2387. Selecting *Clostridium difficile* Infection (CDI) Outcome Measures Relevant to Public Health Concerns: Experience From a Ridinilazole (RDZ) Phase 2 Trial

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**Session:** 250. Treatment of AMR Infections

**Saturday, October 6, 2018: 12:30 PM**

**Background.** CDC recognizes CDI as an immediate public health threat requiring urgent and aggressive action. Recurrent CDT (cDT) occurs in up to 30% following initial therapy and 65% following a second recurrence. Perturbation by prior antibiotic use diminishes host colonization resistance allowing *C. difficile* to overgrow. Current CDT therapy with vancomycin (VAN) or metronidazole causes further collateral damage to the gut microbiota (GUT) priming patients for cDT. Novel antibacterial agents are needed to tackle this life-threatening infection through (1) effectively treating initial CDT, (2) minimizing rCDI and (3) preventing collateral damage to GUT. A phase 2 trial with RDZ points to optimal selection of endpoints to capture these different benefits.

**Methods.** Randomized double-blind phase 2 study to compare 10 days RDZ 200 mg BID to VAN 125 mg QID. The primary endpoint was SCR defined as cure with no recurrence to 30 days post end of treatment. Fecal samples from all patients were collected at baseline, days 5, 10, 25 and 40 and at recurrence and changes to the microbiome were assessed.

**Results.** While clinical cure rates with RDZ and VAN were similar, RDZ-treated patients had a lower recurrence rate. As a result, in the primary efficacy analysis of 69 patients, 24 of 36 (66.7%) on RDZ vs. 14 of 33 (42.4%) on VAN had SCR (treatment difference 21.1%, 90% CI 3.1–39.1) establishing non-inferiority of RDZ (P = 0.0004) and also showing statistical superiority at the prespecified 10% level. Improved SCR with RDZ was associated with limited GUT impact vs. substantial GUT perturbation seen with VAN both through reduced G. difficle to below the limit of detection (LDT).

**Conclusion.** SCR captures the impact of a therapy on both initial cure of CDI and rCDI. Applicable in randomized studies, it avoids methodological issues associated with recurrence as a separate endpoint. Moreover, by capturing impact on rCDI, it can assess superiority of novel therapies over existing agents with high cure rates. SCR should be a preferred measure of CDI treatment outcomes, and will be the primary endpoint in Phase 3 trials of RDZ. These trials will also evaluate GUT effects, so capturing three important determinants of public health impact: initial CDI, GUT impact and rCDI.

**Disclosures.** R. Vickers, Summit Therapeutics: Employee, Salary and Stock options. S. Chowdhury, Summit Therapeutics Inc.: Employee and Shareholder, Salary and Shareholder.

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2388. Efficacy of Humanized Cefiderocol Exposures Over 72 Hours Against a Diverse Group of Gram-Negative Isolates in the Neutropenic Murine Thigh Infection Model

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**Background.** Previous pharmacodynamic (PD) assessments conducted over a 24 hours dosing period have revealed that cefiderocol humanized exposures produced predictable bacterial kill against MDR Gram-negatives with MICs ≤4 mg/L. Our current aim was to evaluate the sustainability of cefiderocol in vivo activity over 72 hours against MDR pathogens. A. baumannii (AB, n = 4), P. aeruginosa (P, n = 2), K. pneumoniae (KP, n = 4) and E. coli (EC, n = 2) displayed cefiderocol MICs of 0.5–16 mg/L were used in the neutropenic murine thigh model.

**Methods.** Mice received either humanized exposures of cefiderocol equivalent to the clinical dose [2g q8h 3h inf.] or cepofime (PEP) reflective of a 2g q8h 3h inf or iv. Efficacy was determined as the change in log CFU at 24, 48 and 72 hours compared with 0 hours controls. MICs were determined on organisms recovered from both the control and treatment animals.

**Results.** In AB, PSA and Enterobacteriaceae (EB) displaying MICs ≤4 (n = 9), infected mice given cepiderocol showed reductions of 0.5–3 log CFU at 72 hours. The killing profile observed among these 9 isolates followed a similar trend, demonstrating initial reduction in bacterial burden at 24 hours which was sustained at 48 and 72 hours. As expected based on the PD profile of cefiderocol, no killing was seen with the AB isolate (MIC = 16). While cepiderocol exposure resulted in the killing of the PEP-resistant phenotype of the EB, mice receiving PEP displayed growth similar to controls. Infection with the remaining 3 organisms (EC 462, MIC = 1; KP 531, MIC = 4) resulted in a cumulative increase in bacterial burden over the study duration resulting in 1–2 logs growth following cepiderocol exposure over 72 hours. Retest MICs revealed an increase (22 dilutions) compared with control in only 1 animal (1/54 samples or 1.8%) observed in EC 462 at 72 hours. Additional samples from this group (23) remained unchanged throughout the study duration. Importantly, the retest MIC for this sample did not exceed the MIC of 4 mg/L.

**Conclusion.** These data show that for isolates demonstrating killing at 24 hours, cefiderocol efficacy was unchanged over the 72 hours treatment period. Despite the MDR profile of the pathogens tested their phenotypic profile remained largely unchanged and adaptive resistance during therapy was not observed.

**Disclosures.** M. Tsuji, Shionogi & Co., Ltd.: Employee, Salary. Y. Yamano, Shionogi & Co., Ltd.: Employee, Salary.

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2389. Effect of Rezafungin on QT Interval in Healthy Subjects

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**Session:** 250. Treatment of AMR Infections

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**Background.** Rezafungin (RZF), a novel, once-weekly echinocandin for treatment and prophylaxis of invasive fungal infections, successfully met safety and efficacy endpoints in Phase 2 and is advancing to Phase 3 studies. RZF is the first echinocandin to undergo a definitive QT evaluation.

