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J. S. Jensen¹, P. Fernandes², M. Unemo³;

¹Statens Serum Inst., Copenhagen, DENMARK, ²Cempra Inc., Chapel Hill, NC,

³WHO Collaborating Ctr. for Gonorrhoea and other STIs, Örebro Univ. Hosp., Örebro, SWEDEN

Background: The cure-rate after treatment of *Mycoplasma genitalium* with a 1 g single dose azithromycin has been decreasing from nearly 90% to 40% in recent trials. Moxifloxacin is currently the only second-line drug, but multi-drug resistant strains of *M. genitalium* are emerging. In this study, we evaluated the *in-vitro* activity of the new fluoroketolide solithromycin. We characterised the genetic basis for solithromycin resistance in the few resistant strains.

Methods: A collection of 40 *M. genitalium* isolates were tested; 15 strains were macrolide resistant with MIC >16 mg/L for erythromycin. MICs of solithromycin, azithromycin, erythromycin, doxycycline, ciprofloxacin, and moxifloxacin were determined by adding a defined inoculum into a Vero-cell culture with dilutions of antibiotic. Growth of *M. genitalium* was determined by quantitative PCR and MIC was defined as the minimal concentration causing 99% inhibition of growth.

Results: The MIC range of solithromycin was ≤ 0.001 - 16 mg/L (MIC₉₀: 2 mg/L). Macrolide susceptible strains had MIC₉₀: ≤ 0.001 mg/L whereas macrolide resistant strains had MIC₉₀: 4 mg/L. Eight strains with a 23S rRNA gene A2059G mutation (*E. coli* numbering) had a lower median MIC than that of five strains with A2058G mutations ($p=0.02$) and of two strains with the rare A2058C mutation ($p=0.04$). Solithromycin activity was significantly superior to azithromycin ($p<0.0001$). All strains, regardless of macrolide susceptibility carried a 23S rRNA gene with a C in position 752 in contrast to the A752 in susceptible *E. coli* strains. No other mutations were found in the region. In the 2609 position known to interact with position 752, all strains were T2609 similar to susceptible *E. coli*. No mutations in ribosomal proteins L4 and L22 explaining the elevated MICs could be identified

Conclusions: The activity of solithromycin was superior to that of azithromycin, erythromycin, quinolones and doxycycline. Mutations in position 2058 lead to higher solithromycin MICs than those in position 2059 and were the only changes explaining solithromycin resistance. In Denmark, 40% of *M. genitalium* strains are azithromycin resistant but our findings suggests that 85% of the resistant strains or 94% of all *M. genitalium* strains would be susceptible to solithromycin.