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 Gram-negative species (*H. influenzae* and *M. catarrhalis*). We report CEM-101 potencies tested against *S. pneumoniae* (SPN) isolates focusing on various multidrug-resistant (MDR) subsets.

Methods: 1,737 SPN strains were collected in 2008 from medical centers in the USA, Europe, and Latin America. A central monitoring laboratory susceptibility (S) tested each isolate against > 25 antimicrobials by CLSI (M07-A8, M100-S19) methods. MDR patterns were defined by resistance (R) to penicillin (PEN), erythromycin (ERY), clindamycin (CLI), tetracycline (TET), and TMP/SMX (T/S). A ketolide, telithromycin (TEL), and levofloxacin (LEV) were also tested.

Results: The CEM-101 inhibition at ≤ 1 µg/ml was compared in a SPN population with the following R-rates (%): PEN (21.4), ERY (36.3), CLI (20.0), TET (25.8), T/S (21.7) and LEV (1.1). CEM-101 ($MIC_{50/90}$, 0.015/0.25 µg/ml) showed increased MIC_{50} and MIC_{90} results for MDR patterns that included ERY and CLI (0.25/0.5 µg/ml, respectively). TEL (S rate, 99.9%) MIC results were slightly higher than CEM-101 (100.0%S). Amoxicillin/clavulanate non-S rate was 12.8%, but 86.9% among isolates R to all 5 listed drugs (Table). Ceftriaxone non-S rate was an alarming 8.6% (8.2% for cefepime). CEM-101 was effective (MIC, ≤ 1 µg/ml) versus all LEV-R isolates and those strains with ciprofloxacin MIC values at ≥ 4 µg/ml (QRDR mutants).

R patterns						No.	MIC (µg/ml)		
PEN	ERY	CLI	TET	T/S	LEV	tested	50%	90%	% ≤ 1µg/ml
X						371	0.06	0.25	100.0
X	X					307	0.06	0.5	100.0
X	X	X				184	0.25	0.5	100.0
X	X	X	X			165	0.25	0.5	100.0
X	X	X	X	X		145	0.06	0.25	100.0
					X	21	0.015	0.12	100.0
All strains						1737	0.015	0.25	100.0

Conclusions: CEM-101 was the most active agent against all SPN at ≤ 1 µg/ml, like glycopeptides and linezolid. MDR isolates with ERY-CLI R showed elevated, yet S-level, CEM-101 MIC values. CEM-101 potency against current SPN indicates potential use against community-acquired bacterial pneumonia.

Introduction

CEM-101 is a novel fluoroketolide selected as a candidate for parenteral and oral therapy of community-acquired respiratory tract infections (CA-RTI). Initial in vitro studies indicated activity comparable or superior to telithromycin, cethromycin, erythromycin, azithromycin and clarithromycin, as well as activity against Gram-positive isolates having documented resistance to macrolides or lincosamides (MLS_B agents). CEM-101 activity is directed against Gram-positive pathogens, but the drug also possesses measurable potencies against fastidious Gram-negative species (*Haemophilus, Moraxella*), some *Enterobacteriaceae* (*Salmonella*, *Shigella*), atypical respiratory tract species, *Helicobacter pylori*, telithromycin-resistant β-haemolytic streptococci, and pathogens causing various sexually transmitted diseases (STD).

In this presentation, we report CEM-101 activity measured by reference Clinical and Laboratory Standards Institute (CLSI) methods when testing *Streptococcus pneumoniae* isolates from CA-RTI. Emerging resistant subsets and various patterns of MLS_B-ketolide resistance found among these tested organisms collected from an international surveillance program in 2008 are analyzed for comparative ketolide activity.

Materials and Methods

Organisms tested. All organisms tested in this 2008 CEM-101 surveillance program were collected from patients in the United States (USA), Europe and Latin America (LA). These pathogenic strains were isolated from CA-RTI e.g. the most common species (*Streptococcus pneumoniae, H. influenzae* and *S. aureus*). The distribution of pneumococci only and the geographic contributions were:

- *S. pneumoniae* (1,737)
  - geography: USA (766), Europe (828), and LA (145)
  - penicillin-susceptible, ≤0.06 µg/ml (1,115)
  - penicillin-intermediate, 0.12-1 µg/ml (251)
  - penicillin-resistant, ≥2 µg/ml (371)

Susceptibility testing. All susceptibility tests were performed by CLSI broth microdilution methods (M07-A8, 2009) by a central monitoring CLIA/GLP-compliant laboratory (JMI Laboratories, North Liberty, Iowa, USA). Testing used cation-adjusted Mueller-Hinton broth (CA-MHB) with 2.5-5% lysed horse blood. CLSI M100-S19 was utilized to interpret MIC results by categories and for quality control (QC) ranges where criteria were available. Tested QC strains included: *S. aureus* ATCC 29213 and *S. pneumoniae* ATCC 49619. All QC results were within published limits.

