**In Vitro** Activity of the New Fluoroketolide Solithromycin (CEM-101) against a Large Collection of Clinical *Neisseria gonorrhoeae* Isolates and International Reference Strains, Including Those with High-Level Antimicrobial Resistance: Potential Treatment Option for Gonorrhea?

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Gonorrhea may become untreatable, and new treatment options are essential. We investigated the *in vitro* activity of the first fluoroketolide, solithromycin. Clinical *Neisseria gonorrhoeae* isolates and reference strains (*n* = 246), including the two extensively drug-resistant strains H041 and F89 and additional isolates with clinical cephalosporin resistance and multidrug resistance, were examined. The activity of solithromycin was mainly superior to that of other antimicrobials (*n* = 10) currently or previously recommended for gonorrhea treatment. Solithromycin might be an effective treatment option for gonorrhea.

*Neisseria gonorrhoeae* resistance to antimicrobials previously recommended for treatment of gonorrhea is common worldwide. Currently, first-line treatment is the extended-spectrum cephalosporins (ESCs) cefixime and ceftriaxone. ESC susceptibility has, however, decreased rapidly during the last decade (1, 4, 8, 12, 15, 16, 18, 19, 28, 29, 36). Treatment failures with cefixime have been verified in Japan (9, 40) and Europe (13, 33–35). With ceftriaxone, three cases of failure treating pharyngeal gonorrhoea were confirmed in Australia (30) and Sweden (32); however, the ceftriaxone MICs of these isolates were only slightly elevated. It is of grave concern that in the past year the two first extensively drug-resistant (XDR) gonococcal strains, H041 (21) and F89 (33), which are highly resistant to all ESCs and related to ESC treatment failure, were described from Japan and France, respectively. If these strains spread internationally, gonorrhea may become untreatable (21, 29, 33), and it is imperative to promptly develop new treatment options. Recently, the first fluoroketolide, solithromycin (CEM-101) (Fig. 1), entered clinical development. Solithromycin has shown advantages over other macrolides in activity against many bacterial pathogens (2, 10, 17, 20, 23, 24, 37, 38). The chemical alterations of solithromycin appear to account for more-potent antimicrobial activity but also greater metabolic stability and tolerability. In a previous study (23), solithromycin was more potent than azithromycin against a small collection of gonococcal isolates. However, only 34 gonococcal isolates were tested, none of which displayed high-level azithromycin resistance.

We investigated the *in vitro* activity of solithromycin (CEM-101) against clinical gonococcal isolates and international reference strains (*n* = 246), including strains with high-level resistance to various antimicrobials, relative to the activities of other antimicrobials (*n* = 10) currently or previously recommended for gonorrhoea treatment and the activity of telithromycin (the first developed ketolide).

In total, 100 consecutive clinical Swedish gonococcal isolates obtained in 2011 and clinical isolates (*n* = 118) and reference strains (*n* = 28) selected for their resistance phenotype (cultured from 1991 to 2011) were examined. The collection contained geographically (mainly global representativeness), temporally, and genetically diverse isolates, including the XDR gonococcal strains H041 (21) and F89 (33), with clinical high-level resistance to all ESCs, additional isolates that showed ESC resistance and that were related to ESC treatment failure (*n* = 4) (32, 34, 35), and isolates with other types of multidrug resistance (MDR) (Table 1). The WHO 2008 *N. gonorrhoeae* reference strains (*n* = 8) (31) were used for quality control. The MICs of solithromycin, azithromycin, erythromycin, and telithromycin were determined by the agar dilution technique recommended by the Clinical and Laboratory Standards Institute (CLSI) (7). The MICs of cefixime, ceftriaxone, ampicillin, ciprofloxacin, spectinomycin, and tetracycline were determined using the Etest (AB bioMérieux, Solna, Sweden) (Table 1).

