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1366. In Vitro and In Vivo Activity of Cefiderocol against Stenotrophomonas maltophilia Clinical Isolates
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Background. Cefiderocol (S-649266, CFDC) is a novel siderophore cephalosporin against Gram-negatives, including carbapenem (CR)-resistant strains. Its spectrum includes both the Enterobacteriaceae but also nonfermenters, including Stenotrophomonas maltophilia—an opportunistic pathogen with intrinsic resistance to carbapenem antibiotics. In this study, in vitro activity and in vivo efficacy of CFDC and comparators against S. maltophilia were determined.

Methods. MICs of CFDC and comparators (trimethoprim/sulfamethoxa-
tole (TMP/SMX), minocycline (MINO), tigecycline (TGC), ciprofloxacin (CPFX), ce-
fepime (CFPM), meropenem (MEPM), and colistin (CL)) were determined by broth microdilution method as recommended by CLSI. The MIC of CFDC was deter-
mined using iron-depleted cation-adjusted Mueller–Hinton broth. In vivo efficacy of CFDC, CFPM, ceftazidime–avibactam (CAZ/AVI), MEPM, and CL was evaluated using neutropenic murine systemic infection model caused by strain SR21970. The 50% effective doses (ED50, s) were calculated by the logit method using the survival number at each dose 7 days after infection.

Results. MICs of CFDC and comparators against the 216 clinical isolates from global countries collected in SIDERO- CR 2014-2016 study are shown in the table. CFDC, TMP/SMX, MINO, and TGC showed good activity with MIC50 of 0.5,
0.25/4.75, 1 and 2 µg/mL, respectively. CFDC, MINO, and TGC inhibited growth of all tested strains at ≤1, ≤4, and ≤8 µg/mL although two strains showed resistance to TMP/SMX. MICs of CFPM, CAZ/AVI, MEPM, and CL were 2-32 µg/mL. The ED50 of CFDC against S. maltophilia strain SR21970 was calculated as 1.17 mg/kg/dose. Conversely, MICs of CFPM, CAZ/AVI, MEPM/CS, and CL against strain SR21970 were 32 µg/mL or higher, and ED50 were >100 mg/kg/dose, showing that CFDC had potent in vivo efficacy against S. maltophilia strain which was resistant to other antibiotics.

Conclusion. CFDC showed potent in vitro activity against S. maltophilia, including TMP/SMX-resistant isolates. CFDC also showed potent in vivo efficacy reflecting in vitro activity against S. maltophilia in murine systemic infection model.

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1367. Clinical Cure in Secondary Efficacy Populations in Patients with Complicated Urinary Tract Infection Treated With ZT1-01 (Fosfomycin for Injection): Findings From the ZEUS Trial
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Background. ZT1-01 (fosfomycin for injection) is an investigational episodic anti-
biotic with a differentiated mechanism of action (MOA) inhibiting an early step in bacterial cell wall synthesis. ZT1-01 has a broad spectrum of in vitro activity, including multidrug-resistant Gram-negative pathogens, and is being developed for the treat-
ment of patients with complicated urinary tract infection (cUTI) and acute pyele-
nephritis (AP) in the United States.

Methods. ZEUS was a multicenter, double-blind, Phase 2/3 trial in hospitalized adults with cUTI and AP to evaluate safety and efficacy. Randomized patients received 6 g ZT1-01 q6h or 4.5 g iv piperacillin/tazobactam (PIP/TAZ) q8h for 7 days; patients
with baseline bacteremia could receive up to 14 days; study continued to late follow-up (LFU, 26 ± 2 days). Oral step-down therapy was prohibited. ZTI-01 met the primary endpoint of noninferiority to PIP-TAZ. Secondary objectives included comparing clinical cure rates (assessed by investigator) in the modified intent-to-treat (MITT), microbiologic MITT (m-MITT), clinical evaluable (CE), and microbiologic evaluable (ME) populations at test of cure (TOC). Day 18 ± 3 days.

Results. There were 464 patients randomized who received study drug. In all populations, clinical cure rates at TOC were high and similar between treatment groups (>90%) (Table). These results demonstrate consistent efficacy in multiple secondary efficacy populations for patients with cUTI and AP who were treated with either ZTI-01 or PIP-TAZ. If approved by FDA, ZTI-01 may provide a new IV option with a different mechanism of action for patients in the United States with serious Gram-negative infections.

