1514. Delayed Dosing of S-033188, a Novel Inhibitor of Influenza Virus Cap-dependent Endonuclease, Exhibited Significant Reduction of Viral Titer and Mortality in Mice Infected with Influenza A Virus

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Background. Both epidemic and pandemic influenza are major public health concerns, but current standard treatment limits its usage by 48 hours on sets. Furthermore, no antiviral drug has been shown to definitively reduce serious complications, hospitalization, or mortality in a randomized clinical trial. S-033188 is an orally available small molecule inhibitor of cap-dependent endonuclease that is essential for transcription and replication of influenza A and B virus. In this study, we evaluated the efficacy of delayed dosing of S-033188, either as single agent or in combination with oseltamivir, in mice infected with lethal doses of influenza A virus.

Methods. BALB/c mice were intranasally inoculated with A/PR/8/34 strain at 8 × 10⁶ tissue culture infectious dose 50 (TCID₅₀)/mouse. Mice were orally treated with S-033188 (0.5, 1.5, 15 or 50 mg/kg), oseltamivir phosphate (10 or 50 mg/kg), S-033188 (0.5 or 1.5 mg/kg) in combination with oseltamivir phosphate (10 or 50 mg/kg), or vehicle BID for 5 days, beginning at 96 hours after virus infection. Survival and body weight were then monitored through a 28-day period after infection. In addition, viral titer in the lung was determined during the treatment. 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. S-033188 monotherapy (15 or 50 mg/kg, BID for 5 days) completely eliminated mortality in mice, whereas oseltamivir monotherapy (10 or 50 mg/kg, BID for 5 days) exhibited only 10% or 40% survival (Figure 1), respectively. S-033188 monotherapy also significantly reduced viral titer and prevented body weight loss, consistent with the prolonged survival. Furthermore, S-033188 (0.5 or 1.5 mg/kg) in combination with oseltamivir phosphate (10 or 50 mg/kg) exhibited significant improvement of mortality as compared with each oseltamivir phosphate monotherapy.

Conclusion. Delayed dosing of S-033188 exhibited significant efficacy in mice infected with lethal doses of influenza A virus compared with clinically equivalent or supratherapeutic dosing of oseltamivir phosphate. Furthermore, delayed dosing of S-033188 in combination with oseltamivir phosphate exhibited significant improvement of mortality as compared with each oseltamivir phosphate monotherapy.

Disclosures. All authors: No reported disclosures.

1515. Pharmacokinetic-Pharmacodynamic Target Attainment Analysis to Support VL-2397 Dose Selection for a Phase 2 Trial in Patients with Invasive Aspergillosis

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Background. VL-2397 is a novel antifungal agent in clinical development for treatment of invasive aspergillosis (IA). The analysis objectives were to: 1) develop a population PK model using data from a Phase 1 trial in healthy adult volunteers, 2) define the PK-PD driver of efficacy in a mouse model of IA, and 3) conduct PK-PD target attainment analyses to aid in Phase 2 dose selection for patients with IA.

Methods. Data from two studies were used: a dose fractionation study in a mouse model of IA and a Phase 1 study in healthy adult volunteers receiving single- and multiple-dosing of VL-2397. PK-PD analysis was performed using standard PBPK modeling in a mouse model of IA and with the prolonged survival. Furthermore, S-033188 (0.5 or 1.5 mg/kg) in combination with oseltamivir phosphate (10 or 50 mg/kg) exhibited significant improvement of mortality as compared with each oseltamivir phosphate monotherapy.

Conclusion. Delayed dosing of S-033188 exhibited significant efficacy in mice infected with lethal doses of influenza A virus compared with clinically equivalent or supratherapeutic dosing of oseltamivir phosphate. Furthermore, delayed dosing of S-033188 in combination with oseltamivir phosphate exhibited significant improvement of mortality as compared with each oseltamivir phosphate monotherapy.

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1517. ZTI-01 Treatment Improves Survival of Animals Infected with Multidrug Resistant Pseudomonas aeruginosa
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Background. ZTI-01 (fosfomycin, FOS, for injection) is currently under US development to treat complicated urinary tract infections. ZTI-01 is unique compared with other antimicrobials in that it inhibits an early step in cell wall synthesis via an efflux effector (EPF). Our goal was to determine the efficacy of ZTI-01 as a monotherapy or in combination with meropenem against MDR P. aeruginosa in a preclinical model of pulmonary infection.

