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Antimicrobial Characterization of CEM-101: Activity Against 331 Respiratory Tract Pathogens Including Multidrug-Resistant Pneumococcal Serogroup 19A Isolates

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ABSTRACT

Background: CEM-101 (CEM), a novel macrolide-ketolide, has potent activity against bacterial pathogens susceptible (S) or resistant (R) to other MLS_B-ketolide agents. Projected for use in therapy of respiratory tract infections (RTI), CEM was tested against contemporary RTI isolates.

Methods: A worldwide sample of organisms included *S. pneumoniae* (SPN; 168, 59.3% erythromycin [ERY]-R and 18 multidrug-resistant [MDR] -19A strains), *M. catarrhalis* (MCAT; 21, 11 ß-lactamase[+]), *H. influenzae* (HI; 100, 48 ß-lactamase[+]), *H. parainfluenzae* and *H. haemolyticus* (12) and *L. pneumophila* (LPN; 30). All S tests were by reference CLSI methods (M7-A7, M100-S18) and breakpoints per CLSI (2008) for comparison agents such as azithromycin (AZ), clarithromycin (CLA), ERY, telithromycin (TEL), clindamycin (CC), Synercid® (SYN), levofloxacin (LEV), linezolid, and rifampin (RIF).

Results: SPN were very S to CEM (MIC_{90}, 0.25 µg/ml; highest MIC at 0.5 µg/ml) and CEM was 2- and 8-fold more potent than TEL and CC, respectively. MDR-19A replacement strains were also CEM-S (MIC_{90}, 0.5 µg/ml). LPN were most S to CEM with all MIC values at ≤0.015 µg/ml (TEL MIC_{90}, 0.03 µg/ml). *Haemophilus* RTI pathogens were less CEM-S (MIC_{90}, CEM/TEL): HI (2/4 µg/ml) and others (2/4 µg/ml) with no variations for ß-lactamase (+) strains. MCAT CEM-101 MICs were all at ≤0.5 µg/ml, equal to TEL.

	CEM MIC (µg/ml)			TEL MIC (µg/ml)		
Organism (no.)	50%	90%	Range	50%	90%	Range
SPN (150)	0.015	0.25	≤0.008-0.5	0.03	0.5	≤0.008-1
MDR-19A (18)	0.25	0.5	0.06-0.5	0.5	1	0.12-1
MCAT (21)	0.12	0.12	≤0.008-0.5	0.12	0.25	≤0.015-0.5
HI (100)	1	2	0.12-4	2	4	0.25-16
Other Haemophilus (12)	2	2	0.12-2	2	4	0.25-8
LPN (30)	≤0.015	≤0.015	≤0.015	0.03[a]	0.03[a]	0.03-0.06[a]

a. RIF results, not TEL.

Conclusions: CEM exhibited the widest spectrum/activity against RTI pathogens among the tested MLS_B-ketolide agents (AZ, CLA, ERY, TEL, CC, SYN) and comparable to LEV. All CEM MIC values were at ≤0.5 and ≤4 µg/ml for SPN or LPN and HI, respectively; expanded studies should be considered.

INTRODUCTION

CEM-101 (formerly OP-1068) is a novel macrolide-ketolide class agent selected as a candidate for oral therapy of community-acquired respiratory tract (CA-RTI) and uncomplicated skin and skin structure infections (uSSSI). Screening in vitro studies indicated a potency comparable or superior to telithromycin, erythromycin, azithromycin and clarithromycin, as well as activity against Gram-positive isolates having documented resistances to macrolides or lincosamides. CEM-101 activity is generally focused against Gram-positive pathogens, but also possesses measurable potencies versus fastidious Gram-negative species (*Haemophilus, Moraxella*), some Enterobacteriaceae (*Salmonella, Shigella*) and pathogens causing various sexual transmitted diseases (STD).

In this presentation, we report CEM-101 activity measured by reference Clinical and Laboratory Standards Institute (CLSI) methods when testing organisms associated with CA-RTI (streptococci, *Haemophilus* spp., *Moraxella catarrhalis, Legionella pneumophila*), emerging resistant subsets (serogroup 19A *S. pneumoniae*) and various patterns of MLS_B-ketolide resistance among the tested streptococci.

