1343. Prophylactic Dosing of Baloxavir Acid Eliminates Mortality in Mice Lethal Influenza A Virus Infection Model
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Session: 144. Novel Agents
Friday, October 5, 2018: 12:30 PM
Background. Baloxavir acid (BXA), an active form of orally available prodrug baloxavir marboxil (BXM, formerly S-033188), is a novel small molecule inhibitor of cap-dependent endonuclease (CEN) of influenza A and B virus, and was recently launched for the treatment of acute and uncomplicated influenza with single dosing of BXM (the trade name XIVLURAZ™) in Japan in March 2018. Here, we evaluated the prophylactic efficacy of BXA in mice lethally infected with influenza A virus.

Methods. To study the prophylactic activity of BXA, groups of 10 mice per group were infected intranasally with an H1N1 influenza strain (VSX-105) and were treated with BXA or saline immediately after infection. Survival was monitored for 14 days. CEN activity in BAL and serum, and lactoferrin levels (µg/mL) were significantly higher for FT positive subjects at 24.3% (3.1, 39.1) and 14.0% (−1.8, 28.8), respectively. Absolute SCR differences between the MITT and ITT subjects from the sensitivity analysis were 26.2% (4.6, 40.6) and 14.3% (−1.7, 29.1). Median BL calprotectin and lactoferrin levels (µg/mL) were significantly higher for FT positive subjects at 1,002 and 87, than for FT negative subjects at 53 and 4, respectively.

Conclusion. RDZ showed improved SCR in comparison with VAN. Treatment differences were greater in MITT subjects. Lower SCR improvement in RDZ ITT subjects is likely due to enrollment of some colonized rather than infected subjects; this explanation is supported by higher calprotectin and lactoferrin levels in FT-positive samples. These data demonstrate the importance of FT testing in-line with CDI guideline recommendations.

Disclosures. R. Vickers, Summit Therapeutics: Employee, Salary and Stock options.
S. Chowdhury, Summit Therapeutics: Employee, Salary and Stock options.
M. Wilcox, Summit Therapeutics: Consultant, Research Contractor and Scientific Advisor, Consulting fee, Research grant and Research support.

1345. Comparative Activity of Plazomicin and Other Aminoglycosides Against Enterobacteriaceae Isolates From Various Infection Sources From Hospitalized Patients in the United States
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Session: 144. Novel Agents
Friday, October 5, 2018: 12:30 PM
Background. Plazomicin is a next-generation aminoglycoside that is currently under review at the United States Food and Drug Administration for complicated urinary tract infections (cUTIs), including acute pyelonephritis, and bloodstream infections (BSIs) due to certain Enterobacteriaceae (ENT) in patients who have limited or no alternative treatment options. We report here activity of plazomicin and aminoglycosides against ENT isolates collected in US hospitals during 2014 to 2017 by site of infection.

Methods. A total of 8,510 ENT isolates were collected from BSIs (2,133), pneumonia in hospitalised patients (PPHP, 1,836), skin and skin structure infections (SSSI, 1,155), intra-abdominal infections (IAIc, 731), UTIs (2,508), and other or unknown infection sites (others; 171) in 71 US hospitals during 2014 to 2017. Isolates were susceptibility (S) tested by reference broth microdilution methods. Results were interpreted using CLSI breakpoints.

Results. Plazomicin (MIC50 ranges, 0.25–0.5/1–2 µg/mL) inhibited 98.8–99.9% of the ENT isolates at ≤4 µg/mL across all infection types (figure). At ≤4 µg/mL, plazomicin inhibited 93.8–100% of the carbapenem-resistant ENT (CRE) isolates stratified by infection type. The rates for amikacin ranged from 98.7% to 99.7% against ENT isolates overall. However, amikacin S rates for CRE ranged from 53.1% for UTI to 100% for IAIc isolates. Gentamicin (89.2–93.6%) and tobramycin (88.8–94.3%) were slightly less active than plazomicin and amikacin against the ENT isolates stratified by infection source. Gentamicin S rates against CRE isolates ranged from 43.8% to 66.7% while tigecycline inhibited <45% of the CRE isolates from the different infection sources.

Conclusion. The activity of plazomicin and amikacin was similar against ENT isolates from US hospitals and did not vary by infection type; however, amikacin activity against CRE isolates varied by infection source while plazomicin remained active against CRE isolates regardless of infection source. These results highlight the potential role of plazomicin for treating serious infections caused by CRE. This project was partially funded under BARDA Contract No. HHSO100201000046C.