Table: Clinical Response at TOC

| Population   | ZTI-01 (n (%) | PIP-TAZ (n %) | Difference (%) | 95% CI |
|--------------|--------------|---------------|---------------|-------|
| MITT         | 233          | 233           |               |       |
| Cure         | 211 (90.6)   | 212 (91.8)    | −1.2          | (−6.8, 4.4) |
| Failure      | 11 (4.7)     | 16 (6.9)      |               |       |
| Indeterminate| 11 (4.7)     | 3 (1.3)       |               |       |
| m-MITT       | 175          | 178           |               |       |
| Cure         | 167 (90.8)   | 163 (91.6)    | −0.8          | (−7.2, 5.6) |
| Failure      | 9 (4.9)      | 12 (6.7)      |               |       |
| Indeterminate| 8 (4.3)      | 3 (1.7)       |               |       |
| CE           | 199          | 198           |               |       |
| Cure         | 188 (94.5)   | 182 (92.9)    | 1.6           | (−3.7, 6.9) |
| Failure      | 11 (5.5)     | 14 (7.1)      |               |       |
| ME           | 155          | 145           |               |       |
| Cure         | 148 (95.5)   | 135 (93.1)    | 2.4           | (−3.5, 8.3) |
| Failure      | 7 (4.5)      | 10 (6.9)      |               |       |

95% confidence intervals (CIs, two-sided) were computed using a continuity-corrected Z-statistic.

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1368. Assessment of the In Vitro Efficacy of Human-Simulated Epithelial Lining Fluid (ELF) Exposure of Meropenem/Nacubactam (MEM/NAC) Combination Against β-Lactamase-Producing Enterobacteriaceae in Neutrophilic Lung Infection Model

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Background. NAC is a novel dual action β-lactamase inhibitor with in vitro activity against class A, class C, and class D β-lactamases and antibacterial activity against Enterobacteriaceae. NAC is being developed as a combination therapy with MEM for the treatment of serious Gram-negative bacterial infections. This study evaluated the efficacy of the human-simulated ELF exposure of MEM/NAC, compared with those of MEM or NAC alone against β-lactamase-producing Enterobacteriaceae isolates in the neutrophilic murine lung infection model.

Methods. Eight clinical MEM-resistant Enterobacteriaceae isolates harboring various β-lactamases (IMI, KPC, OXA, TEM, SHV, and AmpC) were utilized in the study. MEM and MEM/NAC (1:1) combination MICs were determined in triplicate via broth microdilution. ICR mice were rendered transiently neutropenic, and lungs were inoculated with 50 μL bacterial suspensions of 10^9 CFU/mL. Regimens in mice that simulated the human ELF exposures following doses of MEM 2 g q8h and NAC 2 g q8h (1.5 hours infusions) as monotherapies and in combination were established. Treatment mice received MEM human-simulated regimen (HSR), NAC HSR, or MEM/NAC HSR and control mice were vehicle-dosed. Treatment was started 2 hours after inoculation and continued for 24 hours. Efficacy was assessed as the change in log CFU/lung at 24 hours compared with 0 hours controls.

Results. MEM and MEM/NAC MICs were 8–512 and 0.5–8 mg/L, respectively. The average log CFU/lung at 0 hours across all isolates was 6.26 ± 0.26. Relative to 0 hours control, the mean bacterial growth at 24 hours in the untreated control mice, MEM HSR, and NAC HSR treatment groups were 2.93 ± 0.29, 2.72 ± 0.42, and 1.75 ± 0.80 log CFU/lung, respectively. MEM/NAC HSR resulted in up to 2 log-bacterial reductions in isolates with MEM/NAC MIC ≤0.5 mg/L.

Conclusion. MEM/NAC human-simulated ELF exposure produced enhanced efficacy against MEM-resistant β-lactamase-producing Enterobacteriaceae isolates with MEM/NAC MIC ≤0.5 mg/L. These data support a potential role for MEM/NAC for treatment of lung infections due to β-lactamase-producing Enterobacteriaceae and warrant further studies.

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1370. Ceftipime/VNRX-5133 Broad-Spectrum Activity Is Maintained Against Emerging KPC- and PDC-Variants in Multidrug-Resistant K. pneumoniae and P. aeruginosa

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Background. VNRX-5133 is a cyclic boronate β-lactamase inhibitor (BLI) currently in clinical development with ceftipime to treat multidrug-resistant (MDR) infections caused by ESBL- and carbapenemase-producing Enterobacteriaceae (ENT) and...