Efficacy of BC-3781 in Murine Pneumonia Models

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ABSTRACT

BC-3781 is a novel pleuromutilin antimicrobial agent currently in clinical development for inhalational and/or oral treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP). BC-3781 exhibits excellent antimicrobial activity against a range of relevant bacteria frequently identified in CABP, including Streptococcus pneumoniae and Haemophilus influenzae (HI) and methicillin-resistant Staphylococcus aureus (MRSA). CABP is a leading cause of morbidity and mortality. Current treatments are often unsatisfactory and novel antibiotics with improved efficacy against severe CABP infections are urgently needed.

Methods: Murine pneumonia infections caused by SP, HI and MRSA were established in female BALB/c mice. To establish a reproducible MRSA pneumonia in mice, neutropenia was induced by 2 injections of cyclophosphamide (150 and 100 mg/kg) 4 days before infection. The mice were inoculated by placing 50 µl of 10^7 CFU/ml of a standard strain isolated from a clinical isolate of MRSA into the nares. Inoculum size of SP, HI, and MRSA was 3.0±1×10^6, 2.3±1×10^6 and 1.5±1×10^6 CFU/mouse, respectively. Therapy was initiated 2 h p.i. for HI and MRSA pneumonia with single doses of test drugs and continued for two days with a bid dosing regimen. SP induced pneumonia was treated with a single dose 16 h p.i.; dissection at 24 h p.a. The bacterial burden in pulmonary tissues was determined using standard plating techniques. An Emax dose response model was used to obtain the bactericidal dose levels and the maximum killing potential of all tested compounds. Additionally, plasma and ELF concentrations of BC-3781 were investigated.

RESULTS

BC-3781 showed excellent efficacy against SP, HI and MRSA with a reduction of 3 log10 CFU/Lung being achieved with doses of 150-160 mg/kg BC 3781 s.c.. Compared to the standard of care antibiotics, BC-3781 showed excellent activity in lung infections.

CONCLUSIONS

BC-3781 exhibited excellent efficacy in respiratory tract infections caused by S. pneumoniae, H. influenzae, and MRSA, including CA-MRSA. High exposure levels of BC-3781 in the ELF and its broad-spectrum activity against respiratory pathogens are strongly supporting its potential use in the treatment of bacterial respiratory tract infections.

REFERENCES


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