MATERIALS AND METHODS

Organism collection: All organisms tested were collected from patients in the USA and European medical centers from 2005 to present. Sources of recovered isolates included bloodstream, skin and soft tissue and respiratory tract infections. Unusual/rare organism species and phenotypes required use of strains isolated prior to 2005 or from other geographic areas. See list of tested strains below:

- Streptococci (319)
  - *S. pneumoniae* (150 wild type)
  - *S. pneumoniae* (18 serogroup 19A, USA only)
  - ß-haemolytic species (100, five groups)
  - viridans group (51, five species)
- *Haemophilus* species (111)
  - *H. influenzae* (100, 48 ß-lactamase producers)
  - *H. parainfluenzae* (11)
- *M. catarrhalis* (21, 11 ß-lactamase producers)
- *L. pneumophila* (30)

Susceptibility testing: Ninety-six well frozen-form assay panels were produced by JMI Laboratories and consisted of three media types: cation-adjusted Mueller-Hinton broth, cation-adjusted Mueller-Hinton broth with 2.5-5% lysed horse blood (for testing streptococci) and Haemophilus Test Medium (HTM). CLSI broth microdilution and agar dilution methods per M7-A7 [2006] were used. Quality control (QC) ranges and interpretive criteria for comparator compounds were those published in CLSI M100-S18 [2008]. Tested QC strains included *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *S. pneumoniae* ATCC 49619 and *H. influenzae* ATCC 49247 and 49766. All QC results were within published limits.

Agar dilution methods were used for *L. pneumophila* tested on BCYE agar. Comparison agents were tested by Etest, also on BCYE media.

A wide variety of comparison agents were utilized including: amoxicillin/clavulanate (amox/clav), azithromycin, cefdinir, clarithromycin, clindamycin, erythromycin, levofloxacin, linezolid, quinupristin/dalfopristin (Q/D), telithromycin and trimethoprim/sulfamethoxazole (TMP/SMX) all assessed by broth microdilution; and ciprofloxacin, tetracycline, ampicillin and rifampin were additionally tested on agar.

RESULTS

- *S. pneumoniae* were very susceptible to CEM-101 with a MIC_{90} of only 0.25 µg/ml. This documented potency (Table 1) was two-fold greater than telithromycin and eight-fold superior to linezolid (MIC_{90}, 2 µg/ml).
- ß-haemolytic streptococci were also susceptible to CEM-101 (MIC_{90}, 0.03 µg/ml) with this new agent showing a four-fold advantage (MIC_{90}, 0.12 µg/ml; 100.0% susceptibility) over telithromycin. Five groups of ß-haemolytic strains were tested and all strains showed a monomodal MIC (0.015 µg/ml) distribution and the highest CEM-101 MIC was only 0.12 µg/ml (Table 1).
- CEM-101, like telithromycin, was active against all macrolide- and clindamycin-resistant viridans group streptococci (five species groups; 51 strains). All CEM-101 MIC values were at ≤0.12 µg/ml, four-fold more potent than telithromycin and 64-fold more active than erythromycin.
- All CEM-101 MIC results for *Haemophilus* spp. had a narrow range of only 0.5-4 µg/ml (exception two strains of 0.12 µg/ml that did not exhibit an efflux pump). The overall MIC_{90} for strains in this genus was 2 µg/ml, equal to azithromycin and two-fold more active than telithromycin. The various species (*H. influenzae, H. parainfluenzae*) and ß-lactamase production did not significantly alter CEM-101 activity (MIC_{90}, 2 µg/ml; Table 1).
- Among the MLS_B agents, the rank order of potency (MIC_{90} in µg/ml) against *M. catarrhalis* was: azithromycin (0.06) > CEM-101 = clarithromycin (0.12) > erythromycin = telithromycin (0.25) > Q/D (0.5) > clindamycin (2; see Table 1). The ß-lactamase activity had no significant effect on the CEM-101 MIC_{90} values (0.12 µg/ml).
- CEM-101 (MIC_{90}, ≤0.015 µg/ml) was the most active agent tested against *Legionella* spp. (Table 1), superior to other macrolides, levofloxacin and rifampin. Note that the charcoal content of the test media can interfere with the reference MIC testing of this species.
- Where on-scale MIC results were available, CEM-101 (MIC_{90}, 0.015 µg/ml) was two- and eight-fold more active than clarithromycin or telithromycin and azithromycin, respectively, against streptococci susceptible to erythromycin (Table 2). For streptococci non-susceptible to erythromycin, CEM-101 had an elevated MIC (MIC_{90}, 0.25 µg/ml); however, CEM-101 was at least two-fold more active than either telithromycin or clindamycin. When tested against erythromycin- and clindamycin-non-susceptible streptococci, all but one strain remained susceptible to telithromycin, but all were inhibited by CEM-101 at ≤0.5 µg/ml.
- Eighteen serogroup 19A strains exhibited high levels of non-susceptibility to: macrolides (100.0%), clindamycin (83.3%), penicillin (83.3%), amox/clav (88.9%), ceftriaxone (33.3%), tetracyclines (83.3% and TMP/SMX (100.0%). Few therapeutic options remain with only telithromycin (MIC_{90}, 1 µg/ml; 100.0% susceptible), Q/D (MIC_{90}, 1 µg/ml; 100.0% susceptible) and fluoroquinolones (MIC_{90}, 1 µg/ml; 100.0% susceptible) having usable potencies (Table 3). CEM-101 showed a potency two-fold greater than telithromycin.
- Table 4 shows excellent CEM-101 potency against streptococci (all MICs, ≤0.5 µg/ml) and moderate activity against Gram-negative CA-RTI pathogens (MICs, ≤0.008-4 µg/ml).

