CEM-101, a Novel Fluoroketolide, Tested against European Clinical Isolates from 2009 (First Year Surveillance Results)

901

RN JONES, DJ FARRELL, MG STILWELL, M CASTANHEIRA
JMI Laboratories, North Liberty, Iowa, USA

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JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
ph. 319.665.3370
fax 319.665.3371
ronald-jones@jmilabs.com

Amended Abstract

Objectives: To determine the potency and spectrum of CEM-101, a new fluoroketolide, tested against contemporary (2009) European (EU) pathogens. Preliminary results suggest that CEM-101 has expanded activity against multidrug-resistant (MDR) pathogens associated with community-acquired bacterial pneumonia (CABP), and skin and skin structure infections (SSSI) when compared to macrolides (erythromycin [ER], azithromycin [AZ], clarithromycin [CL]), clindamycin (CC) and telithromycin (TE).

Methods: EU CEM-101 surveillance study collected 3,531 strains, as follows: *S. aureus* (SA; 1,398), coagulase-negative staphylococci (CoNS; 454), enterococci (ENT; 613), *S. pneumoniae* (SPN; 485), viridans group (VGS; 98) and beta-haemolytic streptococci (BHS; 212), *H. influenzae* (HI; 242) and *M. catarrhalis* (MCAT; 29). These consecutive strains were susceptibility (S) tested by CLSI methods and results were interpreted by EUCAST breakpoints; TE interpretive criteria were applied to CEM-101 for comparison purposes only. Eleven countries and 24 medical centres were sampled.

Results: CEM-101 was very active against SPN (MIC_{90}, ≤0.06 mg/L), VGS and BHS (MIC_{90}, ≤0.03 mg/L) with 100.0 and 98.1-100.0% of isolates inhibited at ≤1 and ≤0.25 mg/L, respectively. This potency was ≥ two fold greater than TE, and CEM-101 inhibited at 3.7% more SPN at ≤0.25 mg/L. The tested SPN was only 72.0, 74.2 and 82.1% S to penicillin (PEN), ER and CC, respectively. Against HI and MCAT, CEM-101 was quite active (MIC_{90}/% inhibited at ≤4 mg/L): 2/99.6 and 0.06/100.0, respectively (two-fold more active than TE). This activity against Gram-negative CABP pathogens was most like AZ. SA and CoNS (MIC_{50}, 0.06 mg/L for both) were generally S to CEM-101 (92.1 and 71.2% S versus 90.5 and 70.5% S for TE). ENT was only moderately S to CEM-101 ($MIC_{50/90}$, 1/2 mg/L), but was two-fold more potent than TE. *E. faecalis* (EF) isolates were usually more S (MIC_{50} at 0.25 mg/L) than other ENT. The EU collection sampled had 22.7% MRSA, 82.8% MRCoNS, 1.7% vancomycin-resistant (VR) EF, 36.8% VR *E. faecium*, 41% PEN-R VGS, 4.8% TE-R *S. pyogenes* and 16.9% ampicillin-R HI.

	% occurrences at CEM-101 MIC (mg/L):								
Organism (no.)	≤0.03	0.06	0.12	0.25	0.5	1	2	4	>4
S. aureus (1,398)	16.0	71.7	3.5	0.4	0.3	0.3	<0.1	<0.1	7.7
CoNS (454)	31.7	28.0	9.9	0.9	0.7	-[a]	-	0.2	28.6
Enterococci (613)	32.6	2.3	1.8	1.6	8.7	20.1	28.2	4.6	0.2
S. pneumoniae (485)	92.8	2.5	1.4	2.7	0.4	0.2	-	-	-
VGS (98)	93.9	6.1	-	-	-	-	-	-	-
BHS (212)	90.6	3.8	2.4	1.4	1.9	-	-	-	-
H. influenzae (242)	-	-	0.4	1.2	23.6	61.6	12.4	0.4	0.4
M. catarrhalis (29)	20.7	72.4	6.9	-	-	-	-	-	-

a. - = no occurrences, 0.0%; underlined value at MIC_{90}.

Conclusions: CEM-101 clearly exhibited greater potency than currently available MLS_B agents (including TE, a ketolide) against potentially indicated pathogens causing CABP or SSSI. Expanded clinical investigations of CEM-101 appear warranted for oral and parenteral route coverage of emerging MDR strains.

