

## ECCMID 2015

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**Title:** Efficacy of Solithromycin against *Enterococcus faecalis* in a Neutropenic Mouse Thigh Abscess Model

**Objectives:** Solithromycin (SOLI) is a fluoroketolide that is in Phase 3 clinical development for community acquired bacterial pneumonia. It has demonstrated a wider spectrum than the older macrolides with activity against most macrolide-resistant strains. SOLI is unlike older macrolides in that it has in vitro activity against *Enterococcus faecalis* and *E. faecium*. In this study we determined its in vivo activity in a neutropenic mouse thigh abscess model.

**Methods:** Female CD-1 mice (18 to 20 gms) were made neutropenic with two doses of cyclophosphamide (150 and 100 mg/kg) on days -4 and -1 prior to infection. On day 0 mice were infected with *E. faecalis* A2302971 via intramuscular administration of 0.1 mL under light anesthesia. Treatment was administered 1.5 hours post infection for 3 days. SOLI was administered either orally or intravenously (IV), BID or once a day. Linezolid (LZ) administered orally at 10 mg/kg BID was the comparator. At 1.5 and 74 hours post infection mice were euthanized and the infected thighs were removed, weighed, homogenized, serially diluted, and plated on bacterial growth media. The plates were incubated overnight at 37°C in 5% CO<sub>2</sub>. CFU per gram of thigh was calculated by enumerating the plated colonies then adjusting for serial dilutions and the weight of the thigh. The MICs of SOLI and LZ for this strain were 1 mcg/mL and 2 mcg/mL, respectively.

**Results:** SOLI when administered IV demonstrated an efficacious response with a 2.07 log<sub>10</sub> CFU change at the 12.5 mg/kg BID dose and 3.85 log<sub>10</sub> CFU reduction at the 25 mg/kg BID dose compared to the vehicle control (T=74 hours). Linezolid demonstrated a 3.50 log<sub>10</sub> CFU reduction. When administered orally, SOLI demonstrated an efficacious response compared to the vehicle control (T=74 hours). SOLI treated twice daily at 50 mg/kg BID demonstrated a 2.99 log<sub>10</sub> CFU reduction, whereas SOLI treated once daily at 100 mg/kg produced a 2.77 log<sub>10</sub> CFU reduction. Linezolid demonstrated a 3.37 log<sub>10</sub> CFU reduction when treated twice daily at 10 mg/kg.

**Conclusions:** SOLI demonstrated activity against *E. faecalis* in the abscess model in neutropenic mice. SOLI, especially when administered by the IV route, demonstrated comparable activity to linezolid, an antibiotic that is approved for use against this pathogen. The side chain of SOLI undergoes greater metabolism in mice than in humans when administered orally, but not IV. Therefore, this study was conducted using both oral and IV routes of administration in mice. Unlike older macrolides, SOLI has activity against *E. faecalis*, a difficult-to-treat pathogen.

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Key Words: Solithromycin, *E. faecalis*, Abscess model