Efficacy of a Next Generation Fluoroketolide, Solithromycin (CEM-101) for Experimental Otitis Media due to either Nontypeable Haemophilus influenzae and Streptococcus pneumoniae

Background

Solithromycin (CEM-101) is a next-generation macrolide, the first fluoroketolide with in-vitro antibacterial activity against multidrug-resistant Streptococcus pneumoniae, including erythromycin resistant (ER) isolates and both β-lactamase positive and negative nontypeable Haemophilus influenzae (NTHi).

Objectives

To evaluate pharmacokinetics, middle ear fluid (MEF) concentrations, and microbiologic efficacy of solithromycin in a chinchilla model of experimental otitis media (EOM) due to isolates of S. pneumoniae or NTHi. To evaluate in vitro activity (MIC and MBC) of solithromycin against respiratory isolates recovered from children in Boston 2010-2014. Differences in time to killing are observed when comparing strains evaluated. To evaluate in vitro activity (Time kill assays) of solithromycin against S. pneumoniae with mefE and ermB mechanisms of macrolide resistance. To evaluate MIC and MBC for solithromycin and other agents against selected NTHi - lactamase positive and negative nontypeable Haemophilus influenzae (NTHi). To evaluate in vitro activity (MIC and MBC) of solithromycin against respiratory isolates of NTHi. To evaluate in vitro activity (Time kill assays) of solithromycin against S. pneumoniae with mefE and ermB mechanisms of macrolide resistance.

Methods and Results

Methods: Pharmacokinetic parameters (Cmax and AUC0-24) were determined in plasma and MEF on days 1 and 3 after administration of 150 mg/kg daily of solithromycin via orogastric tube once daily.

Methods: Isolates of NTHi or S. pneumoniae with specified antimicrobial susceptibility patterns were inoculated directly into the bullae of adult chinchillas and MEF quantitative cultures were performed to determine solithromycin efficacy in the treatment of EOM.

Conclusions

• In chinchilla model of EOM, solithromycin at 150 mg/kg/day for 3 days sterilized MEF in >85% of animals challenged with NTHi isolates with MIC ≤0.12 μg/ml by day 3 of treatment; no relapse was observed after completion of 3 days of therapy.

• In vitro studies of respiratory isolates of NTHi demonstrate MIC of 2 μg/ml.

• For EOM due to S. pneumoniae; solithromycin at 150 mg/kg/day sterilized EOM due to S. pneumoniae with MIC ≤0.125 μg/ml.

• Differences in time to killing are observed when comparing S. pneumoniae with mefE resistance to S. pneumoniae with mefE resistance; strains with mefE resistance demonstrated delayed killing compared to those with ermB consistent with the reduced sterilization observed in our animal model.

• In chinchillas, solithromycin undergoes greater metabolism than in humans therefore higher mg/kg doses are needed to achieve equivalent drug exposure.

• Solithromycin efficacy against both NTHi and S. pneumoniae in our model suggests further evaluation for treatment of respiratory tract infection, including acute otitis media, is warranted.