Impact of Dose-Administration Strategies of the Antistaphylococcal Lysin Exebacase, (EXE), in addition to Daptomycin (DAP) in an Experimental Infective Endocarditis (IE) Model due to Methicillin-Resistant Staphylococcus aureus (MRSA)

Yan Q. Xiong1,2, Wessam Abdelhady1, Liang Li1, Raymond Schuch2, Cara Cassino3, Dario Lehoux3, and Arnold S. Bayer1,2

1. LA Biomedical Research Institute at Harbor-UCLA, Torrance, CA; 2. Geffen School of Medicine at UCLA, Los Angeles, CA; 3. ContraFect Corporation, Yonkers, NY.

Abstract

Background: MRSA infections, especially involving the endovascular system (e.g., IE), are associated with unacceptably high morbidity and mortality rates. The use of a transgenic/derivative strain, which acts as direct type species, represents a novel approach against the treatment of such pathogens, such as MRSA. The current study examined the efficacy of DAP alone or DAP plus EXE administered on a single day using dosing strategies, in a rabbit model of MRSA IE.

Methods: Aortic valve IE due to MRSA strain MW2 was induced by the IV administration of ~1 × 10^8 cfu in aortic-catheterized rabbits. At 24 h post-infection, animals were randomized into one of five groups (1) controls 2) vehicle controls given twice daily (0.35/1 mg/kg QD alone, 4 mg/kg QD or IV 40), 3) control strains treated with the minimum inhibitory concentration (MIC) of MRSA in experimental IE, 4) EXE, given as an IV dose on the first day of treatment only by 0.35/1 mg/kg IV in 0.2 mL saline at b.w. (0.06/4 mg/kg IV 0.5). All 0.2 mL of the injection were given in a single bolus at time 0. 0.35/1 mg/kg IV 0.23/4 Q8h (0.125/1 mg/kg IV 0.0625). At 24 h, all the last the 12 CFU (0.03 mg/kg) was collected for the CFU tissue model tissues. 2) vehicle controls were treated with gentamicin (0.5 mg/kg QD), and spleen. Data for each organ were calculated as mean ± SD defined by tissue (ID). Results: Treatment with DAP alone caused ~3 log6 cfu, a 4 log6 reduction in CFUs in tissue samples, and at least the lowest dose (0.03 mg/kg), significantly reduced MRSA densities further in all tissues (CFU/DAP alone ~1.05 cfu log6), and vehicle control group log6 cfu). In general, DAP plus EXE given as a single dose tended towards better microbiological efficacy than EXE given at Q3 or Q8h, although this difference was not statistically significant. Conclusion: These results demonstrate that EXE, at a given dose and at different dose-regimens, in addition to sublethal DAP, had significant efficacy in further decreasing MRSA densities in relevant target tissues in the IE model (in DAP-alone and untreated controls). DAP plus a single dose of EXE tended to better efficacy than when it was administered in fractionated-dose strategies.

Results

Bacterial burden in cardiac (heart valve) vegetations following different EXE dosing strategies in addition to DAP.

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Our findings demonstrated that EXE, given at multiple dose strategies and at different dose-regimens, in addition to sublethal DAP, had significant efficacy in further decreasing MRSA densities in relevant target tissues in the IE model (in DAP-alone and untreated controls). DAP plus a single dose of EXE tended to better efficacy than when it was administered in fractionated-dose strategies.

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