Efficacy of Solithromycin (CEM-101) for Experimental Otitis Media (EOM) due to Nontypable Haemophilus influenza (NTHi) and Streptococcus pneumonia (SP)

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Background:

Solithromycin (SOLI, CEM-101) is a next-generation fluoroketolide with in-vitro antibacterial activity against multidrug-resistant SP, including erythromycin A-resistant (ER) isolates and NTHi.

Objectives

The objective was to evaluate pharmacokinetics, middle ear fluid (MEF) concentrations, and microbiologic efficacy of SOLI in a chinchilla model of EOM due to isolates of SP or NTHi.

Methods

Serum pharmacokinetic parameters (C_{max} and AUC_{0-24}) and middle ear fluid concentrations were determined after administration of one of three doses of SOLI (25, 50 and 150 mg/kg) via gavage. Isolates with selected antimicrobial susceptibility patterns were inoculated directly into the middle ear. Serum and middle ear fluid (MEF) were collected for SOLI PK studies and MEF cultures performed to determine efficacy.

Results:

SOLI administered at 150 mg/kg/day resulted in PK parameters (C_{max} of 0.917 µg/ml and AUC_{0-24} of 11.29 µg.h/ml) that best matched single dose human studies. Further PK during challenge studies demonstrated peak serum and MEF concentrations of ~2 µg/ml on the third day of dosing. For NTHi EOM, 3 isolates with MIC/ MBC spectrum [BCH1, 0.5/1; 1247, 2/2; and 1213, 4/4 µg/ml] were selected for study. On day 3 of therapy, only 1 of 7 animals challenged with BCH1 and 1 of 8 with NTHi 1247 remained MEF positive. 48 hours after completing 3 days of SOLI all BCH1 challenged middle ears were sterile; 1/8 animals challenged with 1247 remained MEF positive. Six (86%) animals challenged with NTHi 1213 remained culture positive both on day 3 of therapy and 48 hours after completion For SP EOM, 3 isolates were studied. For SP SP331; erythromycin (E) susceptible with MIC 0.125 µg/ml, 7 of 7 SOLI treated animals sterilized the middle ear fluid by day 3. For two (E) resistant isolates of SP, CP-645 (type 14; MIC 0.06 µg/ml), MLS_B phenotype and PCR positive for erm B and CP-712 (type 19F; MIC 0.5 µg/ml), M phenotype and PCR positive for mef E we observed discordant results. For CP-645, the MEF of 6 of 6 SOLI treated animals sterilized by day 3. For SP 712, only 60% (2 of 5) SOLI treated animals had sterile MEF on day 3.

Conclusions:

In chinchilla model of EOM, SOLI at 150 mg/kg/daily for 3 days sterilized MEF in animals challenged with NTHi isolates with MIC$\leq$ 2 µg/ml. For EOM due to SP; SOLI at 150 mg/kg/daily sterilized EOM due to SP with MIC$\leq$0.125 µg/ml. SOLI sterilized only 50% of EOM due to SP with MIC 0.5 µg/ml.