In Vitro Activity of the Combination of Solithromycin and Cephalosporins against *Neisseria gonorrhoeae*

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Background: *Neisseria gonorrhoeae* has sequentially developed resistance to all antimicrobials previously recommended as first-line treatment for gonorrhea. The Centers for Disease Control and Prevention (CDC) recommends intramuscular ceftriaxone (CRO) plus azithromycin (AZI) as the only remaining recommended treatment for gonorrhea. New treatment regimens are urgently needed to ensure gonorrhea remains a treatable infection. Solithromycin (SOL), a 4th generation macrolide, was demonstrated to have 100% efficacy in a Phase 2 study in treating uncomplicated gonorrhea. The objective of this study was to investigate *in vitro* effects of a combination of SOL and 3rd generation cephalosporins (cefixime [CFX] or CRO).

Methods: Sixty-four *N. gonorrhoeae* strains with varying antimicrobial susceptibility profiles, comprising 56 clinical strains and 8 World Health Organization (WHO) reference strains were tested. MICs were determined by agar dilution method according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. *In vitro* synergy testing was performed using agar dilution method, and the fractional inhibitory concentration index (FICI) for antimicrobial combination was calculated. We interpreted the FICI using the following criteria: Synergy (FICI ≤0.5), indifference (FICI >0.5 to 4.0), and antagonism (FICI >4.0).

Results: SOL MICs (0.004–32 µg/mL) were much lower than AZI MICs (≤0.03–>512 µg/mL) for the 64 strains. The MIC50 and MIC90 values of AZI were 1 and 16 µg/mL, respectively, while those of SOL were 0.125 and 0.25 µg/mL, respectively. CFX MICs (0.002–1 µg/mL) were mostly ≥1 log2 dilution higher than CRO MICs (≤0.001–0.25 µg/mL). The combination of CFX or CRO with SOL for all 64 strains produced the same median FICI of 1.00 (indifference) (CFX + SOL, SD 0.172, CRO + SOL, SD 0.172); and a similar range of FICIs (CFX + SOL, FICI 0.56–1.50; CRO + SOL, FICI of 0.63–1.50). No antagonism was observed for any of the 64 strains.

Conclusion: The combination of SOL and CFX or CRO produced no antagonism. These findings suggest that SOL, which is being evaluated as monotherapy for gonorrhea, could be incorporated into a dual therapy regimen with third generation cephalosporins.

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