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1349. Global Surveillance of Cefiderocol Against Gram-Negative Clinical Strains Collected in North America: SIDERO-WT-2015

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Session: 144. Novel Agents
Friday, October 5, 2018: 12:30 PM

Background. Cefiderocol (CFDC) is a novel parenteral siderophore cephalosporin with potent activity against a wide range of Gram-negative pathogens, including carbapenem-resistant strains. Additionally, a recently conducted *in vivo* murine-based study has demonstrated an incremental exposure-response profile over a dose range without the appearance of adaptive resistance. In this study, we evaluated the *in vitro* activity of CFDC and comparator agents against clinical isolates collected in 2015–2016 from North America from SIDERO-WT-2015 surveillance study.

Methods. A total of 3,602 isolates (2,470 *Enterobacteriaceae*, 223 *A. baumannii*, 85 *Acinetobacter* spp., 619 *P. aeruginosa*, 165 *S. maltophilia* and 17 *Burkholderia* cepacia, and 23 *Burkholderia* spp.) collected from the United States and Canada in 2015–2016 were tested. MICs were determined for CFDC, cefepime (FEP), ceftazidime–avibactam (CZA), ceftolozane–tazobactam (C/T), ciprofloxacin (CIP), colistin (CST), and meropenem (MEM) by broth microdilution and interpreted according to CLSI guidelines. As recommended by CLSI, cefiderocol was tested in iron-depleted cation-adjusted Mueller–Hinton broth (ID-CAMHB). Carbapenem nonsusceptible (Carb-NS) strains were defined as MEM MIC ≥2 μg/mL for *Enterobacteriaceae*, and ≥4 μg/mL for nonfermenters.

Results. CFDC exhibited potent *in vitro* activity against 3,602 strains of Gram-negative bacteria with an overall MIC_{90} of 0.5 mg/mL. As shown in the following table, MIC_{90} of CFDC against *P. aeruginosa*, *A. baumannii*, *S. maltophilia*, and *Enterobacteriaceae* including the subset of Carb-NS isolates were 0.5, 2, 0.5 and 0.5 mg/mL, respectively. At 4 mg/mL, CFDC inhibited the growth of 99.6% of the isolates while 18.1%, 12.6%, and 13.8% showed resistance to CZA, C/T, and CST, respectively.

Conclusion. CFDC demonstrated potent *in vitro* activity against the teat isolates collected from North America with greater than 99.6% of isolates having MIC values ≤4 mg/mL, including Carb-NS isolates of *A. baumannii*, *P. aeruginosa*, and *Enterobacteriaceae*. These findings indicate that this agent has high potential for treating infections caused by these problematic organisms.

Organisms	N	CFDC	FEP	CZA	C/T	CIP	CST	MEPM
Enterobacteriaceae	2470	0.5	4	0.5	1	>8	>8	≤0.06
P. aeruginosa	619	0.5	16	8	2	>8	2	8
A. baumannii	223	2	>64	>64	>64	>8	1	>64
S. maltophilia	165	0.5	>64	64	>64	>8	8	>64

Disclosures. **M. Tsuji**, Shionogi & Co., Ltd.: Employee, Salary. **M. Hackel**, IHMA, Inc.: Employee, Salary. **Y. Yamano**, Shionogi & Co., Ltd.: Employee, Salary. **D. Sahm**, IHMA, Inc.: Employee, Salary.

1350. Therapeutic Effects of Baloxavir Marboxil against Influenza A Virus Infection in Ferrets

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Session: 144. Novel Agents
Friday, October 5, 2018: 12:30 PM

Background. Baloxavir marboxil (BXM) is a novel small molecule inhibitor of cap-dependent endonuclease that is essential for influenza virus transcription and replication. In this study, pharmacokinetic profiles of BXM and baloxavir acid (BXA), an active form of BXM, were first examined in ferrets, and then the therapeutic effects of BXM against influenza A virus infection were compared with that of oseltamivir phosphate in ferrets.

Methods. The plasma exposure of BXA and BXM was examined after a single oral administration of BXM at doses of 10 and 30 mg/kg. The concentrations in plasma were determined by liquid chromatography-tandem mass spectrometry(LC/MS/MS). For efficacy study, ferrets infected intranasally with A/Kadoma/2006 (H1N1) were administrated 10 or 30 mg/kg of BXM orally twice daily for 1 day, starting at 1 day post-infection (p.i.) or administrated 10 mg/kg of BXM orally twice daily for 1 day, starting at 2 days p.i.. Oseltamivir phosphate was administered at doses of 5 mg/kg orally twice daily for 2 days as a comparison. The virus titer in the nasal washes and body temperature change were monitored during infection.