**Methods.** This Phase 1, single-center, randomized, double-blind, comparative study evaluated the effects of RZF on the QTcF (corrected for Fridericia’s formula) interval, heart rate, and other cardiac parameters. There were three dose groups, RZF (600 mg or 1,400 mg IV), IV placebo, and oral moxifloxacin (positive control). The 600 mg (therapeutic) and 1400 mg (supratherapeutic) doses were selected to achieve exposures approximating those after multiple doses of the highest dosage regimen assessed in the Phase 2 study (400 mg once weekly) and exposures ~2.5-fold higher, respectively. The primary endpoint was based on an analysis of change of QTcF from Baseline (ΔΔQTcF) as a function of RZF plasma concentration, to derive the estimated mean placebo-adjusted change of QTcF from Baseline (ΔΔQTcF) for the RZF dose groups at the geometric mean Cmax for each dose level. The outcome was defined by a comparison of the upper bounds of the 2-sided 90% CIs within 10 ms.

**Results.** 60 subjects were enrolled and completed the study. Demographics included 24% females and age (median age 42.2 years), ranging from 20 to 51 years) approximately evenly distributed by treatment. A linear regression model best fit the data, as shown in Figure 1. From this model, the estimated mean ΔΔQTcF at the Cmax for both of the RZF doses had upper bounds <10 ms. The mean ΔΔQTcF at each placebo point by dose, showed all 1-sided 95% upper bounds to be <10 ms, thus supporting the conclusion of the primary analysis. Assay sensitivity was established for moxifloxacin. No clinically significant effects on any of the cardiac parameters tested (RR, QRS, HR) were observed. RZF was generally well tolerated. All adverse events (AEs) were mild to moderate in severity with no discontinuations due to AEs.

**Conclusion.** Rezafungin, in single IV doses up to 1,400 mg, does not prolong the QT interval. This finding supports the clinical safety and continued development of RZF.  

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Background. Avibactam (AV) is a broad-spectrum intravenous non-β-lactam/β-lactamase inhibitor with no reported activity against metallo-β-lactamases such as New Delhi metallo-β-lactamases (NDM). Structural similarities between β-lactamases and bacterial penicillin-binding proteins (PBPs) have led investigators to explore and confirm the hypothesis that AV may interact with PBPs of several Gram-negative and -positive bacterial species. Potential synergy has also been observed between AVI and peptide antibiotics such as polymyxin B. We hypothesized that sub-bacteriostatic concentrations of AVI may bind PBPs to weaken cell wall integrity and enhance lysis by the membrane attack complex of complement and by endogenous cationic antimicrobials. Overall, our biofilm results demonstrated a 43.6% improved eradication using VAN-L of CFZ-L showed a 15.87-fold reduction in comparison to commercial VAN for 494. vs. commercial vancomycin. Also, combination of liposomal VAN MIC in presence of AVI pretreatment dramatically sensitized NDM-KP to neuphil and platelet killing (P < 0.0001 and P < 0.01, respectively) also sensitized NDM-KP to 20% human serum, resulting in 8-log reduction in recoverable NDM-KP CFU within 6 h (P < 0.0001), an effect abrogated by heat treatment to inactivate complement.

Conclusion. AVI demonstrates potent synergy with peptide antibiotics and the innate immune system in vitro. Since AVI alone has shown direct antimicrobial activity and no direct inhibitory effect on metallo-β-lactamases, it is less likely to increase selective pressures toward antibiotic resistance. The use of AVI in combination with other antibiotics against drug-resistant bacterial pathogens warrants further study.

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2392. Fusocymycin Utilization and Outcomes in a Large VA Medical Center Over a Decade Nathan Krautman, MD; Jaela Frederich, PharmD; Brandon DeLuca, PharmD and Infectious Disease Division, University of Florida, Tampa, Florida; Division of Infectious Disease Pharmacy, James A. Haley Veterans’ Hospital, Tampa, Florida, James A. Haley Veterans’ Hospital, Tampa, Florida, Infectious Disease Section, James A. Haley VA Medical Center, Tampa, Florida

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Background. Urinary tract infection (UTI) is one of the most common infections and in 2007 accounted for 10.5 million primary care visits in the US. Developing new treatment options, especially for those with resistance to currently available antibiotics, is crucial. Fusocymycin (FUSO), a lipoglycopeptide, is a novel antibiotic that achieves efficacy against multidrug-resistant and drug-resistant clinical isolates. This study evaluated the utilization and outcomes of fusocymycin at a large VA Medical Center over a decade.

Methods. Antimicrobial stewardship included indication, organism(s), susceptibility, duration of treatment, and clinical success. Treatment success was defined as no representation with UTI symptoms for 30 days.

Results. 117 cases of UTI in which fusocymycin was used were identified with a median patient age of 70 years old and 94% were male. Resistance of 494, 49% complicated cystitis cases, and 64% in catheter associated UTIs. In half of all the cases an ESBL bacillus was isolated and the remaining 49% were successfully treated with fusocymycin. The most common pathogen identified was E. coli 58/118 (49%), followed by Klebsiella 58/118 (21%).

Conclusion. Fusocymycin is an antibiotic recommended for simple cystitis due to its safety profile, less collateral damage (gut flora disturbance), and low resistance as currently known. This study displays the largest ESBL cohort identified in the literature and uniquely used in a predominately male population. These findings suggest that ESBL producing bacteria can be treated successfully with fusocymycin in a male population as well as uncomplicated cystitis. However, caution should be used with catheterized patients as treatment was less effective regardless of isolated bacteria.

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