Activity of CEM-101 Tested Against Emerging Telithromycin-Resistant β-Haemolytic Streptococci

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RN JONES, LN WOOSLEY, GJ MOET, PR RHOMBERG
JMI Laboratories, North Liberty, Iowa, USA

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

Amended Abstract

Objectives: To assess the potency of CEM-101, a fluoroketolide in clinical development, against strains observed to be resistant (R) to other agents in the same class. Reports have documented ketolide-R (telithromycin [TEL]) species worldwide, most recently *S. pyogenes* from Europe. CEM-101 was tested against a collection of 43 TEL-R β-haemolytic streptococci (BHS).

Methods: A total of 53 (1.3%) BHS were identified among 3,958 in the SENTRY Antimicrobial Surveillance Program (2003-2006) that were TEL-R (MIC, ≥2 mg/L). 43 strains (36 Group A, 1 Group C, 6 Group G) were available for testing, from 20 hospitals in Europe (31 strains), North America (11) and Latin America (1). Susceptibility (S) testing used CLSI broth microdilution methods and 3 strains were erythromycin (ERY)-R, clindamycin (CC)-S requiring D-test. Nine comparison agents were tested (4 in Table).

Results: The potency of CEM-101 against each BHS serogroup was the same with an overall MIC_{50} and MIC_{90} of 0.12 and 0.5 mg/L, respectively. CEM-101 activity was 32-fold (MIC_{50} comparisons) greater than TEL. All strains were ERY-R, but 100% S to quinupristin/dalfopristin (Q/D). Three CC-S strains (*S. pyogenes*) were D-test (+) and 2 had (+) induction of R to CEM-101. The S rates for other comparators were: penicillin, tetracycline, ceftriaxone, amoxicillin/clavulanate, and levofloxacin (100.0%); and tetracycline (46.8%).

Table. MIC distributions for CEM-101 and MLS_B-ketolide comparison agents.

	Occurrences at MIC (mg/L):								
Antimicrobial	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	>4
CEM-101	4	0	1	18	10	6	4	0	0	0
Telithromycin	0	0	0	0	0	0	0	8	16	19
Erythromycin	0	0	0	0	0	0	0	0	-	43
Clindamycin	-	-	-	-	2	1	0	0	-	40
Q/D[a]	-	-	-	-	37	6	0	0	-	0

a. Q/D = quinupristin/dalfopristin

Conclusions: CEM-101 remained active against all TEL-R (MIC, ≥2 mg/L) BHS with all MICs at ≤1 mg/L (MIC_{50}, 0.12 mg/L). Highest occurrence of TEL-R strains was in Europe (greatest in Italy). CEM-101 warrants further development for infections caused by BHS.

Introduction

CEM-101 is a novel fluoroketolide selected as a candidate for parenteral and oral therapy of community-acquired respiratory tract (CA-RTI) and for other infections where macrolides are indicated. Initial in vitro studies indicated a potency comparable to or superior to telithromycin (a ketolide), erythromycin, azithromycin and clarithromycin, as well as activity against Gram-positive strains 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; *Neisseria gonorrhoeae, Chlamydia trachomatis*).

In this presentation, we report CEM-101 activity measured by reference Clinical and Laboratory Standards Institute (CLSI) methods when testing organisms recently (2008) recognized as resistant to telithromycin.

These β-haemolytic streptococci have emerged mainly in Europe and possess telithromycin MIC values of ≥2 mg/L for 5.2% of isolates in 2004-2005. *S. pyogenes* (Group A) has been the dominant species sampled in Western Europe with this phenotype.

The collection of the SENTRY Antimicrobial Surveillance Program was searched for these ketolide-non-susceptible strains and tested against CEM-101 to assess the potential advantage for the newer agent in the same structural antimicrobial class.

Materials and Methods

Organisms collected:

All organisms tested were obtained from patients in the United States (USA), Europe or Latin America. A total of 53 (1.3%) β-haemolytic streptococci (3,958 isolates) had elevated telithromycin MIC values at ≥2 mg/L, the level consistent with "non-susceptibility" by USA-FDA and CLSI breakpoint criteria when applied to streptococci such as *S. pneumoniae* (CLSI M07-A8, 2009 and M100-S19, 2009).

Forty-three of these strains were available for further study, from 20 hospitals in Europe (31 strains), USA (11 strains), and Latin America (one strain). The most common species were *S. pyogenes* (Group A; 36 strains), Group C (one strain) and Group G (six strains).

