350. Therapeutic Effects of Baloxavir Marboxil against Influenza A Virus Infection in Ferrets
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Background. Baloxavir marboxil (BXM) is a novel small molecule inhibitor of influenza A virus (IAV) polymerase, which is approved for treatment of uncomplicated IAV infections in adults and children ≥1 year of age. The plasma exposure of BXM after oral administration of 10 and 30 mg/kg was examined after a single oral administration to ferrets. The pharmacokinetic (PK) profiles of BXM 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 or 10 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 days p.i. where ferret exhibit fever that was more than 1 degree higher than 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.

Disclosures. M. Kitano, Shionogi & Co., Ltd.: Employee, Salary. T. Matsuzaki, Shionogi & Co., Ltd.: Employee, Salary. M. Hackel, IHMA, Inc.: Employee, Salary. Y. Yamano, Shionogi & Co., Ltd.: Employee, Salary. D. Saham, IHMA, Inc.: Employee, Salary.

1331. In vitro Activity of Cefiderocol (S-649266), a Siderophore Cephalosporin, Against Enterobacteriaceae with Defined Extended Spectrum β-Lactamases and Carbapenemases
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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 marine-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, 233 A. baumannii, 85 Acinetobacter spp, 165 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), cefepime–tazobactam (CIP), 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 ≥8 mg/mL for Enterobacteriaceae, and ≥4 mg/mL for non-Enterobacteriaceae. Results. CFDC exhibited potent in vitro activity against 3,602 strains of Gram-negative bacteria with an overall MIC50 of 0.5 mg/mL. As shown in the following table, MIC50 of CFDC against P. aeruginosa, A. baumannii, S. maltophilia, and Enterobacteriaceae was 0.5, 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, CIP, and CST, respectively.

Conclusion. CFDC demonstrated potent in vitro activity against the target 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.

Table: Activity of Cefiderocol

| Organisms     | N | CFD | FEP | CZA | CIP | CST | MEM |
|---------------|---|-----|-----|-----|-----|-----|-----|
| Enterobacteriaceae | 4270 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.06 |
| P. aeruginosa  | 619  | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.06 |
| A. baumannii   | 223  | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.06 |
| S. maltophilia | 165  | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.06 |

Disclosures. M. Tsuji, Shionogi & Co., Ltd.: Employee, Salary. M. Hackel, IHMA, Inc.: Employee, Salary. Y. Yamano, Shionogi & Co., Ltd.: Employee, Salary. D. Saham, IHMA, Inc.: Employee, Salary.
1352. A Computational Approach for Exploring the Binding Mechanism of Chebulic Acid on Herpes Simplex Virus-2 and Its Implication on Chikungunya and Dengue

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Background. Chebulic acid (CA), a natural compound isolated from the tree Terminalia chebula, has been recently reported to have shown antiviral activity against Herpes simplex virus-2 (HSV-2). The study showed inhibition activity of CA, preventing the attachment of HSV-2 on the host cells. This activity was speculated to be due to an interaction between CA and viral surface glycoproteins, triggering alterations in its function or making virus particles inert and preventing their attachment to host cells. However, the mechanism of this inhibition was not established. The current study was designed not only to help gain insights of the mechanism of action of CA on HSV-2, but also to computationally check its binding affinity on other enveloped arboviruses, i.e., Chikungunya (ChikV) and Dengue (DenV).

Methods. The viral surface glycoproteins of HSV-2, ChikV, and DenV were subjected to molecular docking with CA using the software, AutoDock Vina. Protein—protein docking was performed with ClusPro online server to elucidate the specific interactions between viral and human host receptors. Due to unavailability of crystal structure of Prohibitin, a human receptor for ChikV, structural modeling was performed with i-Tasser server.

Results. The conformations obtained after docking showed good hydrogen bond interactions with the glycoprotein of HSV-2, with a binding energy of −9.3 kcal/mol on HSV-2, ChikV, and DenV, respectively. In all three viruses, CA was found to bind specifically at the site directly involved in host attachment, suggesting a possible mechanism of action by which CA inhibits the viral attachment that is consistent with the result obtained from the in vitro experiment on HSV-2. Hence the natural bio-molecule Chebulic acid has the potential to inhibit the host attachment step of HSV-2, ChikV, and DenV by directly binding to their viral glycoproteins.

Conclusion. Chebulic acid shows a good propensity as an antiviral agent, capable of acting against multiple enveloped viruses. Additionally, a more potent and specific drug design is required to prepare a stable form of CA by process of molecular modification.

Disclosures. N. Thomas, Department of Science and Technology: Government of India funding agency, Research grant.

1353. In Vitro Activity of Lefamulin (LEF) Against Bacterial Pathogens Commonly Causing Community-Acquired Bacterial Pneumonia (CABP): 2016 SENTRY Data From the United States
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Background. LEF, the first pleuromutilin antibiotic for IV and oral use in humans, is in Phase 3 clinical trials for the treatment of CABP in adults. In the first of these studies, LEF demonstrated no-dose dependency on Days 1–14 and once on the morning of Day 15, LEF inhibits bacterial translation by binding the 50S ribosomal subunit at the A- and P-sites on the peptidyl transferase center. CABP is a leading cause of infectious diseases in the United States and increasing antibacterial resistance complicates its treatment. This study investigated the in vitro activity of LEF and comparators against a contemporary set of bacterial respiratory pathogens collected in the United States.

Methods. Isolates (n = 1674, 1/patient) were collected from 32 medical centers in the United States as part of the SENTRY Surveillance Program. LEF and comparators (MICs in mg/L) were obtained from the in vitro experiment on HSV-2. Hence the natural bio-molecule Chebulic acid has the potential to inhibit the host attachment step of HSV-2, ChikV, and DenV by directly binding to their viral glycoproteins.

Conclusion. LEF displayed potent in vitro activity against a contemporary collection of respiratory pathogens from the United States. LEF was active regardless of resistance phenotype to other antibiotic classes including β-lactams, tetracyclines, or macrolides. These results further support the clinical development of lefamulin for the treatment of CABP or other respiratory tract infections.

Disclosures. S. Paukner, Nabirva: Employee and Shareholder, Salary. R. K. Flamm, Nabirva: Research Contractor, Research grant.

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