The MIC<sub>50</sub>, MIC<sub>90</sub>, and MIC range of solithromycin were 0.125 µg/ml, 0.25 µg/ml, and 0.001 to 32 µg/ml, respectively. The MIC<sub>50</sub> and MIC<sub>90</sub> of the other macrolides (azithromycin, telithromycin, and erythromycin) were substantially higher (Table 1). Only 2.4% (*n* = 6) of the isolates had an MIC of >0.5 µg/ml for solithromycin (1, 4, 4, 16, and 32 µg/ml) (Fig. 2), and the corresponding MICs of azithromycin (telithromycin) for these isolates were 2 (0.5), 4 (4), 8 (4), >256 (>256), >256 (>256), and >256 (>256) µg/ml, respectively. For comparison, 11.0% (*n* = 27), 37.8% (*n* = 93), and 94.3% (*n* = 232) of all isolates had an MIC of >0.5 µg/ml for telithromycin, azithromycin, and erythromycin, respectively. For all isolates with *in vitro* and clinical resistance to cefixime (*n* = 16; 6.5%) and ceftriaxone (*n* = 3; 1.2%), the MIC<sub>50</sub>, MIC<sub>90</sub>, and MIC range of solithromycin were 0.125 µg/ml, 0.25 µg/ml, and 0.064 to 0.25 µg/ml, respectively. None of the isolates resistant to ampicillin, gentamicin (*n* = 2;...
MIC = 96 μg/ml), or spectinomycin had an MIC of >0.5 μg/ml for solithromycin. Only two (0.8%) isolates and three (1.2%) isolates resistant to ciprofloxacin and tetracycline, respectively, displayed an MIC of >0.5 μg/ml for solithromycin.

Herein, we report the first comprehensive evaluation of the activity of the new fluoroketolide solithromycin (CEM-101), relative to the activities of other antimicrobials currently or previously recommended for gonorrhea treatment, against a large collection of N. gonorrhoeae clinical isolates and international reference strains with various clinical XDR and MDR. The activity of solithromycin was superior to that of azithromycin, other macrolides, and many other antimicrobials currently or previously recommended for gonorrhea treatment. Importantly, solithromycin was highly active against gonococcal strains with resistance to ESCs. Consequently, solithromycin may be an effective option for treatment of gonorrhoea and especially ESC-resistant cases and for use in antimicrobial combination therapy, particularly because solithromycin also appears to be effective against Chlamydia trachomatis (24) and Mycoplasma genitalium (37), which are commonly present as concomitant sexually transmitted infections. Combination therapy has been introduced in the United States (39) and the United Kingdom (3), where administration of ESC (ceftriaxone or cefixime [in the United States, if ceftriaxone is not an option]) plus azithromycin (in the United States, azithromycin or doxycycline) is recommended for treatment of uncomplicated anogenital gonorrhea cases. The superior activity of solithromycin combined with the identification of gonococcal isolates with very high-level resistance (>256 μg/ml) to azithromycin in many countries (5, 6, 11, 14, 22, 26) and the gastrointestinal side effects of azithromycin indicates that solithromycin might be a more appropriate choice than azithromycin for treatment of gonorrhoea. Solithromycin also has very high activity against intracellular bacteria (17), due to high intracellular accumulation, and is well distributed in extracellular tissues. Finally, solithromycin is well absorbed orally, with high plasma levels and tissue distribution, has appropriate choice than azithromycin for treatment of gonorrhoea.

