ABSTRACT

Background: BC-3781 is a pleuromutilin antibiotic that inhibits prokaryotic protein synthesis. It is currently undergoing clinical development for intravenous and oral treatment of acute bacterial skin and skin structure infections (ABSSSI) and is under consideration for study in community-acquired bacterial pneumonia (CABP). BC-3781 has completed a phase 2 study in patients with severe ABSSSI caused by Gram-positive pathogens. Here, we describe investigations into the pharmacodynamics of BC-3781 against clinical isolates of S. pneumoniae in murine thigh and lung infection models.

Methods: Thighs or lungs of neutropenic mice infected with S. pneumoniae (n = 5, MIC 0.005-0.05 µg/ml) were treated twice daily with escalating BC-3781 doses from 2.5 to 320 mg/kg/day. At the end of the treatment period (24 h after start of therapy), mice were sacrificed and number of viable organisms at the infection site was determined by agar plating.

Results: The pharmacodynamics of BC-3781 were similar for all S. pneumoniae strains across all infection models. The mean 24 h AUC/MIC ratio for stasis determined using a nonlinear curve fit function over all six strains was 4.5 to 5.6.

Conclusion: BC-3781 warrants further investigation as a potential treatment for both bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP).

INTRODUCTION

A murine thigh infection model as described by W.A. Craig was employed to investigate the efficacy of BC-3781 against S. pneumoniae isolates covering relevant BC-3781 MIC range from G. Mic to >16 µg/ml. For BC-3781 is 0.25 µg/ml, irrespective of penicillin-susceptibility (n = 1473; SENTIF 2010). Based on the results of the published study by W.A. Craig et al., the study described herein was designed to better support the target attainment required for the dose rationale focusing on community-acquired bacterial pneumonia (CABP). Following these PK/PD studies using the thigh infection model, selected bacterial strains with MIC values used in a murine lung infection model to investigate the pharmacodynamics of BC-3781 among pathogens and infection sites.

METHODS

Animals: Female mice weighing 20-30 gms were allowed to acclimate approximately one week and were utilized throughout the experiments. Prior to the infection, mice were rendered neutropenic.

Bacterial and minimal inhibitory concentrations (MIC): MIC were determined by CLSI broth microdilution method. From the list below, the strains used for PK/PD studies (n = 6) were selected to cover the relevant MIC range for BC-3781 against S. pneumoniae and depending on their virulence and therefore suitability in this model.

RESULTS

At the start of therapy (EC, early control), mice had between 5.51 to 6.32 log10 CFU/thigh. In untreated animals (LC, late control) pathogens reached bacterial burdens of at least 9 log10 CFU/thigh. In three tested isolates (B1383, B1388, B1388) untreated control animals showed mortality within the 24 h exceeding bacterial burden of 9.6 log10 CFU/thigh. The mean 24 h AUC/MIC ratio (CI96%) for stasis determined using a nonlinear curve fit function over all six strains was 6.40 (5.48-7.5) showing a good in vitro intracellular correlation (MIC-static dose relationship) as depicted in Figure 2.

To investigate the efficacy of BC-3781 on site of infection (thigh vs. lung) the endpoints (stasis, 1 log10 kill ED20, ED50 and ED80) were used to compare the two sigmoid response curves (Figure 3).

Five of the strains used in the thigh infection model were used to induce a bronchopneumonia in mice. Except one strain (B1379, excluded from the curve fit analysis) all isolates resulted in a stable lung infection in neutropenic mice. At start of therapy the bacterial burden was between 5.64 and 6.95 log10 CFU/lung. The untreated groups of the five remaining strains reached log10 CFU/lung values of 6.20 to 7.98 within 24 h.

The mean dose-response curve, the corresponding 95% confidence interval (CI95%), and stasis and 1 log10 kill ED24 h (AUC/MIC values following treatment with escalating doses of BC-3781 against the five S. pneumoniae isolates are depicted in Figure 2.

CONCLUSIONS

• BC-3781 showed good activity against S. pneumoniae infections with an enhanced activity in lung tissues, compared to thigh.

• This study indicates that BC-3781 warrants further investigation as a potential treatment for community-acquired bacterial infections (CABP).

• The PK/PD information obtained in this study provides a robust basis for target attainment analysis.

SELECTED REFERENCES


Comparative Pharmacodynamics of BC-3781 in Murine Streptococcus Pneumoniae Thigh and Lung Infection Models

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Figure 1. PKPD relationship of BC-3781 against S. pneumoniae in the murine thigh infection model

Figure 2. PKPD relationship of BC-3781 against S. pneumoniae in the lungs of neutropenic mice

Figure 3. Comparative Emax model fits and CI95% of 24 h AUC/MIC as a function of change in CFU against multiple strains of S. pneumoniae in the thighs and lungs of neutropenic mice