Antimicrobial Characterization of CEM-101: Activity Against Staphylococci, β-Haemolytic and Viridans Group Streptococci

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Abstract

Objectives: To address therapy of MLS_B-resistant (R) species, CEM-101, a new fluoroketolide, with enhanced potency against wildtype (WT) respiratory tract (RTI) and cutaneous (SSSI) pathogens is being evaluated. Results of CEM-101 susceptibility (S) testing against 452 staphylococci and selected streptococci are described here.

Methods: A collection of 2006-2007 clinical isolates were S tested by CLSI methods (M07-A8) with associated interpretive criteria (M100-S19) and supplements (2-5% LHB) for streptococcal tests. CEM-101, telithromycin (TEL) and 10 comparators were used versus 201 *S. aureus* (75 WT-MRSA, 75 WT-MSSA, 30 CA-MRSA, 14 VISA or hVISA, 7 VRSA), 100 coagulase-negative staphylococci (CoNS; 10 species), and 100 β-haemolytic (BHS; 30 group A, 31 group B, 14 group C, 9 group F, 16 group G) and 51 viridans group streptococci (VGS; 5 species), see Table.

Results: MSSA strains were slightly more CEM-101-S (MIC_{50}, 0.06 mg/L) than MRSA or CA-MRSA strains (MIC_{50}, 0.12 mg/L). VISA, hVISA and VRSA were generally more refractory to CEM-101 and TEL. CEM-101 was 2-fold more potent than TEL against all staphylococci. Streptococci were very S to CEM-101 (MIC_{90}, 0.03-0.06 mg/L) and TEL was 4-fold less active against non-S isolates of BHS. ERY-R staphylococci remained CEM-101-S except for TEL- and clindamycin (CC)-R isolates, but all BHS and VGS were S to CEM-101.

	CEM-101 MIC (mg/L)			Telithromycin MIC (mg/L)		
Organisms (no.)	50%	90%	Range	50%	90%	Range
MSSA (75)	0.06	0.12	0.03->16	0.12	0.25	0.06->16
MRSA (75)	0.12	>16	0.03->16	0.25	>16	0.06->16
CA-MRSA (30)	0.12	0.12	0.06-0.12	0.25	0.25	0.12-0.5
VISA, hVISA (14)	>16	>16	0.06->16	>16	>16	0.25->16
VRSA (7)	>16	-	0.12->16	>16	-	0.12->16
CoNS (100)	0.06	>16	0.03->16	0.12	>16	0.03->16
BHS (100)	0.015	0.03	≤0.008-0.12	0.03	0.12	≤0.008-2
VGS (51)	≤0.008	0.06	≤0.008-0.12	0.015	0.25	≤0.008-0.5

Conclusions: CEM-101, a novel fluoroketolide, was potent against most MSSA and CA-MRSA (MIC_{50}, 0.06 mg/L), except CC-R strains; and inhibited all streptococci at ≤0.12 mg/L. The activity was greater than TEL by 2- to 4-fold. CEM-101 warrants further evaluation for RTI and SSSI indications

Introduction

CEM-101 is a novel macrolide-fluoroketolide with potent activity against pathogens causing community-acquired respiratory tract infections (CA-RTI; *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis)* and skin and skin structure infections (SSSI; *Staphylococcus aureus,* β-haemolytic streptococci). Although antimicrobial agents in this class have been targeted for use in these infections, the CEM-101 spectrum is compatible with treatment of other infection types and species, especially by the parenteral route for community-acquired bacterial pneumonia (CABP). Emerging resistance mechanisms and greater occurrence of existing resistance rates to the MLS_B-ketolides, have also further limited treatment options.

In this in vitro study, CEM-101 was tested by reference dilution methods against contemporary isolates of staphylococci (*S. aureus* and coagulase-negative staphylococci [CoNS]) and streptococci other than *S. pneumoniae.* These results can guide the clinical development program to investigate CEM-101 for expanded indications, especially for CABP with intravenous use and selected SSSI cases. CEM-101 was directly compared with another ketolide (telithromycin) by reference CLSI methods.

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 strains included bloodstream, skin and skin structure and respiratory tract infections. Unusual/rare organism species and resistance phenotypes required use of strains isolated prior to 2005 or from other geographic areas. See list of tested strains below:

Streptococci (301)
- *S. pneumoniae* (150 wild types; cross resistance analysis only)
- β-haemolytic species (100, five groups)
- Viridans group (51, five species)

Staphylococci (301)
- *S. aureus* (201; includes MSSA [75], MRSA [75], CA-MRSA [30], VISA or hVISA [14] and VRSA [7 from the NARSA collection])
- CoNS (100)

A total of 602 strains were tested, each identified by at least two laboratories including a reference GLP compliant facility (JMI Laboratories, North Liberty, Iowa, USA).