A wide variety of comparison agents were utilized including: amoxicillin/clavulanate, ceftriaxone, cefuroxime, penicillin, tetracycline, vancomycin, azithromycin, cefepime, clarithromycin, clindamycin, erythromycin, ciprofloxacin (screen for possible initial gyrase target mutations, MIC at ≥4 µg/ml), levofloxacin, moxifloxacin, linezolid, imipenem, telithromycin and trimethoprim/sulfamethoxazole (TMP/SMX), all assessed by the broth microdilution method only (Table 1).

Analysis. Resistance profiles using six antimicrobial classes (penicillins, macrolides, clindamycin, tetracycline, TMP/SMX and fluoroquinolones) were assessed, and the influence on CEM-101 and telithromycin MIC/potency is tabulated in Table 2.

Results

- CEM-101 exhibited slightly greater activity against *S. pneumoniae* isolates when directly compared to another ketolide (telithromycin), with all CEM-101 MIC values at ≤1 µg/ml. Telithromycin non-susceptible strains (MIC, ≥2 µg/ml) were detected (0.1%; see Figure 1 and Table 1).

- CEM-101 was quite potent ($MIC_{50/90}$, 0.015/0.25 µg/ml) and showed a wider spectrum (100.0% at ≤1 µg/ml) compared to macrolides (63.3-63.6% susceptible), clindamycin (79.6% susceptible), oral or parenteral cephalosporins (74.6-91.8% susceptible), penicillins (64.2-87.2% susceptible), tetracycline (73.2% susceptible), and TMP/SMX (**only** 66.8% susceptible). As with CEM-101, all tested *S. pneumoniae* strains were inhibited at CLSI susceptible breakpoints for linezolid and vancomycin.

- Lowest CEM-101 MIC results among various MDR patterns (Table 2) were noted for pneumococci having isolated resistance to penicillins (MIC_{90}, 0.25 µg/ml), resistance to all five drug classes (MIC_{90}, 0.25 µg/ml), resistance to levofloxacin and other fluoroquinolones (MIC_{90}, 0.12 µg/ml), and with resistance to macrolides only (MIC_{90}, 0.25 µg/ml). Telithromycin non-susceptible isolates were noted (95.2-99.8% susceptible) for *S. pneumoniae* among six of the eight analyzed resistance patterns (Table 2).

Table 1. Comparative activity of CEM-101 and 19 other antimicrobials tested against 1,737 *S. pneumoniae* isolates from a pre-marketing surveillance program in Europe and the Americas.

Antimicrobial agent	MIC (µg/ml)				% by category[a]
	Mode	50%	90%	Range	Susceptible/resistant
CEM-101	0.015	0.015	0.25	≤0.008-1	100.0/0.0
Telithromycin	≤0.06	≤0.06	0.25	≤0.06-2	99.9/0.0
Azithromycin	≤0.5	≤0.5	>4	≤0.5->4	63.3/36.2
Clarithromycin	≤0.25	≤0.25	>32	≤0.25->32	63.6/35.6
Erythromycin	≤0.06	≤0.06	>8	≤0.06->8	63.4/36.3
Clindamycin	≤0.25	≤0.25	>2	≤0.25->2	79.6/20.0
Penicillin	≤0.03	≤0.03	4	≤0.03->4	64.2/21.4
Amox/clav[b]	≤1	≤1	4	≤1-16	87.2/8.6
Ceftriaxone	≤0.25	≤0.25	1	≤0.25-8	91.4/1.4
Cefepime	≤0.12	≤0.12	1	≤0.12-4	91.8/0.6
Cefuroxime	≤1	≤1	8	≤1-8	74.6/25.4
Imipenem	≤0.12	≤0.12	0.5	≤0.12-2	77.5/6.8
Ciprofloxacin[c]	2	2	2	≤0.03->4	-/(7.0)[b]
Levofloxacin	1	1	2	≤0.5->4	98.8/1.1
Moxifloxacin	≤0.5	≤0.5	≤0.5	≤0.5-4	98.9/0.6
Tetracycline	≤2	≤2	>8	≤2->8	73.2/25.8
Tigecycline[d]	≤0.03	≤0.03	0.12	≤0.03-0.25	89.5/-
TMP/SMX[e]	≤0.5	≤0.5	>2	≤0.5->2	66.8/21.7
Linezolid	1	1	1	≤0.12-2	100.0/-
Vancomycin	≤1	≤1	≤1	≤1	100.0/-

