Antimicrobial Activity of Lefamulin, an Investigational Pleuromutilin Antibiotic, against Staphylococcus aureus Strains with Decreased Susceptibility to Vancomycin

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ABSTRACT

Background: Lefamulin (BC-3781) is currently in late-stage development for intravenous and oral administration for the treatment of community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections.

Methods: Lefamulin and comparators were tested in vitro against strains of Staphylococcus aureus with decreased vancomycin (VAN) susceptibility, including 10 VAN-resistant (susceptibility ratio >32) S. aureus (VISA) strains. Isolates were tested by reference broth microdilution methods and quality control (QC) strain included S. aureus ATCC 29213, Mu50 and Mu3.

Results: Lefamulin and tigecycline were the most potent compounds tested (MIC50 0.06/0.25 μg/mL for both). The MIC50 and MIC90 ranges of tigecycline were very similar among the resistance subsets tested and the highest lefamulin MIC value was only 0.5 μg/mL (one VISA strain; see Table). Only two isolates (6.7%; one VISA and one MRSE) were oxacillin-resistant. S. aureus was sensitive to daptomycin (MIC50 0.5/2 μg/mL) and cefotaxime (MIC50 0.5/2 μg/mL). Among VISA, 90.0 and 80.0% of strains were S and DAP, respectively; whereas among MRSA, S rates to DAP and CPT were 20.0 and 90.0%, respectively. All VISA strains were S to DAP and CPT.

Conclusions: Lefamulin was highly active against VISA, and may be useful for the treatment of extremely resistant S. aureus isolates affected by the mechanism of VAN susceptibility.

INTRODUCTION

Lefamulin (BC-3781) is a novel antimicrobial agent belonging to the pleuromutilin class. Pleuromutilins inhibit bacterial protein synthesis by selectively binding to the translocase, a bacterial ribosome. Lefamulin is the first representative of pleuromutilin class in clinical development for systemic administration. Phase 1 and 2 trials have demonstrated that IV and oral administration of lefamulin are well tolerated. In a Phase IIb randomized, double-blind, placebo-controlled trial in skin and skin structure infections (ABSSSI) comparing lefamulin 100mg or 155mg IV q12h to vancomycin, lefamulin administered daily for 5-5 days demonstrated comparable efficacy to vancomycin. Currently lefamulin is in late stage development for the treatment of community-acquired bacterial pneumonia (CAPB).

The antibacterial profile of lefamulin covers all relevant background pathogens causally associated with ABSSSI including Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Moraxella catarrhalis, β-hemolytic and viridans group streptococci, as well as organisms causing atypical pneumonia, such as Mycoplasma pulmonis, Legionella pneumophila and Legionella longbe. No cross-resistance has been observed with macrolides, tetracyclines, fluoroquinolones, trimethoprim-sulfamethoxazole, and β-lactam antibiotics. In previous resistance development studies, lefamulin displayed low spontaneous mutation frequencies and the in vitro resistance development by multi-passage at subinhibitory concentrations was found to be very slow. Particularly for vancomycin-resistant clinical isolates of S. aureus (VRSA) and heteroresistant VISA (hVISA) strains, development of resistance to lefamulin appeared to be as slow as for the other S. aureus isolates. The Phase I study (IOIOO115B) was a multicenter, parallel group, open-label Phase I study conducted in collaboration with the National Institutes of Health (NIH), National Institute of General Medical Sciences (NIGMS), and Community-Acquired Methicillin-resistant S. aureus (CA-MRSA) and hospital-acquired (HA) MRSA.

In this study, we evaluated the in vitro activity of lefamulin against S. aureus isolates with reduced susceptibility to glycopeptides, vancomycin-intermediate S. aureus (VISA), vancomycin-resistant S. aureus (VRSA), and VISA, which are related to different mechanisms of resistance such as vanA for VISA and a variety of glucose and galactose, wall autolytic activity and metabolism of the cell that is responsible for vancomycin non-susceptibility of VISA and VRSA.

MATERIALS AND METHODS

Susceptibility Testing Methods: Organisms were tested by broth microdilution and Clinical and Laboratory Standards Institute (CLSI) procedures. Lefamulin was produced by JMI Laboratories (North Liberty, Iowa, USA) with a quality control strain provided by Duan Wicha (JMI Laboratories, Newport News, Virginia, USA). In vitro criteria for VAN susceptibility (MIC ≤0.5 μg/mL) and hVISA resistance (MIC >32 μg/mL) were those of the CLSI M100-S25 (2015) and EUCAST (2015), as published for comparison control agents, and consensus quality control (QC) testing using S. aureus ATCC 29213, Mu3 (ATCC 700698) and Mu50 (ATCC 700699).

Organisms: The collection included 10 VISA strains from the Network on Antimicrobial Resistance in Staphylococcus aureus (NABSSI) MRSA strain repository (all were tested positive for vanA; http://www.nabssi.net), 10 VISA strains and 10 VRSA strains confirmed by population analysis profiling.

RESULTS

• Lefamulin and tigecycline were the most potent compounds tested with MIC50 values of 0.06/0.25 μg/mL (Table 1).

• Lefamulin MIC distributions were very similar among the resistance phenotypes including VISA, VRSA, and hVISA. The highest lefamulin MIC value was 0.5 μg/mL (one VISA strain; Table 1). Of a total of 120 VISA and VRSA strains tested, 100.0% of strains were susceptible to lefamulin MIC of 0.06 μg/mL (Table 1).

• Only two isolates (6.7%) were susceptible to oxacillin, one VISA isolate (MIC = 0.06 μg/mL) and one VRSA isolate (MIC = 0.06 μg/mL) (Table 1). Of a total of 120 VISA and VRSA strains tested, 100.0% of strains were susceptible to lefamulin MIC of 0.06 μg/mL (Table 1).

• Susceptibility rates to daptomycin (MIC50 0.5/2 μg/mL) and cefotaxime (MIC50 0.5/2 μg/mL) were 70.0 and 90.0%, respectively, and all isolates were susceptible to linezolid (MIC50 0.5 μg/mL), daptomycin (MIC50 0.5 μg/mL), and tigecycline (MIC50 0.5 μg/mL) (Table 1).

• Among VISA, 90.0 and 80.0% of strains were susceptible to daptomycin and cefotaxime, respectively; whereas among VISA, susceptibility rates to daptomycin and cefotaxime were 20.0 and 90.0%, respectively. All VISA strains were susceptible to daptomycin and cefotaxime (Table 1).

CONCLUSIONS

• Lefamulin was highly active against VISA, VISA, and VRSA strains.

• Lefamulin’s activity was not affected by the mechanism or degree of resistance to vancomycin.

• These data support the continued clinical development of lefamulin for the treatment of S. aureus infections including CABC and ABSSSI.

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REFERENCES