Susceptibility testing methods: Clinical and Laboratory Standards Institute (CLSI) methods were used for all testing as follows:
For staphylococci, the M07-A8 (2009) broth microdilution method with cation-adjusted Mueller-Hinton broth (CA-MHB) medium
For streptococci, the M07-A8 (2009) broth microdilution method was 2.5-5% lysed horse blood supplemented CA-MHB.

CEM-101 and 16 selected antimicrobial agents from 10 drug classes were tested (12 reported here; Table 2). Results were validated by testing the following CLSI-recommended quality control (QC) strains: *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, *S. pneumoniae* ATCC 49619, *H. influenzae* ATCC 49247, and *C. difficile* ATCC 700057. All QC values were within published ranges, see CLSI M100-S19 (2009).

Results

- Fluoroketolide (CEM-101)-susceptible staphylococci had modal MIC values for CEM-101 at only 0.06 mg/L, while resistant strains had CEM-101 MIC values at ≥16 mg/L. Generally, resistance to vancomycin or oxacillin did not influence the CEM-101 MIC values (Table 1).
- All tested streptococci (β-haemolytic or viridans group species) were CEM-101-susceptible at ≤0.12 mg/L (Table 1).
- Comparisons with other agents demonstrated CEM-101 activity that was at least two-fold more potent than telithromycin and with an expanded spectrum compared to macrolides (azithromycin, clarithromycin, erythromycin) and clindamycin versus staphylococci. Streptococci were markedly susceptible to CEM-101 (Table 1-3).
- Cross-susceptibility and -resistance varied by species for the ketolides (CEM-101 and telithromycin), each showing greatest breadth of activity and potency against erythromycin- and clindamycin-resistant strains (Table 3).

Table 1. CEM-101 MIC distributions for all tested Gram-positive organisms (452 strains).

	Occurrences at CEM-101 MIC (mg/L):											
Organism (no. tested)/group	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	≥16
S. aureus												
All (201)	0	0	2	97	47	2	0	1	0	0	1	51
MSSA (75)	0	0	1	59	12	0	0	0	0	0	0	3
MRSA (75)	0	0	1	24	16	2	0	1	0	0	1	30
CA-MRSA (30)	0	0	0	13	17	0	0	0	0	0	0	0
VISA/hVISA (14)	0	0	0	1	1	0	0	0	0	0	0	12
VRSA (7)	0	0	0	0	1	0	0	0	0	0	0	6
CoNS (100)	0	0	12	52	9	0	0	0	0	0	0	27
β-haemolytic streptococci (100)	21	65	4	8	2	0	0	0	0	0	0	0
Viridans group streptococci (51)	27	11	4	7	2	0	0	0	0	0	0	0

Table 2. CEM-101 activity compared to 11 other agents when tested against 452 strains of staphylococci and streptococci.

Organism group (no. tested)/ Antimicrobial agent	MIC (mg/L) 50%	90%	%susceptible /resistant[a]
S. aureus (All; 201)			
CEM-101	0.12	>16	-/-
Telithromycin	0.25	>16	73.6/26.4
Erythromycin	>4	>4	39.3/60.2
Clarithromycin	>16	>16	40.3/59.2
Azithromycin	>16	>16	39.3/60.7
Clindamycin	≤0.12	>4	73.6/26.4
Q/D[b]	0.5	1	99.5/0.0
A/C[b]	8	>8	42.3/57.7
Cefdinir	>4	>4	40.8/58.7
Levofloxacin	0.5	>4	53.2/46.3
TMP/SMX[b]	≤0.25	≤0.25	96.5/3.5
Linezolid	2	2	100.0/-
MSSA (75)			
CEM-101	0.06	0.12	-/-
Telithromycin	0.12	0.25	96.0/4.0
Erythromycin	0.5	>4	81.3/18.7
Clarithromycin	0.25	>16	81.3/18.7
Azithromycin	1	>16	81.3/18.7
Clindamycin	≤0.12	≤0.12	96.0/4.0
Q/D	0.5	0.5	100.0/0.0
A/C	0.5	1	100.0/0.0
Cefdinir	0.25	0.5	100.0/0.0
Levofloxacin	0.25	0.5	93.3/6.7
TMP/SMX	≤0.25	≤0.25	98.7/1.3
Linezolid	2	2	100.0/-
MRSA (75)			
CEM-101	0.12	>16	-/-
Telithromycin	0.25	>16	57.3/42.7
Erythromycin	>4	>4	22.7/76.0
Clarithromycin	>16	>16	25.3/74.7
Azithromycin	>16	>16	22.7/77.3
Clindamycin	≤0.12	>4	57.3/42.7
Q/D	0.5	1	100.0/0.0
A/C	>8	>8	9.3/90.7
Cefdinir	>4	>4	6.7/92.0
Levofloxacin	>4	>4	10.7/88.0
TMP/SMX	≤0.25	1	94.7/5.3
Linezolid	2	2	100.0/-

