CEM-101, a Novel Fluoroketolide: Activity against Recent (2008) Isolates of Multidrug-resistant S. pneumoniae

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Abstract
Background: CEM-101 is a new fluoroketolide with potent activity against Gram-positive pathogens and key respiratory tract organisms (S. pneumoniae, H. influenzae and M. catarrhalis). We report CEM-101 potency against MDR-19A, S. pneumoniae, Enterobacteriaceae and community-acquired respiratory tract infections (CA-RTI). Routine in vitro studies indicate activity comparable to or superior to cethromycin, ceftaroline, erythromycin, azithromycin and clarithromycin, as well as active against inducible clindamycin and macrolide-lincosamide-streptogramin B (MLSB) resistance mutations. CEM-101 was utilized to interpret MIC results by clinical breakpoints, and multiresistant pneumococci were grouped by susceptible/deleterious mutations.

Methods: 7,377 S. pneumoniae strains were collected in 2008 from medical centers in the United States, Europe, and Latin America. A central monitoring laboratory susceptibility program (3) tested each isolate against > 25 antimicrobials by CLSI (M100-S19) and MDR patterns. MDR patterns were defined by resistance (R) to penicillin (PEN), erythromycin (ERY), tetracycline (TET), and trimethoprim/sulfamethoxazole (T/S). A ketolide, telithromycin (TEL), and levofloxacin (LEV) were also tested.

Results: The CEM-101 inhibition at ≤ 0.015 µg/ml was compared in a SPN population with the following R patterns MIC (µg/ml): 0 ≤ ≤ 1 ≤ 2 ≤ 4 ≤ > 4. A wide variety of comparison agents were utilized including cephalosporins, macrolides, cefuroxime, penicillin, tetracycline, vancomycin, erythromycin, ciprofloxacin (screen for possible initial gyrA mutations), clindamycin (79.6% susceptible), oral cephalosporins, and a ketolide, telithromycin (TEL, 99.9% susceptible). All QC results were within published limits.

Conclusions: CEM-101 MIC results among various MDR-SPN patterns (Table 2) were noted for pneumococci having isolated resistance to penicillin (MIC90, 0.12 µg/ml), resistance to levofloxacin and other fluoroquinolones (MIC90, 0.12 µg/ml), and MIC at > 4 µg/ml, indicating proportion of possible single (95.2-99.8% susceptible) or multiple drug resistant pneumococci among six of the eight analyzed resistance patterns (Table 2).

Material and Methods
Organisms tested. All organisms tested in this 2008 S. pneumoniae surveillance program were collected from patients in the United States, Europe and Latin America (LA). These pathogens were isolated from CA-RTI in the most common species (Streptococcus pneumoniae, H. influenzae and S. aureus). The distribution of pneumococcal only and the geographic contributions were: S. pneumoniae (7,377); geography: USA (766), Europe (828), and LA (145). Efficacy against drug-resistant strains was assessed against community-acquired bacterial pneumonia.

References

1 Comparative activity of CEM-101 and 12 other antimicrobials tested against > 1,700 S. pneumoniae isolates from an antimicrobial surveillance program in Europe and the Americas.
3 JMI Laboratories.

Table 2. Activity of CEM-101 and Telithromycin tested against various pneumococcal resistance patterns.

<table>
<thead>
<tr>
<th>MIC µg/ml</th>
<th>CEM-101 Telithromycin</th>
<th>CEM-101 MIC90</th>
<th>Telithromycin MIC90</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 0.015</td>
<td>0.015; 0.25</td>
<td>0.015</td>
<td>0.12</td>
</tr>
<tr>
<td>≥ 0.015</td>
<td>0.03 0.25</td>
<td>0.03</td>
<td>0.12</td>
</tr>
<tr>
<td>≥ 0.015</td>
<td>0.12 0.25</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>≥ 0.015</td>
<td>0.25 4.0</td>
<td>0.25</td>
<td>0.12</td>
</tr>
<tr>
<td>≥ 0.015</td>
<td>4.0 32</td>
<td>4.0</td>
<td>0.12</td>
</tr>
<tr>
<td>≥ 0.015</td>
<td>&gt; 32 1024</td>
<td>&gt; 32</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Conclusions: CEM-101 was the most active agent against all S. pneumoniae at ≤ 0.015 µg/ml, which is comparable to telithromycin and cethromycin. Efficacy against clinical isolates of S. pneumoniae was assessed against community-acquired bacterial pneumonia.

Susceptibility testing. All susceptibility tests were performed by CLSI broth microdilution methods (M7-T7, 2009) by a central monitoring CLSI/GLP-compliant laboratory (JMI Laboratories North Liberty, Iowa, USA). Tested using cation-adjusted Mueller-Hinton broth (2.5 ± 0.1% NaCl). CEM-101 MIC was utilized to interpret MIC results by clinical breakpoints, and multiresistant pneumococci were grouped by susceptible/deleterious mutations.

CEM-101 is a novel fluoroketolide selected as a candidate for clinical material by its potent activity against community-acquired respiratory tract infections (CA-RTI). In vitro studies indicate comparable activity against cethromycin, ceftaroline, erythromycin, azithromycin and clarithromycin, as well as active against inducible clindamycin and documented resistance to macrolides or lincosamides (MIC90uzzars). CEM-101 exhibits slight greater activity against Gram-positive pathogens, but the drug also possesses measurable potencies against fastidious Gram-negative pathogens (Escherichia coli, Shigella spp., Haemophilus influenzae, Neisseria meningitidis, Salmonella spp., group B Streptococci, and Trimethoprim/Sulfamethoxazole (T/S)). All QC results were within published limits.

A wide variety of comparison agents were utilized including cephems, cefuroxime, penicillin, tetracycline, vancomycin, clindamycin, erythromycin, azithromycin, and clarithromycin. Telithromycin is active against various sexually transmitted diseases (STD).