Introduction

Increased antimicrobial resistance among Gram-positive pathogens is occurring worldwide. Methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE) and penicillin-resistant *Streptococcus pneumoniae* are becoming increasingly difficult to treat. Additionally, emerging cases of macrolide-resistant *S. pneumoniae* and *Streptococcus pyogenes* are causing global alarm. Therefore, new oral and/or parenteral antimicrobial agents with activity against these Gram-positive pathogens are in demand.

Ketolides are semisynthetic antimicrobial agents derived from erythromycin A, and were designed to overcome macrolide-resistant *S. pneumoniae*. Ketolides possess a keto-group at the C-3 position of the lactone ring, rather than L-cladinose, as seen in erythromycin. CEM-101 is a new fluoroketolide displaying activity against many pathogens that cause respiratory tract infections (RTI), uncomplicated skin and skin structure infections (SSSI) and urogenital infections. This new compound has potent activity against Gram-positive pathogens, including macrolide-resistant strains and various fastidious Gram-negative strains, including *Haemophilus* spp., *Moraxella* spp., and species of *Mycoplasma* and *Ureaplasma*.

In the study presented here, the *in vitro* potency and spectrum of activity of CEM-101 and comparator agents were evaluated against 3,531 bacterial pathogens collected from European medical centres in 2009.

Materials and Methods

Bacterial isolates. A total of 3,531 consecutive collected non-duplicate bacterial isolates originated from 24 European medical sites located in 11 countries were evaluated. These organisms were isolated from bloodstream infections (BSI), community-acquired respiratory tract infections, pneumonia in hospitalized patients, SSSI or wound infections and urinary tract infections. Identifications were confirmed as needed by the Vitek system (bioMerieux, Hazelwood, Missouri, USA) or conventional tests.

Antimicrobial susceptibility testing. Isolates were susceptibility tested against CEM-101 and comparators using the Clinical Laboratory Standards Institute (CLSI) M07-A8 (2009) broth microdilution method. All strains were tested in validated, broth microdilution panels manufactured by TREK Diagnostics (Cleveland, Ohio, USA). Mueller-Hinton Broth (MHB) adjusted to contain physiological levels of calcium (50 mg/L) was used when testing daptomycin. The following quality control (QC) organisms were concurrently tested: *Enterococcus faecalis* ATCC 29212, *S. aureus* ATCC 29213, *S. pneumoniae* ATCC 49619 and *H. influenzae* ATCC 49247; all QC results were within ranges specified by the CLSI (M100-S20, 2010).

Results

- A total of 92.1% of the *S. aureus* were inhibited by CEM-101 at ≤1 mg/L (current CLSI breakpoint for another ketolide, telithromycin, Table 1).
- The activity of CEM-101 against *S. aureus* and CoNS strains was similar (MIC_{50}, 0.06 mg/L for both groups; Table 2). Susceptibility rates for vancomycin, daptomycin and linezolid were near complete (>99%) against staphylococcal strains.
- Overall, the activity of CEM-101 was at least two-fold greater than the activity of telithromycin against enterococci. Vancomycin resistance was observed in 15.0% (16.1% by EUCAST criteria) of tested strains. Susceptibility rates were high against all isolates for daptomycin (99.9%), and linezolid (99.4%, see Table 2).
- CEM-101 was among the most active antimicrobial agents tested against *S. pneumoniae* (MIC_{90}, ≤0.03 mg/L), inhibiting 99.8% of the strains at 1 mg/L (CLSI breakpoint for telithromycin).
- CEM-101 was very active against all viridans group streptococci (VGS; MIC_{50} and MIC_{90}, ≤0.03 mg/L). Erythromycin and penicillin susceptibility rates were only 65.3% and 74.5%, whereas clindamycin susceptibility was 90.8%. All other comparator agents were very active against VGS.
- CEM-101 showed potent activity against all beta-haemolytic streptococci (BHS; MIC_{50} and MIC_{90}, ≤0.03 mg/L), inhibiting all strains at ≤0.5 mg/L. Telithromycin resistance (by EUCAST criteria) was 2.8%. All other comparator agents were also very active against BHS (Table 2).
- The activity of CEM-101 (MIC_{50}, 1 mg/L) was comparable to azithromycin and greater than other macrolides or ketolides when tested against *H. influenzae* (Table 2). Agents showing >99% susceptibility rates according to CLSI breakpoint criteria included levofloxacin, amoxicillin/clavulanate, ceftriaxone and levofloxacin.
- All comparators showed acceptable potencies against *M. catarrhalis* strains from European medical centres (Table 2). CEM-101 inhibited all these strains at ≤0.12 mg/L.

Table 1. Frequency distributions of CEM-101 when tested against bacterial pathogens recovered in European medial centers in 2009.