Organism group (no. tested)/ Antimicrobial agent	MIC (mg/L) 50%	90%	%susceptible /resistant[a]
CA-MRSA (30)			
CEM-101	0.12	0.12	-/-
Telithromycin	0.25	0.25	100.0/0.0
Erythromycin	>4	>4	0.0/100.0
Clarithromycin	>16	>16	0.0/100.0
Azithromycin	>16	>16	0.0/100.0
Clindamycin	≤0.12	≤0.12	100.0/0.0
Q/D	0.5	0.5	100.0/0.0
A/C	>8	>8	0.0/100.0
Cefdinir	>4	>4	0.0/100.0
Levofloxacin	0.25	0.25	96.7/3.3
TMP/SMX	≤0.25	≤0.25	100.0/0.0
Linezolid	2	2	100.0/-
VISA/hVISA (14)			
CEM-101	>16	>16	-/-
Telithromycin	>16	>16	14.3/85.7
Erythromycin	>4	>4	0.0/100.0
Clarithromycin	>16	>16	0.0/92.9
Azithromycin	>16	>16	0.0/100.0
Clindamycin	>4	>4	14.3/85.7
Q/D	1	1	92.9/0.0
A/C	>8	>8	14.3/85.7
Cefdinir	>4	>4	7.1/92.9
Levofloxacin	>4	>4	0.0/100.0
TMP/SMX	≤0.25	0.5	92.9/7.1
Linezolid	2	2	100.0/-
VRSA (7)			
CEM-101	>16	-	-/-
Telithromycin	>16	-	14.3/85.7
Erythromycin	>4	-	14.3/85.7
Clarithromycin	>16	-	14.3/85.7
Azithromycin	>16	-	14.3/85.7
Clindamycin	>4	-	14.3/85.7
Q/D	0.5	-	100.0/0.0
A/C	>8	-	14.3/85.7
Cefdinir	>4	-	14.3/85.7
Levofloxacin	>4	-	0.0/100.0
TMP/SMX	≤0.25	-	85.7/14.3
Linezolid	2	-	100.0/-

Organism group (no. tested)/ Antimicrobial agent	MIC (mg/L) 50%	90%	%susceptible /resistant[a]
Coagulase-negative staphylococci (100)[c]			
CEM-101	0.06	>16	-/-
Telithromycin	0.12	>16	73.0/27.0
Erythromycin	>4	>4	35.0/63.0
Clarithromycin	>16	>16	37.0/62.0
Azithromycin	>16	>16	35.0/64.0
Clindamycin	≤0.12	>4	71.0/29.0
Q/D	0.5	0.5	99.0/0.0
A/C	1	>8	76.0/24.0
Cefdinir	1	>4	51.0/42.0
Levofloxacin	2	>4	48.0/50.0
TMP/SMX	≤0.25	>4	64.0/36.0
Linezolid	1	1	97.0/-
β-haemolytic streptococci (100)[d]			
CEM-101	0.015	0.03	-/-
Telithromycin	0.03	0.12	-/-
Erythromycin	≤0.12	>4	74.0/25.0
Clarithromycin	0.03	>16	75.0/25.0
Azithromycin	0.12	>16	74.0/26.0
Clindamycin	≤0.12	>4	85.0/13.0
Q/D	0.5	0.5	100.0/0.0
A/C	≤0.25	≤0.25	-/-
Cefdinir	≤0.12	0.5	-/-
Levofloxacin	0.5	1	98.0/2.0
TMP/SMX	≤0.25	≤0.25	-/-
Linezolid	1	1	100.0/-
Viridans group streptococci (51)[e]			
CEM-101	≤0.008	0.06	-/-
Telithromycin	0.015	0.25	-/-
Erythromycin	≤0.12	4	56.9/43.1
Clarithromycin	0.03	2	56.9/33.3
Azithromycin	0.12	4	56.9/39.2
Clindamycin	≤0.12	≤0.12	98.0/2.0
Q/D	0.5	1	96.1/0.0
A/C	≤0.25	0.5	-/-
Cefdinir	0.25	1	92.2/7.8
Levofloxacin	1	2	-/-
TMP/SMX	≤0.25	1	-/-
Linezolid	1	2	100.0/-