Results. BXA was detected in ferret plasma after a single oral administration of BXM at 10 and 30 mg/kg, in more than a dose-proportional manner. When the treatment was initiated at 1 day p.i., BXM at 10 and 30 mg/kg showed reduction of virus titer to an undetectable level on day 2 p.i. and statistically significant reduction in virus titer over time from day 2 to 3 p.i. compared with vehicle and oseltamivir phosphate. Moreover, the change of body temperature over time from 8 hours after the first administration to 3 days p.i. was significantly lower in BXM at 10 and 30 mg/kg than vehicle and oseltamivir phosphate. These effects were also observed in ferrets treated with BXM at 10 mg/kg even when administered at 2 day p.i. where ferret exhibit fever that is more than 1 degree higher than on 1 day p.i..

Conclusion. Single-day oral administration of BXM had beneficial effects on viral titer and symptoms in ferrets infected with influenza A virus, which were superior to those observed with oseltamivir phosphate and vehicle.

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1351. *In vitro* Activity of Cefiderocol (S-649266), a Siderophore Cephalosporin, Against Enterobacteriaceae With Defined Extended-Spectrum B-Lactamases and Carbapenemases

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Session: 144. Novel Agents
Friday, October 5, 2018: 12:30 PM

Background. Cefiderocol is a novel siderophore cephalosporin targeted for activity against carbapenem and multidrug-resistant Gram-negative species, including extended-spectrum β-lactamase (ESBL) and carbapenemase-producing strains. The Consortium on Resistance Against Carbapenems in Klebsiella and other Enterobacteriaceae (CRACKLE) is a federally funded, prospective multi-center consortium of 20 hospitals from nine US healthcare systems to track carbapenem-resistant Enterobacteriaceae.

Methods. Minimum inhibitory concentrations (MICs) of cefiderocol and meropenem were determined by broth microdilution according to current CLSI guidelines. Cefiderocol was tested in iron-depleted cation-adjusted Mueller–Hinton (MH) broth, meropenem was tested in cation-adjusted MH broth. Cefiderocol MICs were read as the first drug well in which the growth was significantly reduced (i.e., a button of <1 mm or light/faint turbidity) relative to the growth observed in the growth control well containing the same medium. Trailing endpoints were disregarded. Isolates tested included 35 *Escherichia coli*, five Enterobacter/Citrobacter group, and 794 *Klebsiella pneumoniae*. Isolates had characterized β-lactamases including TEM, SHV, and CTX-M ESBLs and KPC, NDM, and OXA carbapenemases.

Results. Cefiderocol MICs ranged from ≤0.03 to >64 mg/L, with overall MIC50 of 0.5 mg/L and MIC90 of 4 mg/L (table). MIC90 value (≤0.03 mg/L) was lowest against isolates with no ESBLs or carbapenemases. MIC90 was 1 mg/L for OXA and TEM/SHV groups, 2–4 mg/L for KPC-3 groups and 8 mg/L for NDM and KPC-2 groups.

Conclusion. Compared with isolates without ESBLs and carbapenemases, cefiderocol shows higher MICs against isolates with ESBLs, including TEM, SHV, and CTX-M and carbapenemases including KPC, NDM, and OXA. The clinical utility of cefiderocol against ESBL and carbapenemase-producing *Enterobacteriaceae* is dependent on the pharmacokinetic and pharmacodynamic properties of cefiderocol.

Table: Activity of Cefiderocol

β-Lactam Resistance	N	MIC range (mg/L)	MIC50 (mg/L)	MIC90 (mg/L)
ampC	3	0.25 to 2	NA	NA
KPC-2	255	≤0.03 to 32	0.5	8
KPC2 + Other	101	≤0.03 to 16	2	8
KPC-3	276	≤0.03 to 64	0.25	2
KPC3 + Other	106	≤0.03 to 16	0.5	4
NDM	28	0.25 to >64	2	8
OXA	8	≤0.03 to 1	0.25	1
TEM/SHV ESBL	42	≤0.03 to >64	2	1
None	15	≤0.03 to 0.12	≤0.03	≤0.03
All	834	≤0.03 to >64	0.5	4