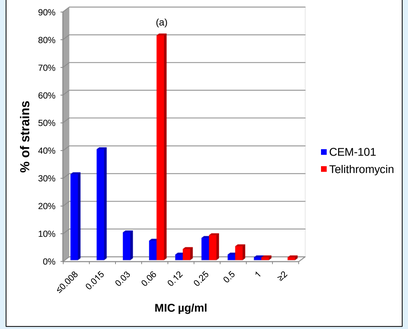
a. Interpretive criteria of the CLSI (M100-S19, 2009).
b. Amox/clav = amoxicillin/clavulanate.
c. Percentage of values at ≥4 µg/ml, indicating proportion of possible single-step target mutations.
d. Interpretive criteria from the USA-FDA product labeling.
e. TMP/SMX = trimethoprim/sulfamethoxazole.

Table 2. Activity of CEM-101 and telithromycin tested against *S. pneumoniae* isolates having various antimicrobial resistance patterns.

Resistance patterns[a]							MIC (µg/ml)					
							CEM-101			Telithromycin		
PEN	ERY	CLI	TET	T/S	LEV	No. tested	50%	90%	% ≤1 µg/ml	50%	90%	% ≤1 µg/ml
X[b]						371	0.06	0.25	100.0	0.12	0.5	99.7
X[c]						13	0.12	0.25	100.0	0.25	0.5	100.0
X	X					307	0.06	0.5	100.0	0.25	0.5	99.7
X	X	X				184	0.25	0.5	100.0	0.25	0.5	99.5
X	X	X	X			165	0.25	0.5	100.0	0.25	0.5	100.0
X	X	X	X	X		145	0.06	0.25	100.0	0.25	0.5	100.0
					X	21	0.015	0.12	100.0	≤0.06	0.25	95.2
	X	X				347	0.03	0.5	100.0	≤0.06	0.5	99.7
	X					631	0.06	0.25	100.0	0.12	0.5	99.8

a. PEN = penicillin (MIC, ≥2 µg/ml or >4 µg/ml; see footnotes b and c), ERY=erythromycin (MIC, ≥1 µg/ml), CLI = clindamycin (MIC, ≥1 µg/ml), TET = tetracycline (MIC, ≥8 µg/ml), T/S or TMP/SMX = trimethoprim/sulfamethoxazole, and LEV = levofloxacin (MIC, ≥4 µg/ml).
b. MIC at ≥2 µg/ml per penicillin V interpretive criteria (CLSI, 2009).
c. MIC at > 4 µg/ml per high-dose parenteral regimens (CLSI, 2009).

Figure 1. MIC distribution for CEM-101 and telithromycin tested against over 1,700 *S. pneumoniae* isolates from an international surveillance program (2008). Telithromycin was not tested at concentrations below 0.06 µg/ml.[a]



Conclusions

- CEM-101, a novel fluoroketolide, provides complete coverage (100.0% inhibition at ≤1 µg/ml; telithromycin breakpoint) against contemporary (2008) isolates of *S. pneumoniae* from patients on three continents.
- CEM-101 potency and overall spectrum was slightly superior to telithromycin and was at least four-fold more active than linezolid or vancomycin.
- CEM-101 appears to be a viable candidate for the therapy of CA-RTI (CABP) caused by *S. pneumoniae* that may be resistant to other antimicrobial classes such as macrolides, lincosamides, β-lactams (penicillin, cephalosporins, carbapenems) and even so-called "respiratory fluoroquinolones" (levofloxacin and moxifloxacin). Further clinical development seems warranted via parenteral and/or oral delivery.

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