Disclosures. M. Castanheira, Achaogen: Research Contractor, Research support.
J. M. Streit, Achaogen: Research Contractor, Research support.
A. W. Serio, Achaogen: Employee, Salary.
K. M. Krause, Achaogen: Employee, Salary.
R. K. Flamm, Achaogen: Research Contractor, Research support.

1346. The Tetrazole VT-1958 is Efficacious in a Murine Model of Invasive Aspergillosis with a PK/PD Expected of a Mold-Causing CYP51 Inhibitor
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Session: 144. Novel Agents
Friday, October 5, 2018: 12:30 PM
Background. Diagnosis of CDI includes fecal detection of a C. difficile toxigenic strain (TS) or free toxins (FT). TS detection does not distinguish infection from colonization. Guidelines recommend an FT test be part of diagnostic algorithms. Here we report outcome differences, based on diagnostic method at enrollment, from a Phase 2b clinical trial of RDZ, a novel CDI antibiotic designed to treat CDI and reduce recurrence of CDI (rCDI).

Methods. This double-blind study randomized 100 patients 1:1 to 10 days RDZ 200 mg BD or vancomycin (VAN) 125 mg QD treatment. Subjects were enrolled with CDI symptoms and a positive diagnostic result (FT or TS). Baseline (BL) stool samples were assessed for the presence of FT. All subjects entered the intent to treat (ITT) population; those subjects positive for FT entered a modified ITT (mITT), the primary analysis population. Primary endpoint was sustained clinical response (SCR) defined as cure at end of therapy and no rCDI for the next 30 days. rCDI was defined as CDI symptoms, a positive diagnostic test and need for therapy; a sensitivity analysis considered positive FT rCDI cases. BL fecal concentrations of lactoferrin and calprotectin were determined by enzyme immunoassay.

Results. Of 100 subjects enrolled, 69 (36 RDZ: 33 VAN) were FT positive at BL. RDZ compared with VAN recipients had improved SCR rates via reduced rCDI. Absolute differences in SCR between RDZ and VAN (prespecified 90% CI) for MITT (FT positive) and ITT subjects were 24.3% (3.1, 39.1) and 14.0% (~1.8, 28.8), respectively. Absolute SCR differences between the MITT and ITT subjects from the
inoculation. In vivo antifungal activity was determined in a tail-vein IA model in neutropenic mice inoculated with A. fumigatus (AF) ATCC 204305 (N = 10 per dose). Two separate studies were conducted, with oral VT-1598 treatment starting either 48 hours prior (prophylaxis) or 5 hours postinoculation (delayed), with 4 days of postinoculation dosing, and kidney fungal burden measured 1 day post last dose by both CFU and qPCR. Drug control was 1 mg/kg Ambisome (AmB).

**Results.** The MIC for VT-1598 against AF 204305 was 0.25 μg/mL. The plasma PK of VT-1598 was linearly proportional between the 5 and 40 mg/kg once-daily doses, with AUCs of 155 and 1,033 μg·h/mL for the two doses, respectively. VT-1598 was similar effective in reducing fungal burden when given delayed treatment compared with prophylaxis, and both studies demonstrated a full-dose–response (i.e., no to full reduction of fungal burden). When comparing fungal burdens of each dose group to the fungal burden at the start of treatment, the dose of VT-1598 to achieve fungal eradication ranged from 20.5–25.9 mg/kg and to achieve a 1-log₉ fungal kill ranged from 30.9 to 50.5 mg/kg. Using the previously measured mouse plasma binding (>99.9%), the free AUC/MIC values for stasis and 1-log₉ killing ranged from 2.1–2.7 and 3.2–5.2, respectively. These values are within the range of 1–11 that have been reported for posaconazole and isavuconazole (Lepak, AAC, 2013).

**Conclusion.** VT-1598 had potent antifungal activity in a murine model of IA. The PK/PD relationship was the same as clinically used mold-active CYP51 agents, suggesting that it could have similar clinical efficacy. If correct, the tetrazole-based greater selectivity may significantly differentiate VT-1598 from current IA therapies.

**Disclosures.** E. P. Garvey, Viamet Pharmaceuticals, Inc.: Employee, Salary. A. Sharp, Evotec (UK) Ltd.: Employee, Salary. P. Warn, Evotec (UK) Ltd.: Employee, Salary. C. M. Yates, Viamet Pharmaceuticals, Inc.: Employee, Salary. R. J. Schotzinger, Viamet Pharmaceuticals, Inc.: Board Member and Employee, Salary.