Table 1. Activity of CEM-101 tested against streptococci, *H. influenzae, M. catarrhalis* and *Legionella spp.* by reference MIC methods (463 strains).

Organism (no. tested)/ resistance subset	Antimicrobial Agents	MIC (µg/ml) 50%	90%	Range	% by category[f] Susceptible/Resistant
S. pneumoniae (150)	CEM-101	0.015	0.25	≤0.008-0.5	-/-
	Telithromycin	0.03	0.5	≤0.008-1	100.0 / 0.0
	Erythromycin	>4	>4	≤0.12->4	40.7 / 59.3
	Clarithromycin	>16	>16	≤0.008->16	40.7 / 59.3
	Azithromycin	>16	>16	0.03->16	40.7 / 59.3
	Clindamycin	0.25	>4	≤0.12->4	50.0 / 50.0
	Q/D	0.5	1	0.25-2	99.3 / 0.0
	Amox/clav	2	>8	≤0.25->8	66.7 / 26.7
	Cefdinir	4	>4	≤0.12->4	39.3 / 59.3
	Levofloxacin	1	1	0.5->4	94.0 / 6.0
	TMP/SMX	4	>4	≤0.25->4	38.0 / 55.3
	Linezolid	1	2	0.5-2	100.0 / -
ß-haemolytic streptococci (100)[b]	CEM-101	0.015	0.03	≤0.008-.0.12	-/-
	Telithromycin	0.03	0.12	≤0.008-2	-/-
	Erythromycin	≤0.12	>4	≤0.12->4	74.0 / 25.0
	Clarithromycin	0.03	>16	≤0.008->16	75.0 / 25.0
	Azithromycin	0.12	>16	0.015->16	74.0 / 26.0
	Clindamycin	≤0.12	>4	≤0.12->4	85.0 / 13.0
	Q/D	0.5	0.5	0.25-1	100.0 / 0.0
	Levofloxacin	0.5	1	0.25->4	98.0 / 2.0
	Linezolid	1	1	0.5-2	100.0 / -
Viridans gr. streptococci (51)[c]	CEM-101	≤0.008	0.06	≤0.008-0.12	-/-
	Telithromycin	0.015	0.25	≤0.008-0.5	-/-
	Erythromycin	≤0.12	4	≤0.12->4	56.9 / 43.1
	Clarithromycin	0.03	2	≤0.008-8	56.9 / 33.3
	Azithromycin	0.12	4	≤0.008-16	56.9 / 39.2
	Clindamycin	≤0.12	≤0.12	≤0.12->4	98.0 / 2.0
	Q/D	0.5	1	≤0.12-2	96.1 / 0.0
	Levofloxacin	1	2	0.25->4	92.2 / 7.8
	Linezolid	1	2	0.25-2	100.0 / -
H. influenzae					
ß -lactamase-positive (48)	CEM-101	1	2	0.12-4	-/-
	Telithromycin	2	4	0.25-8	97.9 / 0.0
	Clarithromycin	8	8	0.25-16	91.7 / 0.0
	Azithromycin	1	2	0.25-4	100.0 / -
	Amox/clav	1	2	0.5-4	100.0 / 0.0
	Cefdinir	0.25	0.5	≤0.12-1	100.0 / -
	Levofloxacin	≤0.12	≤0.12	≤0.12-0.25	100.0 / -
	TMP/ SMX	≤0.25	>4	≤0.25->4	68.8 / 31.3
ß-lactamase-negative (52)	CEM-101	1	2	0.5-4	-/-
	Telithromycin	2	4	1-16	96.2 / 1.9
	Clarithromycin	8	8	4-16	90.4 / 0.0
	Azithromycin	2	2	0.5-4	100.0 / -
	Amox/clav	0.5	1	≤0.25-4	100.0 / 0.0
	Cefdinir	0.25	0.5	≤0.12-2	96.2 / -
	Levofloxacin	≤0.12	≤0.12	≤0.12-0.25	100.0 / -
	TMP/SMX	≤0.25	>4	≤0.25->4	80.8 / 13.5
H. parainfluenzae (11)	CEM-101	2	2	1-2	-/-
	Telithromycin	4	4	2-8	90.9 / 0.0
	Clarithromycin	8	16	2-16	81.8 / 0.0
	Azithromycin	1	2	0.5-2	100.0 / -
	Amox/clav	0.5	0.5	≤0.25-1	100.0 / 0.0
	Cefdinir	≤0.12	0.25	≤0.12-1	100.0 / -
	Levofloxacin	≤0.12	≤0.12	≤0.12	100.0 / -
	TMP/SMX	≤0.25	≤0.25	≤0.25-2	90.9 / 0.0
M. catarrhalis (21)[d]	CEM-101	0.12	0.12	≤0.008-0.5	-/-
	Telithromycin	0.12	0.25	0.015-0.5	-/-
	Erythromycin	0.25	0.25	≤0.12-0.5	-/-
	Clarithromycin	0.12	0.12	0.03-0.5	-/-
	Azithromycin	0.03	0.06	0.03-0.5	-/-
	Clindamycin	2	2	0.5->4	-/-
	Q/D	0.5	0.5	≤0.12-4	-/-
	Amox/clav	≤0.25	≤0.25	≤0.25	-/-
	Cefdinir	≤0.12	≤0.12	≤0.12-0.25	-/-
	Levofloxacin	≤0.12	≤0.12	≤0.12	-/-
	TMP/SMX	≤0.25	≤0.25	≤0.25	-/-
L. pneumophila (30)	CEM-101[e]	≤0.015	≤0.015	≤0.015	-/-
	Azithromycin[f]	1	2	0.25-4	-/-
	Clarithromycin[f]	0.5	0.5	0.25-1	-/-
	Levofloxacin[f]	0.25	0.5	0.25-0.5	-/-
	Rifampin[f]	0.03	0.03	0.03-0.06	-/-