a. Criteria as published by the CLSI (2009); β-lactam susceptibility should be directed by the oxacillin test results for staphylococci; a dash indicates no susceptibility/resistance criteria have been established.
b. Q/D = quinupristin/dalfopristin; A/C = amoxicillin/clavulanate; TMP/SMX = trimethroprim/sulfamethoxazole.
c. Includes *S. auricularis* (four strains), *S. capitis* (10 strains), *S. epidermidis* (24 strains), *S. haemolyticus* (17 strains), *S. hominis* (13 strains), *S. lugdunensis* (10 strains), *S. saprophyticus* (four strains), *S. simulans* (five strains), *S. warnerii* (nine strains), and *S. xylosis* (four strains).
d. Includes: Group A (30 strains), Group B (31 strains), Group C (14 strains), Group F (nine strains) and Group G (16 strains).
e. Includes: *S. anginosus* (11 strains), *S. constellatus* (11 strains), *S. intermedius* (10 strains), *S. mitis* (9 strains), and *S. oralis* (10 strains).

Table 3. Comparative spectrums of CEM-101, telithromycin and quinupristin/dalfopristin tested against staphylococci and streptococci having various resistance (R) patterns to erythromycin (ER), clindamycin (CC) and telithromycin (TM).

	MIC (mg/L):			
Organism/ Group (no.)/Antimicrobial Agent	50%	90%	Range	%Susceptible/ resistant[a]
Staphylococci				
ER-S, CC-S, TM-S (114)				
CEM-101	0.06	0.12	0.03-0.12	-/-[b]
Telithromycin	0.12	0.25	0.03-0.25	100.0/0.0
Q/D[c]	0.5	0.5	0.12-1	100.0/0.0
ER-R, CC-S, TM-S (105)				
CEM-101	0.06	0.12	0.03-0.25	-/-
Telithromycin	0.12	0.25	0.06-0.5	100.0/0.0
Q/D	0.5	0.5	0.25-1	100.0/0.0
ER-R, CC-R, TM-R (80)				
CEM-101	>16	>16	1->16	-/-
Telithromycin	>16	>16	4->16	0.0/100.0
Q/D	0.5	1	0.25-2	97.5/0.0
Streptococci[d]				
ER-S, CC-S, TM-S (164)				
CEM-101	≤0.008	0.015	≤0.008-0.03	-/-
Telithromycin	0.03	0.03	≤0.008-0.06	100.0/0.0
Q/D	0.5	0.5	≤0.12-2	99.4/100.0
ER-R, CC-S, TM-S (48)				
CEM-101	0.03	0.12	≤0.008-0.25	-/-
Telithromycin	0.12	0.5	0.03-1	100.0/0.0
Q/D	0.5	1	0.25-2	97.9/0.0
ER-R, CC-R, TM-S (88)				
CEM-101	0.06	0.25	≤0.008-0.5	-/-
Telithromycin	0.12	1	0.03-1	100.0/0.0
Q/D	0.5	1	0.25-2	98.9/0.0

a. Criteria as published by the CLSI (2009).
b. No susceptibility criteria have been recommended.
c. Q/D = Quinupristin/dalfopristin.
d. Analysis includes 150 *S. pneumoniae.*
NOTE: Only 3 of 602 strains (0.5%) did not conform to these listed resistance patterns or groups.

Conclusions

- CEM-101 demonstrated the most potent activity among the ketolides, and these compounds were the most active agents against MLS_B organisms.
- CEM-101 was two-fold more active than telithromycin when tested against staphylococci (MRSA MIC_{50} at 0.12 mg/L).
- CEM-101 inhibited all streptococci at 0.12 mg/L; ≥25.0% of β-haemolytic streptococci were macrolide-resistant while susceptible to the ketolides.
- CEM-101, the first fluoroketolide, represents a clear improvement in ketolide potency against targeted Gram-positive pathogens associated with respiratory tract infection (CABP, early HAP) and many SSSI. Expanded clinical studies appear warranted.

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