Solithromycin (CEM-101) displays high antimicrobial activity against intra and extracellular Neisseria gonorrhoeae

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Abstract
The goal of this study was to evaluate in vitro activity of solithromycin, a fluoroquinolone, against clinical gonococcal isolates, and to test its intracellular activity against isolates highly resistant to macrolides.

Clinical isolates (N=196) collected from 2008 to 2011 at the Public Health Ontario Laboratories, Toronto, Canada, were used, including isolates previously characterized and a collection of strains with different levels of resistance to azithromycin (MIC2). MICs of solithromycin and A2 were compared by agar dilution method, and the role of pH in these determinations was defined (pH range, 5.6 to 7.6). Monolayers of HeLa epithelial cells infected with gonococci expressing different A2 susceptibility profiles were treated with solithromycin to test its intracellular activity by bacterial counting after 3 and 20 hours of exposure.

Strains. 196 N. gonorrhoeae clinical isolates, collected from 2008 to 2011, were studied, including 67 isolates previously studied, as well as strains susceptible, with reduced susceptibility, and resistance to azithromycin. Macrolide resistant isolates included in this study were genetically characterized as described. Determination of MICs. The MICs of solithromycin and azithromycin were determined using the CLSI agar dilution method. N. gonorrhoeae strains W32C1/3 (intermediate resistance to azithromycin, 0.5 mg/L) and P (resistant to azithromycin, 2 mg/L) were included as quality control strains.

Materials & Methods
Intracellular activity of solithromycin. Five N. gonorrhoeae clinical strains demonstrating susceptibility (NS640) and resistance (NS644, NS646 and NS726) to azithromycin were used for all experiments. HeLa cells were infected at an MOI of 20. After internalization of the bacteria, cells were exposed to solithromycin at 4K, 1K and 1/4 the MIC of each strain. At indicated times, cells were harvested and bacterial viability was determined.

Introduction
Resistance to extended-spectrum cephalosporins (ESC, ceftaxime and ceftazidime) has recently emerged in Asia and Europe, threatening their use as first-choice antimicrobials.10-11 Solithromycin (CEM-101), a novel fluoroquinolone, has reported high potency against gram-positive and negative pathogens.12-13 Chabane et al. have reported that the in vitro activity of solithromycin against clinical gonococcal isolates and international reference strains, including strains with various high-level antimicrobial resistance, was superior to that of azithromycin and many other antimicrobials.14 Solithromycin has demonstrated to have good oral bioavailability with good tissue and intracellular distribution. It has been safe and well tolerated.15 It has progressed through Phase 2 in trials in CABP and has shown good efficacy, safety and tolerability in these studies.16

Objectives
To evaluate the in vitro potency of solithromycin against N. gonorrhoeae.
To investigate the pH stability and the intracellular activity of solithromycin using a tissue culture model.

Results
Table 1. Susceptibility of N. gonorrhoeae isolates to solithromycin and azithromycin in pH-adjusted GC agar

<table>
<thead>
<tr>
<th>Strain</th>
<th>MIC (mg/L)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEM-101</td>
<td>0.0625</td>
<td>1</td>
</tr>
<tr>
<td>CEM-101</td>
<td>0.0625</td>
<td>0.1</td>
</tr>
<tr>
<td>CEM-101</td>
<td>0.0625</td>
<td>0.05</td>
</tr>
<tr>
<td>CEM-101</td>
<td>0.0625</td>
<td>0.01</td>
</tr>
<tr>
<td>CEM-101</td>
<td>0.0625</td>
<td>0.0025</td>
</tr>
</tbody>
</table>

Conclusions
Solithromycin demonstrated efficient intracellular activity against strains with different levels of susceptibility to azithromycin, including isolates highly resistant to the macrolides. The intracellular activity of solithromycin combined with the low MICs of this agent for N. gonorrhoeae make it a potential option for treatment of gonococcal infections, especially when multidrug-resistant strains are now clinically emerging.

Additional in vitro studies combined with clinical trials need to be performed to demonstrate that this drug can be used for this indication.

REFERENCES