a. Criteria as published by the CLSI [2008].
b. Includes: Group A (30 strains), Group B (31 strains), Group C (14 strains), Group F (9 strains), and Group G *Streptococcus* (16 strains).
c. Includes: *Streptococcus anginosus* (11 strains), *S. constellatus* (11 strains), *S. intermedius* (10 strains), *S. mitis* (9 strains), and *S. oralis* (10 strains).
d. Includes:11 ß-lactamase-positive strains.
e. Tested using the agar dilution (BCYE agar) method.
f. Tested by Etest using manufacturer's recommendations (AB BIODISK) and rounded to nearest $\log_2$ dilution schedule.

Table 2. Activity of CEM-101 and selected comparison agents against streptococci having various MLS_B resistance patterns (three groups, 300 strains*).

MLS_B-ketolide resistance pattern (no. tested)[a]	Antimicrobial agent	MIC (µg/ml) 50%	90%	Range
ER-S (164)[b]	CEM-101	≤0.008	0.015	≤0.008-0.03
	Telithromycin	0.03	0.03	0.008-0.06
	Clarithromycin	0.03	0.03	≤0.008-0.25
	Azithromycin	0.06	0.12	≤0.008-0.5
	Clindamycin	≤0.12	≤0.12	≤0.12-0.5
	Q/D	0.5	0.5	≤0.12-2
	Amox/clav	≤0.25	2	≤0.25->4
	Levofloxacin	1	1	0.25->4
	Linezolid	1	2	0.25-2
ER-NS, CC-and TEL-S (48)[c]	CEM-101	0.03	0.12	≤0.008-0.25
	Telithromycin	0.12	0.5	0.03-1
	Clindamycin	≤0.12	0.25	≤0.12-0.25
	Q/D	0.5	1	0.25-2
	Amox/clav	≤0.25	2	≤0.25->4
	Levofloxacin	1	2	0.25->4
	Linezolid	1	2	0.5-2
ER-and CC-NS, TEL-S (88)[d]	CEM-101	0.06	0.25	≤0.008-0.5
	Telithromycin	0.12	1	0.03-1
	Q/D	0.5	1	0.25-2
	Amox/clav	2	>8	≤0.25->8
	Levofloxacin	1	1	0.25-2
	Linezolid	1	1	0.5-2