Methods. 8 week old neutropenic mice were infected with a MDR strain of P. aeruginosa via intubation-mediated intratracheal instillation. 3 hours after instillation, mice received treatment with ZTI-01, meropenem, or ZTI-01 plus meropenem (combination therapy) q8h for 5 days. Mice were monitored every 8 hours for 7 days for development of disease and morbidity and were euthanized. Lungs and spleens were harvested at euthanasia, or at 7 days for survivors, and processed for bacterial enumeration and development of pathology.

Results. Mice were challenged with a lethal dose of P. aeruginosa UNC-12. Mock treated animals succumbed to infection within 36 hours post-infection. Animals that received 6 kg/day for 5 days post-infection. Animals that received 6 kg/day for 5 days post-infection. ZTI-01 showed an increase in the MTD (52 hours) and 25% of the cohort were protected from lethal disease. Combining ZTI-01 with meropenem, resulted in a significant increase in survival (≥75% of cohorts survived infection). Combining ZTI-01 with meropenem, resulted in a significant increase in survival (≥75% of cohorts survived infection). Combining ZTI-01 with meropenem, resulted in a significant increase in survival (≥75% of cohorts survived infection). Combining ZTI-01 with meropenem, resulted in a significant increase in survival (≥75% of cohorts survived infection). Combining ZTI-01 with meropenem, resulted in a significant increase in survival (≥75% of cohorts survived infection). Combining ZTI-01 with meropenem, resulted in a significant increase in survival (≥75% of cohorts survived infection). Combining ZTI-01 with meropenem, resulted in a significant increase in survival (≥75% of cohorts survived infection). Combining ZTI-01 with meropenem, resulted in a significant increase in survival (≥75% of cohorts survived infection). Combining ZTI-01 with meropenem, resulted in a significant increase in survival (≥75% of cohorts survived infection). Combining ZTI-01 with meropenem, resulted in a significant increase in survival (≥75% of cohorts survived infection). Combining ZTI-01 with meropenem, resulted in a significant increase in survival (≥75% of cohorts survived infection). Combining ZTI-01 with meropenem, resulted in a significant increase in survival (≥75% of cohorts survived infection).

Conclusion. Here we report that combination therapy with ZTI-01 and meropenem provides significant improvements in all disease manifestations over treatments with each drug individually in a preclinical model for pulmonary infection with MDR P. aeruginosa. These data strongly support further evaluation of ZTI-01 in combination with other antibiotics as potential therapies against pulmonary infections with MDR bacteria.

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1518. Evaluation of the Efficacy of CD101, a Novel Echinocandin, in the Treatment of Candida auris Infection Using a Murine Model of Disseminated Candidiasis
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Background. The first case of an invasive infection caused by C. auris was reported in July of 2016. Multiple cases have since been reported with high mortality rates due to the multidrug-resistant nature of C. auris. Although C. auris shows increased susceptibility to the echinocandin class of antifungals, the use of these drugs is restricted to multiple IV administrations. CD101 is a novel echinocandin with enhanced stability and pharmacokinetics, allowing for once weekly high dose administration. In this study, we evaluated the efficacy of CD101 in the treatment of disseminated C. auris infection using a murine model of disseminated candidiasis.

Methods. Female 6–8 week old CD-1 mice were immunosuppressed with cyclophosphamide (200 mg/kg) 3 days prior to infection and 150 mg/kg 1 day post-infection. On the day of infection, mice were inoculated with 3 x 10^7 C. auris blastospores via the lateral tail vein. Mice were randomized into 5 groups (n = 5 for colony forming units (CFU) and n = 10 for survival): CD101 20 mg/kg administered by intraperitoneal (IP) injection, fluconazole 20 mg/kg administered per os (PO), amphotericin B 0.3 mg/kg IP, and a vehicle control. Treatments were administered 2 hours post-infection (day 1) and again on day 4 of the study for a total of 2 doses. Mice were monitored daily and a survival curve was generated. CFU groups were sacrificed on day 8 of the study. One kidney was removed from each mouse, homogenized, plated on potato dextrose agar (PDA), and incubated at 35°C for 2 days to determine CFU. The remaining survival mice were monitored until the end of the study (day 14).

Results. CD101 showed an average 3 log reduction in kidney CFU compared with fluconazole, amphotericin B, and vehicle treated groups, which was statistically significant (P = 0.03, 0.03, and 0.04, respectively). At the end of the study, percent survival of mice in CD101, fluconazole, amphotericin B, vehicle, and untreated groups was 80, 0, 30, 20, and 0%, respectively (Figure 1).

Conclusion. Taken together, our findings show that CD101 possesses potent antifungal activity against C. auris infection in a disseminated model of candidiasis. Additionally, treatment with CD101 resulted in a significantly higher overall percent survival. Further investigation of this drug is warranted.

Figure 1. Survival curve of mice in all treatment groups after 14 days.

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