Single- and Multistep Resistance Selection with the Pleuromutilin Antibiotic BC-3781

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ABSTRACT

BC-3781, a novel pleuromutilin antibiotic in clinical development, is characterized by excellent antibiotic activity against pathogens causing acute bacterial skin and skin structure infections and respiratory tract infections such as Staphylococcus aureus, group A and B Streptococcus spp. and Strep throat pneumococcus among others. This study tested the ability to select for resistant mutants of BC-3781.

INTRODUCTION

BC-3781 is a novel systemically available pleuromutilin antibiotic displaying potent antimicrobial properties against staphylococcal species and being suitable for treating community-acquired infections, including those of the respiratory tract. Pleuromutilins inhibit protein biosynthesis by specific interaction with the peptidyl transferase center of the 30S ribosomal subunit. The interaction is unique to this class of antibiotics and characterized by a specific interaction with a unique part of domain V of 23S rRNA, subsequently preventing the correct positioning of the CCA-ends of tRNAs for peptide transfer. Additionally, retapamulin, a topical pleuromutilin, was shown to inhibit the correct positioning of fmet-tRNA binding to the P-site in vitro suggesting its potential for topical application.

RESULTS

The spontaneous mutation frequency in S. aureus (MSSA and MRSA) at BC-3781 concentrations of 2, 4- and 8-fold MIC was with 1.3 x 10^-11 to 1.9 x 10^-10 very low and no stable resistant clones were selected.

Overall, the in vitro resistance development for BC-3781 appeared to be a slow process. Multi-passage selection in the presence of sub-MIC concentrations yielded S. aureus clones with BC-3781 MIC values which rose from 0.06-0.25 µg/ml to 1-4 µg/ml (MIC values after ten drug-free passages 0.2-2 µg/ml) after 22 passages.

The resistance development to BC-3781 in VISA and HISA appeared to be as slow as for the other MSSA, CA-MRSA, and SA-MRSA strains tested.

For S. pneumoniae and S. pyogenes, no stable non-susceptible clones could be generated within 20 and 50 passages, respectively.

All selected clones were passed 10 times in antibiotic-free medium and susceptibility tested against various antibacterial agents. The results for BC-3781 selected clones are shown in Table 1.

Table 1. MIC (µg/ml) of BC-3781 and comparators against S. aureus parent strains and clones selected in presence of BC-3781 (multi-passage) after 10 antibiotic-free subcultures

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Figure 1. Resistance development in S. aureus

The low mutation frequency in combination with a very slow and step-wise resistance development for BC-3781 suggest a potential for a delayed emergence of resistance under selective pressure during clinical exposure. Further monitoring and characterization of non-susceptible isolates in surveillance studies and clinical trials are warranted.

SELECTION REFERENCES


ACKNOWLEDGEMENTS

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