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Paper Poster Session I

New antibacterial drugs

Relationship between arbekacin exposure and resistance amplification in a hollow-fibre infection model

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Objectives: Arbekacin inhalational solution (ME1100) is in clinical development for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia (HAP and VAP, respectively). Given the high-bacterial density associated with both life-threatening pneumonia and therapy duration, it is especially important to understand the impact of antibiotic exposure and treatment duration on resistance amplification.

Methods: In these studies, a 14 day hollow fiber infection model was utilised to evaluate the relationships between resistance amplification and each of two variables, arbekacin exposure and treatment duration. The range of ME1100 exposures chosen for evaluation were based upon observed concentration versus time profiles for epithelial lining fluid (ELF) collected from healthy adult volunteers, and the treatment duration was based upon the standard of care for the treatment of HAP/VAP. The challenge isolate was an aminoglycoside non-susceptible, beta-lactamase-producing (Kpc-2) *Klebsiella pneumoniae* (arbekacin MIC, 8 mg/L). The challenge inoculum was 1 X 10^8 CFL/mL. Within the hollow fiber infection model, drug concentrations were simulated in a manner that mimicked the concentration-time profile following administration of ME1100 by inhalation administered every 12 hours (Q12). The ME1100 dose ranged from 10 to 450 mg Q12, which for this isolate, equated to an AUC_{0-24}:MIC ratio from 16.4 to 779.9. Negative and positive control arms included no treatment and tobramycin 300 mg Q12, respectively. All studies were conducted in duplicate.

Results: The control regimens behaved as expected with both regimens achieving concentrations greater than 1 X 10 $\log_{10}$ CFU/mL by 24 hours. The targeted arbekacin ELF concentration versus time profile was simulated adequately, as evidenced by the good agreement between observed and targeted concentrations (no bias and r^2 = 0.98). An inverted-U shaped function described the relationship between bacterial drug-resistance amplification and arbekacin exposure (see figure). At low (AUC:MIC ratio = 16.4) and high (AUC:MIC ratio = 779.9) arbekacin exposures, the resistant subpopulation was not amplified. At intermediate arbekacin exposures (AUC:MIC ratio = 63.5 to 627.9), the drug-resistant subpopulation was amplified and became the dominate population by the second day of therapy. Arbekacin AUC:MIC ratios of 562 to 627.9 were associated with an initial 2 to 4 $\log_{10}$ CFU kill of the drug-susceptible subpopulation while an AUC:MIC ratio of 779.9 resulted in the elimination of both the drug-sensitive and –resistant subpopulations from the model system by the second day of therapy. As evidenced by the median MIC value of the 128 mg/L, the drug-resistant bacterial subpopulation represented a true resistant population generated within the system.

Conclusions: These data will help to support the selection of an ME1100 dosing regimen by providing insight into the exposure and duration of therapy that miminises the likelihood of the development of on-therapy drug-resistance amplification.