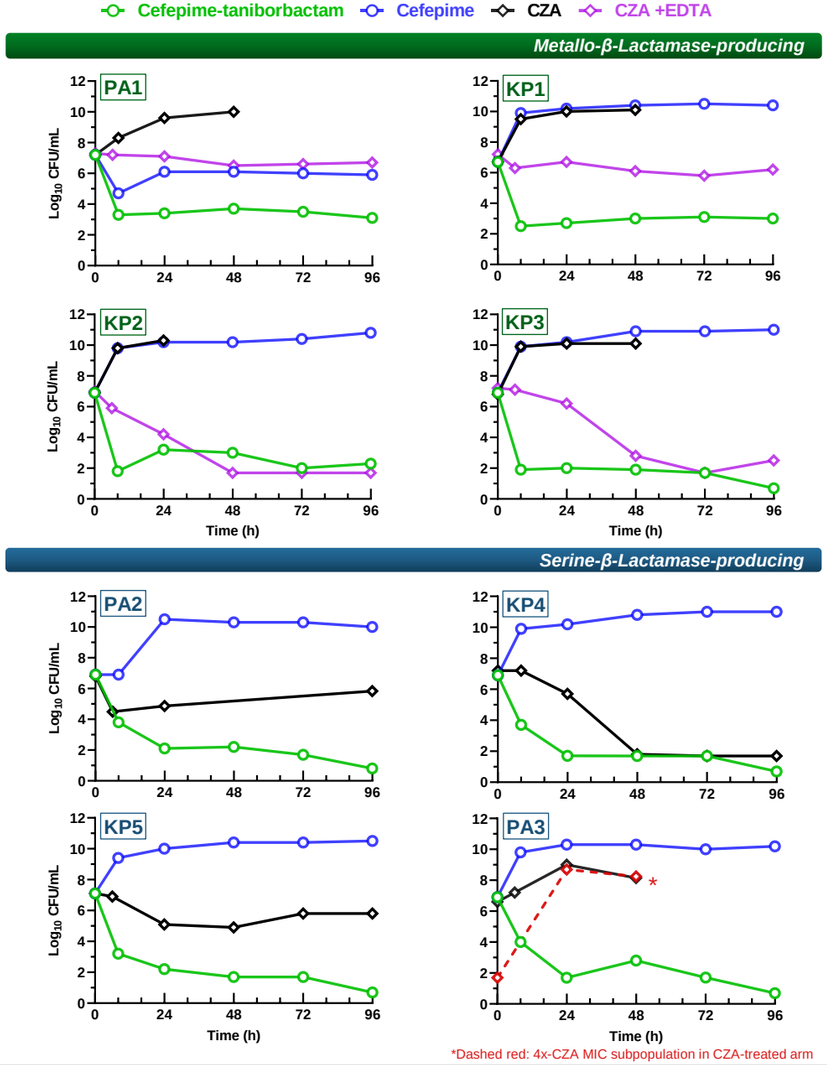
- **Carbapenem resistance rates** among the most frequently isolated pathogens in hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP), Enterobacterales and *Pseudomonas aeruginosa*, have increased to 8% and 30%, respectively.[1]
- **Cefepime-taniborbactam**, an antipseudomonal cephalosporin-novel boronate β-lactamase inhibitor combination, was safe and effective in adults with complicated urinary tract infections in the CERTAIN-1 Phase 3 clinical trial and is also under development for HABP/VABP.
- **Taniborbactam**, a potent inhibitor of serine-β-lactamase (SBL) and metallo-β-lactamase (MBL) enzymes, restored susceptibility to cefepime (MIC ≤ 8 μg/mL) among 90% and 81% of meropenem-nonsusceptible Enterobacterales (N=637) and *P. aeruginosa* (N=1222) strains from global surveillance, respectively.[2] Efficacy of cefepime-taniborbactam humanized exposures was also demonstrated in a translational mouse lung infection model.[3]
- **Hollow fiber infection models (HFMs)** are dynamic in vitro infection models that allow intensive study of antibacterial activity associated with clinical exposures.
- **Objective:** The HFM was used to investigate the potential for treatment-emergent resistance to humanized exposures of cefepime-taniborbactam or ceftazidime-avibactam among SBL- and/or MBL-producing *K. pneumoniae* and *P. aeruginosa* strains.

Methods

- ***Bacterial strains and susceptibility testing.*** Clinical isolates (N=8) were sourced from the FDA-CDC Antimicrobial Resistance (AR) Bank, Antibacterial Resistance Leadership Group (ARLG), or International Health Management Associates, Inc. Minimum inhibitory concentrations (MICs) were measured by broth microdilution according to Clinical and Laboratory Standards Institute methodology.
- ***Hollow fiber model.*** HFMs were set up as previously described.[4] Cartridges (C2011, FiberCell Systems, New Market, MD) were inoculated with log-phase bacterial cultures to achieve a target inoculum of ≥ 10^8 colony forming units (CFU), confirmed by quantitative culture. Programmable syringe pumps infused humanized doses equivalent to cefepime-taniborbactam 2g-0.5g every 8 hours (q8h, 4 h infusion) and ceftazidime-avibactam (CZA) 2g-0.5g q8h (2 h infusion); the CZA dosage is approved by the FDA for HABP/VABP treatment. Cefepime monotherapy served as a negative control. For MBL-producing strains, CZA was assessed in cation-adjusted Mueller Hinton broth (CAMHB, i.e., standard procedure) and in a separate HFM in which CAMHB was supplemented with a concentration of EDTA required to reduce the CZA MIC to ≤ 8 μg/mL via sequestration of zinc in growth media.
- ***Resistance assessment.*** Total bioburden was quantified by serial dilution and plating onto Mueller Hinton (MH) agar at least once daily over the 4-day treatment period. Subpopulations with elevated MICs (4x) were enumerated on drug-supplemented MH agar according to treatment arm; recovered colonies underwent confirmatory MIC testing by broth microdilution, whole-genome sequencing (Genewiz, South Plainfield, NJ), and genomic analysis (Dr. Tsuyoshi Uehara, Venatorx). The lower limit of quantification was 5 CFU/100 μL (1.7 $\log_{10}$ CFU/mL) at all time points except 96-hour (5 CFU/1 mL= 0.7 $\log_{10}$ CFU/mL).
- ***Pharmacokinetic (PK) analysis.*** Targeted concentration-time profiles in HFMs were based on free drug concentrations in plasma according to preliminary population PK models constructed with Phase 1 data for cefepime-taniborbactam and PK data listed in AVYCAZ® Prescribing Information (Allergan USA, Inc.; 2019) for ceftazidime-avibactam.
- ***Bioanalytical assay.*** Validated UPLC-MS/MS methods were developed and used to (1) confirm equilibration between central and extracapillary HFM compartments for all drugs and (2) monitor concentrations in the central compartments in all HFM experiments.