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>MIC (μg/ml)</th>
<th>50%</th>
<th>90%</th>
<th>Resistance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solithromycin</td>
<td>0.001–32</td>
<td>0.125</td>
<td>0.25</td>
<td>ND</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>0.001–&gt;256</td>
<td>0.5</td>
<td>8</td>
<td>37.8</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>0.001–&gt;256</td>
<td>0.25</td>
<td>1</td>
<td>ND</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>0.064–&gt;2f</td>
<td>&gt;2f</td>
<td>&gt;2f</td>
<td>94.3</td>
</tr>
<tr>
<td>Cefixime</td>
<td>&lt;0.016–8</td>
<td>0.032</td>
<td>0.25</td>
<td>6.5</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>&lt;0.002–4</td>
<td>0.016</td>
<td>0.125</td>
<td>1.2</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>&lt;0.016–&gt;256</td>
<td>1</td>
<td>16</td>
<td>24.4</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.002–&gt;32</td>
<td>4</td>
<td>&gt;32</td>
<td>64.2</td>
</tr>
<tr>
<td>Spectinomycin</td>
<td>4–&gt;1,024</td>
<td>16</td>
<td>16</td>
<td>2.0</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>0.125–256</td>
<td>4</td>
<td>64</td>
<td>69.5</td>
</tr>
</tbody>
</table>

*MIC determination using the agar dilution technique was performed for solithromycin, azithromycin, telithromycin, and erythromycin according to the instructions from the Clinical and Laboratory Standards Institute (CLSI) (7). MIC determination with Etest was performed for the remaining antimicrobials according to the instructions from the manufacturer (AB bioMérieux, Solna, Sweden). MIC results from Etest were rounded up to whole MIC dilutions.

*ND, not determined. Where available, resistance criteria from the CLSI (7) were used. Where interpretative criteria from CLSI were not available, such as for azithromycin and ampicillin, resistance criteria from the European Committee on Antimicrobial Susceptibility Testing (EUCAST; http://eucast.org/ [accessed 30 January 2012]) were applied. For erythromycin, the resistance breakpoint determined by the EUCAST (http://eucast.org/ [accessed 30 January 2012]) for azithromycin was used. No resistance breakpoints for cefixime and ceftriaxone have yet been determined by the CLSI (7), and accordingly, the “resistance” category in the table may include isolates with intermediate susceptibility as well as resistance.

*MICs at which 50% of the isolates are inhibited.

*MICs at which 90% of the isolates are inhibited.

*Also known as CEM-101.

*The collection included 93 gonococcal isolates (37.8%; 1.2% with a MIC of >256 μg/ml and 10.2% with a MIC of ≥8 μg/ml) with azithromycin resistance, caused by many different resistance mechanisms.

*Most isolates were resistant to erythromycin and had high MICs; accordingly, these were not titrated to endpoint MIC.

*MIC of >32 μg/ml for 28%.

*MIC of >1,024 μg/ml for 1.6%.
FIG 2 MIC (µg/ml) distribution of solithromycin, azithromycin, and telithromycin for 246 clinical N. gonorrhoeae isolates and international reference strains.

a long postantimicrobial effect and anti-inflammatory properties, and appears safe and well tolerated at high doses (1.6-g single dose) (27).

In conclusion, solithromycin had superior activity against gonococcal isolates compared to activities of azithromycin, other macrolides, and many other classes of antimicrobials. Solithromycin might be an effective option for gonorrhea treatment, as single-antimicrobial treatment especially for ESC-resistant cases and in antimicrobial combination therapy. However, it will be crucial to perform additional in vitro studies investigating solithromycin susceptibility and also the selection and mechanisms of solithromycin resistance in N. gonorrhoeae (and other pathogens and commensals exposed to the drug during gonorrhoea treatment). Furthermore, additional studies regarding pharmacokinetics/pharmacodynamics of solithromycin (for single-drug treatment and combination therapy, including measurement of concentration and activity of drug in urethral secretions) and clinical trials (measuring parameters such as efficacy, cost, and toxicity) are crucial.

ACKNOWLEDGMENTS

The present work was funded by the Örebro County Council Research Committee, the Foundation for Medical Research at Örebro University Hospital, Sweden, and Cempra Pharmaceuticals, Inc., Chapel Hill, NC. The work was performed at the WHO Collaborating Centre for Gonorrhoea and other STIs, National Reference Laboratory for Pathogenic Neisseria, Department of Laboratory Medicine, Microbiology, Örebro University Hospital, Örebro, Sweden.

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