Abstract

Background: BC-7013 [OH-(3-hydroxymethyl-phenylsulfanyl)-acetyl]-mupirocin] is a novel semi-synthetic pleuromutilin derivative that inhibits bacterial ribosome synthesis. BC-7013 is in early-stage clinical development for topical treatment of uncomplicated and severe skin structure infections (SSSI). We assessed BC-7013 in vitro activity against a wide range of clinical isolates.

Methods: BC-7013 and comparators were susceptible (S) tested by the CLSI broth microdilution method against 405 skin, skin structure, and urinary tract infections (205 CoNS (105) and 100 S. aureus, 117 S. pyogenes, and 84 S. pneumoniae) strains. BC-7013 was tested against methicillin-resistant S. aureus (MRSA), CoNS and S. pneumoniae isolates with minimum inhibitory concentration (MIC) values at ≤0.03 ≤0.03–0.12 ≤0.06–1.0 ≤1.0 ≤1.0 µg/ml. MIC values were determined according to the CLSI guidelines (MSSA, 151), (CA-MRSA) (MIC90, 0.03 µg/ml) and penicillin-resistant (PR) S. pneumoniae (MIC90, 0.06 µg/ml). Against S. pyogenes and coagulase-negative staphylococci (CoNS) (MIC90, 0.03-0.25 µg/ml), and beta-hemolytic streptococci (152) including S. pyogenes (50 strains), Group C streptococci (26 strains), and Group G streptococci (26 strains) 404 isolates were very susceptible to the comparator mupirocin. MIC values were determined according to the CLSI guidelines.

Susceptibility test methods: MIC values were determined according to the CLSI guidelines (MSSA, 151) and CA-MRSA (105). Disk diffusion results were evaluated in accordance with CLSI guidelines (111,152). Etest results were determined using the CLSI interpretative criteria for comparator antibiotics (153).

Results

• BC-7013 potency was the same for MSSA and MRSA. The rank order of potency for these BC-7013-resistant isolates (MIC range 0.03 µg/ml) was mupirocin, tetracycline and minocycline (0.12 µg/ml). Neomycin (MIC, ≤1.7 µg/ml) was also active against these isolates. MSSA isolates were much less susceptible to clarithromycin (11.8-fold), erythromycin (20.7-fold) and linezolid (98.2-fold) but fully susceptible to BC-7013. CA-MRSA resistant to linezolid were also fully susceptible to BC-7013 (MIC range 0.03–0.95 µg/ml).

• BC-7013 was also the most potent compound tested against CoNS. Among the oxacillin-resistant isolates, four of the five linezolid-resistant strains had only slightly elevated BC-7013 MIC values (0.03–0.12 µg/ml). 14% of these isolates had a higher minimum inhibitory concentration (MIC >0.12 µg/ml) and higher MIC values were noted among the oxacillin-resistant CoNS isolates, all of them being fully susceptible to BC-7013.

• Against phenylallylpleuromutilin including Z. pyogenes and S. aureus BC-7013 was the most active agent against all tested isolates. Against BC-7013-resistant S. aureus isolates with MIC values >0.03 µg/ml and >0.06 µg/ml the higher MIC values were also noted among the oxacillin-resistant S. aureus isolates, all of them being fully susceptible to BC-7013.

• Against phenylallylpleuromutilin including Z. pyogenes and S. aureus BC-7013 was the most active agent against all tested isolates. Against BC-7013-resistant S. aureus isolates with MIC values >0.03 µg/ml and >0.06 µg/ml the higher MIC values were also noted among the oxacillin-resistant S. aureus isolates, all of them being fully susceptible to BC-7013.

• Against phenylallylpleuromutilin including Z. pyogenes and S. aureus BC-7013 was the most active agent against all tested isolates. Against BC-7013-resistant S. aureus isolates with MIC values >0.03 µg/ml and >0.06 µg/ml the higher MIC values were also noted among the oxacillin-resistant S. aureus isolates, all of them being fully susceptible to BC-7013.

• Against phenylallylpleuromutilin including Z. pyogenes and S. aureus BC-7013 was the most active agent against all tested isolates. Against BC-7013-resistant S. aureus isolates with MIC values >0.03 µg/ml and >0.06 µg/ml the higher MIC values were also noted among the oxacillin-resistant S. aureus isolates, all of them being fully susceptible to BC-7013.

• Overall, BC-7013 has an excellent activity against Gram-positive skin pathogens being clearly superior to that of antibiotics currently in clinical use at an MIC 0.03 µg/ml concentration.

Conclusions: BC-7013 exhibits potent antibacterial activity against the most prevalent Gram-positive pathogens isolated in clinical settings being active against antibiotics currently available and inhibited growth of 100% of S. aureus at an MIC 0.03 µg/ml concentration.

BC-7013 was the most active compound against common Gram-positive bacterial pathogens such as S. aureus, S. pyogenes and S. agalactiae when compared with other topical antibiotics.

BC-7013 also exhibited potent activity against group A (MIC of ≤0.03 µg/ml) and group B (MIC of ≤0.06 µg/ml) streptococci being the most common cause of streptococcal infections.

All bacterial isolates resistant to macrolides, clindamycin, tetracyclines, mupirocin and fusidic acid were fully susceptible to BC-7013. As expected no cross-resistance was noted with these agents.

Conclusion: BC-7013 has an excellent activity against Gram-positive skin pathogens being clearly superior to that of antibiotics currently in clinical use at an MIC 0.03 µg/ml concentration.

Selected References