Results

P. aeruginosa (PA) and *K. pneumoniae (KP)* in the hollow fiber model



*Dashed red: 4x-CZA MIC subpopulation in CZA-treated arm

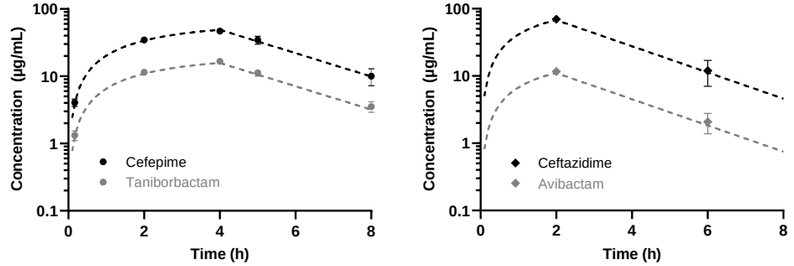
Strain characterization

Key	Strain	Known Encoded β-Lactamases: Metallo-	Known Encoded β-Lactamases: Serine-	MIC (μg/mL): FEP	FTB	CAZ	CZA	MEM	EDTA MIC (μg/mL)*: CAZ	CZA
PA1	1978557	VIM-5	---	16	4	>32	>32	>32	8	8
KP1	AR-0135	VIM-1	OXA-9, SHV-12, TEM-1	>32	0.5	>32	>32	16	>32	8
KP2	AR-0041	NDM-1	CMY-4, CTX-M-15, OXA-10, SHV-11	>32	1	>32	>32	16	>32	1
KP3	ARLG-1002	NDM	CTX-M-1 group, SHV, TEM	>32	2	>32	>32	32	>32	1
PA2	1131170	---	CTX-M-2, OXA-10, OXA-486, PDC-8	>32	8	16	4	16	NT	NT
KP4	874525	---	CTX-M-15, OXA-48, TEM-1, SHV-11	>32	8	>32	2	32	NT	NT
KP5	882752	---	CTX-M-3, KPC-3, SHV-11, TEM-1	>32	0.5	>32	2	>32	NT	NT
PA3	1013996	---	KPC-2	>32	8	>32	4	>32	NT	NT
CZA-emergent mutant		---	Ser insertion at KPC-2 Ambler Ser182	>32	8	>32	>32	8	NT	NT

*EDTA was fixed at 30 μg/mL and 100 μg/mL for VIM-producing and NDM-producing strains, respectively; NT: Not tested

Target pharmacokinetic profiles and observed concentrations in HFMs

PK profiles are shown as dashed lines and observed values (solid circles on left for cefepime-taniborbactam and diamonds on right for ceftazidime-avibactam) are means and standard deviations of 8 values (1 per strain).



Summary

Ceftazidime-avibactam (CZA) 2g-0.5g infused over 2 hours every 8 hours for 4 days in a hollow fiber model suppressed regrowth of **3 of 4 SBL-producing**, CZA-susceptible *P. aeruginosa* and *K. pneumoniae* strains.

- Resistance to CZA emerged in a KPC-producing *P. aeruginosa* strain after 1 day of CZA treatment.
- CZA was inactive against **4 of 4 MBL-producing** strains but prevented regrowth when zinc was sequestered.

Cefepime-taniborbactam 2g-0.5g infused over 4 hours every 8 hours for 4 days maintained bactericidal activity in the hollow fiber model against **all 8 cefepime-resistant strains** (cefepime-taniborbactam MIC range, 0.5–8 μg/mL).

- Resistance to cefepime-taniborbactam did not emerge.
- These data support the clinical development of cefepime-taniborbactam to treat HABP/VABP caused by SBL- and MBL-producing respiratory gram-negative pathogens.

Abbreviations

CAZ: ceftazidime
CZA: ceftazidime-avibactam
EDTA: ethylenediaminetetraacetic acid
FEP: cefepime
FTB: cefepime-taniborbactam
HFM: hollow fiber infection model
KP: *Klebsiella pneumoniae*
MBL: metallo-β-lactamase
MEM: meropenem
PA: *Pseudomonas aeruginosa*
SBL: serine-β-lactamase

References

1. Bart et al. CID 2020, doi: 10.1093/cid/ciaa1712.
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3. Abdelraouf et al. ASM Microbe 2022. Poster 2321.
4. Avery et al. IDWeek 2020 (virtual). Poster 1263. Abstract 907145, doi: 10.1093/ofid/ofaa439.1447.

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