P0250 In vitro bactericidal activity of lefamulin against Streptococcus pneumoniae isolates

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Background: Targeted antibiotics that are effective against key pathogens causing community-acquired bacterial pneumonia (CABP) are needed. Lefamulin, the first pleuromutilin antibiotic for IV and oral use in humans, is currently in Phase 3 trials for the treatment of CABP. Lefamulin specifically inhibits bacterial protein synthesis by binding to the PTC via 4 H-bonds and other interactions at the A- and P-site resulting in an “induced fit.” Lefamulin is highly active in vitro against pathogens causing CABP including S. pneumoniae (the leading cause of CABP in adults), Haemophilus influenzae, Moraxella catarrhalis, and Staphylococcus aureus, as well as atypical pathogens such as Mycoplasma pneumoniae. This study investigated the bactericidal activity of lefamulin against S. pneumoniae by growth kill-curve determinations.

Materials/methods: Kill-curves were determined for lefamulin at concentrations 1-, 2-, 4-, 8- and 16-fold the MIC and measured by broth microdilution according to Clinical and Laboratory Standards Institute guidelines. Azithromycin served as the control at 1x MIC. S. pneumoniae strains assayed included ATCC49619, ATCC6303, and 8 clinical isolates collected in 2010 showing lefamulin MICs of 0.015–0.12 mg/L. The maximum duration of incubation was 8 hours due to autolysis observed for the growth controls at 24 hours.

Results: Lefamulin displayed potent bactericidal activity against all strains tested and showed dependency on concentration and time of incubation. Living cell counts of all strains were rapidly reduced and reached ≥3 log₁₀ within 8 hours of incubation at 8- to 16-fold MIC corresponding to 0.12–1.92 mg/L. At 4-fold MIC, lefamulin was bactericidal against 9 of 10 strains with a mean kill rate of −3.35 log₁₀ CFU/mL (Figure). The concentration required for bactericidal activity at 8 hours was 0.5 mg/mL, which is significantly lower than plasma and epithelial lining fluid concentrations achieved with the clinical dose of 150 mg IV or 600 mg PO in humans.

Conclusions: Lefamulin demonstrated rapid bactericidal activity against all S. pneumoniae isolates tested. Killing was dependent on the lefamulin concentration and time of incubation. These results correlate with in vivo data supporting AUC:MIC as the primary pharmacokinetic/pharmacodynamic index and support the development of lefamulin for the treatment of CABP.
Bactericidal Activity of Lefamulin at T=8 h
*S. pneumoniae* (n=10)

**Figure. Concentration Response of Lefamulin against S. pneumoniae**