Organism group (no. tested)	Number (cumulative %) of strains inhibited at MIC (mg/L):								
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	>4
S. aureus (1,398)	223 (15.9)	1002 (87.6)	49 (91.1)	6 (91.6)	4 (91.8)	4 (92.1)	1 (92.2)	1 (92.2)	108 (100.0)
CoNS (454)	144 (31.7)	127 (59.7)	45 (69.6)	4 (70.5)	3 (71.1)	0 (71.1)	0 (71.1)	1 (71.4)	130 (100.0)
Enterococcus spp. (613)	200 (32.6)	14 (34.9)	11 (36.7)	10 (38.3)	53 (47.0)	123 (67.0)	173 (95.3)	28 (99.8)	1 (100.0)
E. faecalis (357)	158 (44.3)	10 (47.1)	10 (49.9)	9 (52.4)	18 (57.4)	57 (73.4)	84 (96.9)	10 (99.7)	1 (100.0)
E. faecium (234)	27 (11.5)	4 (13.2)	1 (13.7)	1 (14.1)	33 (28.2)	62 (54.7)	88 (92.3)	18 (100.0)	
S. pneumoniae (485)	410 (84.5)	40 (92.8)	12 (95.3)	7 (96.7)	13 (99.4)	2 (99.8)	1 (100.0)		
Viridans group streptococcus (98)	92 (93.9)	6 (100.0)							
β-haemolytic streptococcus (212)	192 (90.6)	8 (94.3)	5 (96.7)	3 (98.1)	4 (100.0)				
H. influenzae (242)			1 (0.4)	3 (1.6)	57 (25.2)	149 (86.8)	30 (99.2)	1 (99.6)	1 (100.0)
M. catarrhalis (29)	6 (20.7)	21 (93.1)	2 (6.9)						

Table 2. Antimicrobial activity of CEM-101 and comparator antimicrobial agents when tested against European bacterial strains collected in 2009.

