Fosfomycin (FOS) Plus Meropenem (MER) Suppresses Resistance Emergence Against *P. aeruginosa* (PA) PAO1 in the Hollow Fiber Infection Model (HFIM)

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Background: FOS (ZTI-01, fosfomycin for injection) is an epoxide antibiotic that covalently binds MurA, an earlier step in cell wall synthesis inhibition. FOS has demonstrated synergistic killing with other classes of agents, including carbapenems. PA, among other non-fermentors, are difficult to treat pathogens and combination therapy is important to ensure killing and suppress emergence of resistance. Here, we examine the combination of FOS + MER in the HFIM against PA.

Methods: The experimental design was fully factorial (3 FOS and 3 MER arms and all combinations). Simulated FOS doses were 4, 6 and 8 g 8 hourly (Q8). MER doses were 0.5, 1 and 2 g Q8. The experiment lasted 10 days. Concentrations from the central compartment were measured in all arms by LC/MS/MS. Total bacterial burden and resistant subpopulations for both drugs were measured. Resistance plates were infused with 3XBaseline MIC. Starting inoculum was 6.86 Logs.

Results: FOS/MER MIC's were 64 mg/L (broth) and 0.5 mg/L. Mutational frequency to resistance were -5.27 (FOS) and -6.7 (MER). There were 15 drug-containing arms and a no-treatment control. All drug arms had concentration-time profiles accurately reproduced. All FOS alone arms had rapid resistance emergence. MER 0.5 gm alone had resistance emerge at Day1. FOS 4 g + MER 0.5 g allowed resistance to both agents as did FOS 6g + MER 0.5 g. FOS 6 g + MER 1 g allowed MER resistance, but not FOS. All other combination regimens fully suppressed all resistant mutants. The effect of combination therapy is shown in Figures 1-3. MIC's for MER-resistant isolates were 2 mg/L early and up to 16 mg/L late (day4 and after). FOS-resistant isolates generally had MIC values between 128 and >1024 mg/L.

Conclusion: The combination of FOS + MER is promising for therapy of a wild-type PA. Doses of FOS of 6 and 8 g Q8 tended to suppress resistance emergence to either agent when combined with 1 or 2 g Q8 of MER. We intend on examining the impact of resistance mutations to MER (oprD downregulated and MexAB upregulated) with this combination to identify any potential therapeutic advantage of this combination regimen