134. Omadacycline for Acute Bacterial Skin and Skin Structure Infections: Integrated Analysis of Randomized Clinical Trials

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**Methods.** OMC in Acute Skin and Skin Structure Infections Study (OASIS) I initiated patients on intravenous (IV) OMC or linezolid (LZD) with a possible transition to oral formulation after at least 3 days of IV therapy. OASIS-2 investigated oral-only OMC. Treatment duration in both studies was 7–14 days. Early clinical response (ECR) in the mITT population, the primary endpoint in both studies, was defined as a ≥20% reduction in lesion size at 48–72 hours after treatment initiation. The secondary endpoint was investigator assessment of clinical response (IACR) at post-therapy evaluation (PTE) in the mITT and CE populations, 7–14 days after treatment initiation.

**Results.** A total of 691 patients receiving OMC and 689 patients receiving LZD were included. The mean age of patients was 45 years, 64% were male, and 83% enrolled at US sites. Primary etiologies were wound infections (46.8%), cellulitis/erysipelas (30.5%), and pyogenic osteomyelitis (22.7%). Median lesion size was 316 cm² in OMC and LZD patients, respectively. S. aureus was detected in 74.6% of patients, of which 43.4% had MRSA. 71% were similar across different infection types, lesion sizes, and baseline pathogens. Treatment-emergent adverse events (TEAEs), most mild or moderate, were reported by 51% and 41% of patients receiving OMC or LZD, respectively. Nausea and vomiting were more frequent for OMC patients in the OASIS-2 oral only study while receiving the loading dose on Day 1 and 2. Serious AEs were reported by 2.3% and 1.9%, respectively. TEAEs leading to study drug discontinuation were reported by 1.7% and 1.5%, respectively.

**Conclusion.** The integrated analysis of OASIS trials showed that oral and IV omadacycline was effective in the treatment of ABSSSI and was safe and generally well-tolerated by patients.

**Disclosures.** F. M. Abrahamian, Allergan: Speaker’s Bureau, Speaker honorarium. Mdinta: Speaker’s Bureau, Speaker honorarium. Merck: Speaker’s Bureau, Speaker honorarium. Navab: Scientific Advisor, Consulting fee. Paratek: Scientific Advisor, Consulting fee. G. Sakoula, Allergan: Consultant and Speaker, Consulting fee and Speaker honorarium. Sunovion Pharmaceuticals: Speaker, Speaker honorarium. The Medicines Company: Speaker, Speaker honorarium. Paratek Pharmaceuticals: Consultant, Consulting fee. Cidara Therapeutics: Scientific Advisor, Consulting fee. Arsani Pharmaceuticals: Scientific Advisor, Consulting fee. E. Tzanis, Paratek Pharmaceuticals: Employee, Salary. A. Manley, Paratek Pharmaceuticals: Employee and Shareholder, Salary. J. N. Steenbergen, Paratek Pharmaceuticals: Employee and Shareholder, Salary. A. Das, Achaogen: Consultant, Consulting fee. Cempra: Consultant, Consulting fee. Contrafect: Consultant, Consulting fee. Navab: Consultant, Consulting fee. Paratek: Consultant, Consulting fee. Tetraphase: Consultant, Consulting fee. Theravance: Consultant, Consulting fee. Wockhardt: Consultant, Consulting fee. P. Eckburg: Paratek: Consultant, Consulting fee. P. McGovern, Paratek Pharmaceuticals: Employee, Salary.

134.8. In vitro Activity of Plazomicin, a Next-Generation Aminoglycoside, Against Carbapenemase-Producing Klebsiella pneumoniae

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**Background.** OMC is effective in the treatment of ABSSSI and was safe and generally well-tolerated in patients receiving OMC and LZD. In OASIS-2 oral-only study while receiving the loading dose on Day 1 and 2, serious AEs were reported by 2.3% and 1.9%, respectively. TEAEs leading to study drug discontinuation were reported by 1.7% and 1.5%, respectively.

**Conclusion.** The integrated analysis of OASIS trials showed that oral and IV omadacycline was effective in the treatment of ABSSSI and was safe and generally well-tolerated by patients.

**Disclosures.** M. R. Jacobs, Achaogen: Investigator, Research grant. Shionogi: Investigator, Research grant. L. Connolly, Achaogen, Inc.: Consultant, Consulting...