Organism (no.tested)/ Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% Susceptible/% Resistant	
				CLSI[a]	EUCAST[a]
S. aureus (1,398)					
CEM-101	0.06	0.12	≤0.03 – >4	- / -	- / -
Oxacillin	0.5	>2	≤0.25 – >2	77.3 / 22.7	77.3 / 22.7
Erythromycin	0.5	>2	≤0.25 – >2	71.4 / 27.5	72.4 / 27.5
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	91.0 / 8.7	90.3 / 9.0
Telithromycin	≤0.25	≤0.25	≤0.25 – >2	91.4 / 8.4	- / -
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
Vancomycin	1	1	≤0.12 – 2	100.0 / 0.0	100.0 / 0.0
Linezolid	2	2	0.5 – 2	100.0 / -	100.0 / 0.0
Tetracycline	≤2	≤2	≤2 – >8	94.8 / 4.3	94.4 / 5.6
Levofloxacin	≤0.5	>4	≤0.5 – >4	75.1 / 24.7	75.1 / 24.7
TMP/SMX	≤0.5	≤0.5	≤0.5 – >2	98.9 / 1.1	98.9 / 1.1
CoNS (454)					
CEM-101	0.06	>4	≤0.03 – >4	- / -	- / -
Oxacillin	>2	>2	≤0.25 – >2	17.2 / 82.8	17.2 / 82.8
Erythromycin	>2	>2	≤0.25 – >2	35.7 / 63.7	35.7 / 63.7
Clindamycin	≤0.25	>2	≤0.25 – >2	69.2 / 30.0	66.7 / 30.8
Telithromycin	≤0.25	>2	≤0.25 – >2	70.5 / 29.3	- / -
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	100.0 / 0.0
Vancomycin	1	2	≤0.12 – 4	100.0 / 0.0	100.0 / 0.0
Linezolid	1	1	0.25 – 4	100.0 / -	100.0 / 0.0
Tetracycline	≤2	>8	≤2 – >8	85.9 / 12.3	77.8 / 22.2
Levofloxacin	4	>4	≤0.5 – >4	43.0 / 54.0	43.0 / 54.0
TMP/SMX	≤0.5	>2	≤0.5 – >2	59.4 / 40.6	59.4 / 40.6
Enterococcus spp. (613)					
CEM-101	1	2	≤0.03 – >4	- / -	- / -
Ampicillin	2	>16	≤1 – >16	62.2 / 37.8	61.8 / 37.8
Erythromycin	>2	>2	≤0.25 – >2	6.2 / 70.1	- / -
Telithromycin	2	>2	≤0.25 – >2	- / -	- / -
Daptomycin	1	2	0.12 – 4	100.0 / -	- / -
Teicoplanin	≤2	>16	≤2 – >16	87.4 / 11.6	86.5 / 12.6
Vancomycin	1	>16	0.5 – >16	83.8 / 15.0	83.8 / 16.1
Quinupristin/dalfopristin	>2	>2	≤0.25 – >2	28.7 / 64.1	28.7 / 64.1
Linezolid	2	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Levofloxacin	>4	>4	≤0.5 – >4	45.4 / 52.7	- / -
TMP/SMX	>2	>2	≤0.5 – >2	- / -	45.3 / 54.0
E. faecalis (357)					
CEM-101	0.25	2	≤0.03 – >4	- / -	- / -
Ampicillin	≤1	2	≤1 – >16	100.0 / 0.0	99.7 / 0.0
Erythromycin	>2	>2	≤0.25 – >2	7.3 / 56.9	- / -
Telithromycin	0.5	>2	≤0.25 – >2	- / -	- / -
Quinupristin/dalfopristin	>2	>2	1 – >2	0.3 / 94.4	0.3 / 94.4
Daptomycin	1	2	0.12 – 4	100.0 / -	- / -
Teicoplanin	≤2	≤2	≤2 – >16	99.2 / 0.8	99.2 / 0.8
Vancomycin	1	2	0.5 – >16	98.0 / 1.7	98.0 / 2.0
Linezolid	2	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Levofloxacin	2	>4	≤0.5 – >4	64.1 / 35.0	- / -
TMP/SMX	≤0.5	>2	≤0.5 – >2	- / -	61.0 / 38.1
E. faecium (234)					
CEM-101	1	2	≤0.03 – 4	- / -	- / -
Ampicillin	>16	>16	≤1 – >16	3.4 / 96.6	3.4 / 96.6
Erythromycin	>2	>2	≤0.25 – >2	1.7 / 92.7	- / -
Telithromycin	>2	>2	≤0.25 – >2	- / -	- / -
Quinupristin/dalfopristin	1	>2	≤0.25 – >2	73.1 / 18.8	73.1 / 18.8
Daptomycin	2	4	0.25 – 4	100.0 / -	- / -
Teicoplanin	≤2	>16	≤2 – >16	68.8 / 28.6	66.2 / 31.2
Vancomycin	1	>16	0.5 – >16	63.2 / 36.3	63.2 / 36.7
Linezolid	1	2	1 – 2	100.0 / 0.0	100.0 / 0.0
Levofloxacin	>4	>4	1 – >4	14.1 / 82.9	- / -
TMP/SMX	>2	>2	≤0.5 – >2	- / -	18.0 / 81.6