Susceptibility testing:

Broth microdilution (96-well) panels were produced by TREK Diagnostics (Cleveland, Ohio, USA) to be used with 2.5-5% lysed horse blood supplement to test fastidious streptococci. More than 30 antimicrobials were tested (10 shown here) including investigational agents such as CEM-101. All tests used the CLSI M07-A8 (2009) method and quality control (QC)/breakpoints guidelines from CLSI M100-S19 (2009). 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 MIC results were within published ranges.

Those organisms having clindamycin susceptibility, but resistance to erythromycin were tested for inducible lincosamide resistance by the CLSI D-test per M100-S19 (2009) method. This was only used for three strains (all *S. pyogenes*).

Results

- Telithromycin-non-susceptible β-haemolytic streptococci were more commonly *S. pyogenes* (2.4%) when compared to all strains tested (1.3%) during 2002-2006 (3,958 isolates); see Table 1.

Table 1. Telithromycin MIC distributions for *S. pyogenes* and all β-haemolytic streptococci (BHS) tested in the SENTRY Antimicrobial Surveillance Program (2002-2006).

	Cum. % inhibited at MIC (mg/L)				
Organism (no. tested)	≤0.5	1	2	4	>4
S. pyogenes (1,631)	96.6	97.6[a]	98.1	99.1	100.0
All BHS (3,958)	97.9	98.7[a]	98.9	99.3	100.0

a. Underlined % indicates susceptible population (CLSI breakpoint for *S. pneumoniae*).

- Table 2 shows that CEM-101 had MIC values at ≤1 mg/L for all of the 43 available telithromycin-non-susceptible β-haemolytic streptococcal strains (MIC_{50}, 0.12 mg/L; Table 3).

Table 2. Activity of CEM-101 and nine comparitive agents tested against 43 β-haemolytic streptococci with elevated telithromycin MIC values (≥2 mg/L).

	No. of occurrences at MIC (mg/L)								
Antimicrobial agent	≤0.03	0.06	0.12	0.25	0.5	1	2	4	>4
CEM-101	4	1	18	10	6	4	0	0	0
Telithromycin	0	0	0	0	0	0[a]	8	16	19
Erythromycin	0	0	0	0	0	0	0	-[b]	43
Clindamycin	-	-	-	2	1	0	0	-	40
Q/D[c]	-	-	-	37	6	0	0	-	0
Penicillin	42	1	0	0	0	0	0	0	0
Ceftriaxone	-	-	-	43	0	0	0	0	0
Levofloxacin	-	-	-	-	39	3	1	0	0
Tetracycline	-	-	-	-	-	-	21	0	22
TMP/SMX[c]	-	-	-	-	43	0	0	0	0

a. Underline value at breakpoint concentration (CLSI). TMP/SMX has no breakpoint criteria.
b. - = untested concentration.
c. Q/D = quinupristin/dalfopristin and TMP/SMX = trimethoprim/sulfamethoxazole.

- Antimicrobials remaining active against these telithromycin refractory strains were (MIC_{90}/% susceptible): Q/D (0.5/100.0), penicillin (≤0.03/100.0), ceftriaxone (≤0.25/100.0), and levofloxacin (1/100.0), see Table 2. Only 46.8% of these strains were tetracycline-susceptible.

- Macrolides and clindamycin were not active against the test strains and the three clindamycin-susceptible strains were D-test-positive (data not shown), i.e., inducible clindamycin-resistant.

- Table 3 illustrates that the total population of telithromycin-non-susceptible strains and the *S. pyogenes* subset had identical $MIC_{50/90}$ results. Group G isolates (six total) had a slightly higher MIC_{50} (0.5 mg/L; data not shown).

Table 3. Comparative activity of CEM-101 tested against *S. pyogenes* and all β-haemolytic streptococci (BHS) with telithromycin resistance.

	MIC (mg/L)			
Organism (no. tested)	50%	90%	Range	% ≤1 mg/L
S. pyogenes (36)	0.12	0.5	≤0.015-1	100.0
All BHS (43)	0.12	0.5	≤0.015-1	100.0

Conclusions

- Telithromycin resistance has emerged in β-haemolytic streptococci, most commonly in Europe (72.1% of occurrences by region) and among *S. pyogenes* (83.7% of occurrences by species).
- A new fluoroketolide, CEM-101, was 32-fold more potent than telithromycin and all MIC values were ≤1 mg/L, that breakpoint used for telithromycin when testing other streptococci such as *S. pneumoniae*.
- CEM-101 activity against β-haemolytic streptococci appears to be superior to telithromycin and could provide a wider and sustained coverage of tested species. Further development is warranted, especially in endemic areas (Europe) of ketolide resistance (*erm* [B] and 23S rRNA mutations).

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