1343. Prophylactic Dosing of Baloxavir Acid Eliminates Mortality in Mice Lethal Influenza A Virus Infection Model

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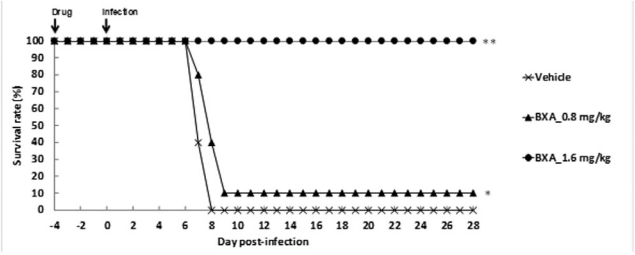
Background. Baloxavir acid (BXA), an active form of orally available prodrug baloxavir marboxil (BXM, formerly S-033188), is a novel small molecule inhibitor of cap-dependent endonuclease (CEN) of influenza A and B virus, and was recently launched for the treatment of acute and uncomplicated influenza with single dosing of BXM (the trade name XOFLUZA™) in Japan in March 2018. Here, we evaluated the prophylactic efficacy of BXA in mice lethally infected with influenza A virus.

Methods. $T_{1/2}$ of BXA in human is more than 10 times longer than that in mice. Therefore, suspension of BXA was subcutaneously administered at 0.8 or 1.6 mg/kg in mice to maintain the plasma concentration of BXA as seen in humans, and then mice were intranasally inoculated with a lethal dose of A/PR/8/34 strain at 48, 72, or 96 hours after the administration of BXA. Survival time and body weight change were then monitored through a 28-day period after virus infection. Mice were euthanized and regarded as dead if their body weights were lower than 70% of the initial body weights according to humane endpoints.

Results. Single dosing of BXA (1.6 mg/kg) completely eliminated mortality in mice, when the mice were administrated the drug at 48, 72, or 96 hours before virus infection (Figure 1). BXA treatment also significantly prevented body weight loss, consistent with the prolonged survival.

Conclusion. Prophylactic dosing of BXA exhibited significant protective efficacy against mortality and body weight loss in mice following a lethal infection with influenza A virus. The significant prophylactic efficacy observed in our mouse model suggests the potential utility of BXM for the prophylaxis of influenza in human.

Figure 1 Effect of prophylactic treatment with baloxavil acid on mortality due to infection witha lethal dose fo A/PR/8/34 strain in mice



BXA,baloxavir acid. The following P values were calculated by log-rank test and the fixed-sequence procedure: *P<0.05, **P<0.0001 vs vehicle

Disclosures. **S. Shano**, Shionogi & Co., Ltd.: Employee, Salary. **K. Fukao**, Shionogi & Co., Ltd.: Employee, Salary. **T. Noshi**, Shionogi & Co., Ltd.: Employee, Salary. **K. Sato**, Shionogi & Co., Ltd.: Employee, Salary. **M. Sakuramoto**, Shionogi & Co., Ltd.: Employee, Salary. **K. Baba**, Shionogi TechnoAdvance Research & Co., Ltd.: Employee, Salary. **T. Shishido**, Shionogi & Co., Ltd.: Employee, Salary. **A. Naito**, Shionogi & Co., Ltd.: Employee, Salary.

1344. Ridinilazole (RDZ) for *Clostridium difficile* Infection (CDI): Impact of Diagnostic Method on Outcomes From a Phase 2 Clinical Trial

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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 2 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 BID or vancomycin (VAN) 125 mg QID 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 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.

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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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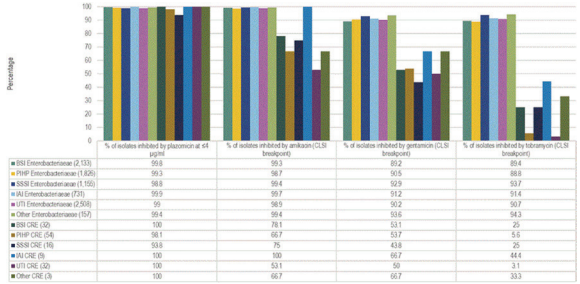
Background. Plazomicin is a next-generation aminoglycoside that is currently under review at the United States Food and Drug Administration for complicated urinary tract infections (cUTIs), including acute pyelonephritis, and bloodstream infections (BSIs) due to certain *Enterobacteriaceae* (ENT) in patients who have limited or no alternative treatment options. We evaluated the 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 hospitalized patients (PIHP; 1,826), skin and skin structure infections (SSSIs; 1,155), intra-abdominal infections (IAIs; 731), UTIs (2,508), and other or unknown infection sites (others; 157) in 71 US hospitals during 2014 to 2017. Isolates were susceptibility (S) tested by reference broth microdilution methods and results were interpreted using CLSI breakpoints.

Results. Plazomicin ($MIC_{50/90}$ 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 S 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 IAI isolates. Gentamicin (89.2–93.6%S) and tobramycin (88.8–94.3%S) 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 tobramycin 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-1598 Is Efficacious in a Murine Model of Invasive Aspergillosis with a PK/PD Expected of a Mold-Active CYP51 Inhibitor

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Background. VT-1598 is a novel fungal CYP51 inhibitor with potent *in vitro* activity against yeast, mold, and endemic pathogenic fungi (Wiederhold, JAC, 2017). Its tetrazole-based rational drug design imparts much greater selectivity vs. human CYPs (Yates, BMCL, 2017), which could reduce human CYP-related side effects and DDIs. We report here VT-1598's *in vivo* activity in an invasive aspergillosis (IA) model.

Methods. MIC was determined as outlined in CLSI M38-A2. Plasma PK was measured after 4 days of oral doses in neutropenic ICR mice without fungal