a. ER = erythromycin, CC = clindamycin and TEL = telithromycin, S = susceptible and NS = non-susceptible e.g. includes intermediate and resistant strains.
b. Includes: *Streptococcus anginosus* (9 strains), *S. constellatus* (8 strains), *S. intermedius* (7 strains), *S. mitis* (2 strains), *S. oralis* (3 strains), *S. pneumoniae* (61 strains), Group A (29 strains), Group B (17 strains), Group C (11 strains), Group F (6 strains) and Group G *Streptococcus* (11 strains).
c. Includes: *Streptococcus anginosus* (2 strains), *S. constellatus* (2 strains), *S. intermedius* (3 strains), *S. mitis* (7 strains), *S. oralis* (7 strains), *S. pneumoniae* (14 strains), Group A (1 strain), Group B (7 strains), and Group G *Streptococcus* (5 strains).
d. Includes: Streptococcus constellatus (1 strain), *S. pneumoniae* (75 strains), Group B (7 strains), Group C (2 strains), and Group F *Streptococcus* (3 strains).
*Note: One strain (group C *streptococcus*) was NS to ER, CC and TEL, but had a CEM-101 MIC at 0.06 µg/ml. This is an important emerging pattern, especially in Europe.

Table 3. Activity of CEM-101 and 12 comparator agents test against serogroup 19A *S. pneumoniae* (18 strains).

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/resistant[a]
CEM-101	0.25	0.5	0.06-0.5	-/-
Telithromycin	0.5	1	0.12-1	100.0 / 0.0
Erythromycin	>32	>32	8->32	0.0 / 100.0
Azithromycin	>16	>16	8->16	0.0 / 100.0
Clarithromycin	>32	>32	8->32	0.0 / 100.0
Clindamycin	>16	>16	0.06->16	16.7 / 83.3
Q/D	≤0.5	1	≤0.5-1	100.0 / 0.0
Penicillin	4	>4	2->4	16.7 / 16.7
Amox/clav	8	>8	2->8	11.1 / 88.9
Ceftriaxone	1	4	1-8	66.7 / 11.1
Levofloxacin	1	1	1-2	100.0 / 0.0
Tetracycline	>16	>16	0.25->16	16.7 / 83.3
TMP/SMX	>4	>4	1->4	0.0 / 94.4

a. Criteria as published by the CLSI [2008].

Table 4. CEM-101 MIC distributions for all tested RTI organisms (398 strains).

Organism (no. tested)/group	Occurrences at MIC (µg/ml) ≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	≥16
S. pneumoniae (150)	62	25	8	9	7	33	6	0	0	0	0	0
ß-haemolytic streptococci (100)	21	65	4	8	2	0	0	0	0	0	0	0
Viridans group streptococci (15)	27	11	4	7	2	0	0	0	0	0	0	0
M. catarrhalis (21)	1	1	1	5	12	0	0	1	0	0	0	0
H. influenzae (100)	0	0	0	0	1	0	5	48	42	4	0	0
Haemophilus, other (12)	0	0	0	0	0	1	0	0	4	7	0	0

CONCLUSIONS

- CEM-101, a novel macrolide-ketolide, exhibited potent activity against streptococci (MIC_{50}, 0.015 µg/ml), and various other Gram-positive cocci including strains resistant to erythromycin and clindamycin (Table 1-4). CEM-101 showed complete activity against MDR serogroup 19A pneumococci (16 of 18 MIC values at 0.25 or 0.5 µg/ml) and was two-fold more active than telithromycin and Q/D.
- CEM-101 also inhibited Gram-negative species associated with CA-RTI (*H. influenzae* [MIC_{90}, 2 µg/ml], *Legionella* spp. [MIC_{90}, ≤0.015 µg/ml], and *M. catarrhalis* [MIC_{90}, 0.12 µg/ml]).
- CEM-101 appears to be an attractive candidate for treatment of CA-RTI, offering potency and spectrum advantages over telithromycin and clindamycin.

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