Organism (no.tested)/ Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% Susceptible/% Resistant	
				CLSI[a]	EUCAST[a]
S. pneumoniae (485)					
CEM-101	≤0.03	≤0.03	≤0.03 – 1	- / -	- / -
Penicillin[b]	≤0.03	2	≤0.03 – 8	96.1 / 0.2	- / -
Penicillin[c]	≤0.03	2	≤0.03 – 8	72.0 / 15.3	72.0 / 3.9
Amoxicillin/clavulanate	≤1	2	≤1 – 16	94.6 / 2.5	- / -
Ceftriaxone	≤0.25	1	≤0.25 – 4	92.8 / 0.4	82.9 / 0.4
Erythromycin	≤0.25	>2	≤0.25 – >2	74.2 / 25.4	74.2 / 25.4
Clindamycin	≤0.25	>2	≤0.25 – >2	81.4 / 17.9	82.1 / 17.9
Telithromycin	≤0.25	≤0.25	≤0.25 – 2	99.8 / 0.0	95.9 / 0.6
Levofloxacin	1	1	≤0.5 – >4	99.0 / 0.4	99.0 / 1.0
Tetracycline	≤2	>8	≤2 – >8	77.7 / 22.1	77.7 / 22.3
TMP/SMX	≤0.5	>2	≤0.5 – >2	78.7 / 13.4	84.7 / 13.4
Viridans Group Streptococci (98)					
CEM-101	≤0.03	≤0.03	≤0.03 – 0.06	- / -	- / -
Penicillin	0.06	1	≤0.015 – 32	74.5 / 4.1	83.7 / 4.1
Amoxicillin/clavulanate	≤1	2	≤1 – >16	- / -	- / -
Erythromycin	≤0.25	>2	≤0.25 – >2	65.3 / 34.7	- / -
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	90.8 / 8.2	91.8 / 8.2
Telithromycin	≤0.25	≤0.25	≤0.25	- / -	- / -
Daptomycin	0.25	0.5	≤0.06 – 1	100.0 / -	- / -
Vancomycin	0.5	1	0.25 – 1	100.0 / -	100.0 / 0.0
Linezolid	1	2	≤0.5 – >4	99.0 / 1.0	- / -
Levofloxacin	1	1	0.12 – 2	100.0 / -	- / -
TMP/SMX	≤0.5	>2	≤0.5 – >2	- / -	- / -
β-haemolytic Streptococci (212)					
CEM-101	≤0.03	≤0.03	≤0.03 – 0.5	- / -	- / -
Penicillin	0.03	0.06	≤0.015 – 0.12	100.0 / -	100.0 / 0.0
Amoxicillin/clavulanate	≤1	≤1	≤1	- / -	100.0 / 0.0
Erythromycin	≤0.25	>2	≤0.25 – >2	82.5 / 16.0	82.5 / 16.0
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	90.0 / 9.0	91.0 / 9.0
Telithromycin	≤0.25	≤0.25	≤0.25 – >2	- / -	94.8 / 2.8
Daptomycin	0.12	0.25	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Vancomycin	0.5	0.5	0.25 – 1	100.0 / -	100.0 / 0.0
Levofloxacin	≤0.06	≤0.06	≤0.06	- / -	100.0 / 0.0
Linezolid	1	1	0.5 – 2	100.0 / -	100.0 / 0.0
TMP/SMX	≤0.5	≤0.5	≤0.5 – >2	- / -	99.1 / 0.5
H. influenzae (242)					
CEM-101	1	2	0.12 – >16	- / -	- / -
Ampicillin	≤1	>16	≤1 – >16	83.1 / 16.9	83.1 / 16.9
Amoxicillin/clavulanate	≤1	2	≤1 – 4	100.0 / 0.0	88.4 / 11.6
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 1	100.0 / -	99.2 / 0.8
Azithromycin	1	2	≤0.5 – >4	99.6 / -	11.6 / 0.4
Clarithromycin	8	16	≤0.25 – >32	82.6 / 2.1	0.8 / 0.4
Telithromycin	2	2	0.12 – >8	99.6 / 0.4	0.4 / 0.4
Levofloxacin	≤0.5	≤0.5	≤0.5	100.0 / -	100.0 / 0.0
Tetracycline	≤2	≤2	≤2 – 8	99.6 / 0.4	99.6 / 0.4
TMP/SMX	≤0.5	>2	≤0.5 – >2	70.7 / 22.7	70.7 / 26.9
M. catarrhalis (29)					
CEM-101	0.06	0.06	≤0.008 – 0.12	- / -	- / -
Penicillin	4	>4	0.5 – >4	- / -	- / -
Amoxicillin/clavulanate	≤1	≤1	≤1	- / -	100.0 / -
Ceftriaxone	≤0.25	0.5	≤0.25 – 0.5	- / -	100.0 / -
Cefuroxime	≤1	≤1	≤1	- / -	100.0 / -
Erythromycin	0.25	0.25	0.12 – 0.5	- / -	93.1 / 6.9
Telithromycin	0.12	0.12	≤0.06 – 0.25	- / -	100.0 / -
Levofloxacin	≤0.5	≤0.5	≤0.5	- / -	100.0 / -
Tetracycline	≤2	≤2	≤2	- / -	100.0 / -
TMP/SMX	≤0.5	1	≤0.5 – 1	- / -	89.6 / 10.4

a. Criteria as published by the CLSI [2010] and EUCAST [2009].
b. Trimethoprim/sulfamethoxazole.
c. Criteria as published by the CLSI [2010] for 'Penicillin parenteral (non-meningitis)'.
d. Criteria as published by the CLSI [2010] for 'Penicillin (oral penicillin V)'.

Conclusions

- CEM-101 demonstrated wide coverage for different streptococci groups, including *S. pneumoniae,* VGS and BHS, showing a potency comparable or superior to telithromycin and currently marketed macrolides (erythromycin, azithromycin, and clarithromycin).
- Overall, CEM-101 displayed similar activity when compared to telithromycin against staphylococcal groups (*S. aureus* and CoNS), and was more active than this ketolide against *Enterococcus* spp.
- CEM-101 is a promising agent for treatment of bacterial pathogens causing RTI and uSSSI, especially those organisms having resistances to currently used MLS_B agents.

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