Poster abstract submission

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Poster title

Inhaled AJ-099 in treatment of Mycobacteria avium complex and Pseudomonas aeruginosa pulmonary infection

Poster abstract

Purpose: The limitation of effective therapy for chronic Mycobacterium avium complex (MAC) and P. aeruginosa pulmonary infections highlights an urgent need for novel therapeutic strategies. In this study, we investigated AJ-099, a novel thiopeptide derivative with improved solubility and enhance antibacterial potency, in various MAC and P. aeruginosa infection models.
Method: MICs of AJ-099 were assessed in MAC strains using resazurin-based microdilution method and against P. aeruginosa strains using a nutrient-limiting broth following CLSI guidelines. Checkerboard assays were performed to evaluate the interaction between AJ-099 and CLR. Intracellular activity of AJ-099 and CLR against MAC isolates were assessed in BMDMs isolated from BALB/c mice. In vivo activity of AJ-099 was investigated in a mouse MAC lung infection model. At 5 weeks post infection, mice were treated daily for 3 weeks with intranasal AJ-099 (20mg/kg), oral CLR (100mg/kg), oral EMB (100mg/kg), and oral RIF (10mg/kg). AJ-099 in vivo activity (intranasal) against P. aeruginosa was tested in an acute lung infection mouse model.
Results: AJ-099 exhibited potent in vitro activity with MICs ranging from 0.125 to 0.5 μg/ml against MAC strains and macrolide-susceptible and -resistant clinical isolates. The fractional inhibitory concentration indexes (FIC) were <0.5 for all tested strains, confirming a synergistic interaction between AJ-099 and CLR. AJ-099 significantly reduced intracellular MAC infection in murine BMDMs and its synergy with macrolides (CLR) significantly enhanced its intracellular activity. In the chronic mouse model of MAC lung infection, the combination of AJ-099 and CLR outperformed the current standard of care (CLR+EMB+RIF) in reducing bacterial burden and lung inflammation. AJ-099 showed potent activity against standard and clinical isolated of P. aeruginosa (including tobramycin-resistant) with MIC range of 0.5-16 μg/ml. In acute P. aeruginosa lung infection mouse model, single dose of intranasal AJ-099 (8 mg/kg) significantly

reduced lung bacterial burden, outperforming tobramycin.
Conclusions: collectively, these results highlight that AJ-099 is a promising candidate for the treatment of chronic MAC and P. aeruginosa pulmonary infections. Moreover, AJ-099 potent activity against macrolide-resistant MAC may offer an effective treatment option for patients with refractory MAC pulmonary disease.

Research topic

Small molecule therapeutics