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O0581 Efficacy of lysin CF-301 in addition to daptomycin (DAP) or vancomycin (VAN) in a rabbit model of infective endocarditis (IE) due to methicillin-resistant Staphylococcus aureus (MRSA)

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Background: CF-301 is a novel, recombinantly-produced, bacteriophage-derived lysin (cell wall hydrolase) which is in Phase 2 of clinical development for the treatment of S. aureus bacteremia including IE used in addition to standard of care antibiotics. We present data from a rabbit model of MRSA IE which compares treatment with either DAP or VAN alone vs treatment with CF-301 in addition to either DAP or VAN.

Materials/methods: A well described indwelling transcarotid artery-to-left ventricle catheter-induced model of aortic valve IE in rabbits utilizing MRSA strain MW2 was used. Early Controls (EC) animals were sacrificed 24 hr post-infection to determine MRSA burden at the initiation of treatment. Animals were dosed with DAP (4 mg/kg, IV QD x 4 d) or VAN (7.5 mg/kg, IV, BID x 4 d) alone or with the addition of a single-dose of CF-301 (doses ranged from 0.09 mg/kg to 1.4 mg/kg; IV). Vehicle controls and animals dosed with a single dose of CF-301 (0.18 mg/kg to 1.4 mg/kg; IV) were also included. At 24 h after the last dose of DAP or VAN, animals were humanely euthanized and cardiac valve vegetations, kidneys and spleens were sterilely removed and quantitatively cultured.

Results: DAP treatment alone provided ~3 log10 cfu/gm reductions compared with EC (bactericidal effect) while VAN-treated animals had similar burdens compared with EC (bacteriostatic effect). Single dose regimens of CF-301 alone did not reduce MRSA counts. Importantly, a single dose of CF-301 (0.09 mg/kg to 1.4 mg/kg) administered in addition to DAP significantly reduced MRSA counts by 2 - 3 log10 cfu/g tissue respectively ($p<0.05$) and CF-301 (0.18 mg/kg to 1.4 mg/kg) in addition to VAN reduced MRSA counts by 1 - 6 log10 cfu/g tissue respectively ($p<0.05$) in all target tissues compared to antibiotic treatment alone.

Conclusions: In this rigorous model of endovascular infection, the addition of CF-301 to either DAP or VAN, significantly reduced MRSA counts in all target organs. This work further supports the potential for CF-301 to improve clinical outcomes for S. aureus bacteremia and endocarditis compared to treatment with conventional anti-staphylococcal antibiotics, alone, which frequently result in suboptimal outcomes.