ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 2010, p. 2182–2187 Vol. 54, No. 5
0066-4804/10/$12.00 doi:10.1128/AAC.01662-09

CEM-101 Activity against Gram-Positive Organisms[▽]

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Received 23 November 2009/Returned for modification 19 January 2010/Accepted 8 February 2010

The *in vitro* activity of CEM-101, a new fluoroketolide, was determined against Gram-positive organisms with various macrolide susceptibility profiles. Experiments for determination of the MICs and minimum bactericidal concentrations (MBCs), timed killing, single-step and multistep mutation rates, the erythromycin induction of resistance, postantibiotic effect (PAE), and drug interactions were performed for CEM-101; and the results were compared to those obtained with telithromycin, macrolides, and lincosamides. The MBCs of CEM-101 remained lower overall than those of telithromycin, and CEM-101 displayed a 2-fold greater potency than the ketolide. Timed-killing curve testing showed that CEM-101 had greater bactericidal activity than telithromycin (a ≥3-$\log_{10}$-CFU/ml decrease in the initial inoculum at 24 h) against the staphylococcal isolates tested. The propensity of CEM-101 to cause resistance was low, as determined from the rates of resistance determined in single-step mutational studies ($<10^{-8}$ or 10^{-9}). In multipassaging studies, mutants of two strains (both of which were USA300 isolates) resistant to CEM-101 emerged. That number was comparable to the number resistant to clindamycin but less than the number resistant to telithromycin. Erythromycin induced CEM-101 resistance in *Staphylococcus aureus* and *Streptococcus pneumoniae*, similar to telithromycin; however, in seven of eight beta-hemolytic streptococci, CEM-101 resistance induction was not observed. CEM-101 showed a significant concentration- and exposure-dependent PAE against the strains tested, with the values ranging from 2.3 to 6.1 h for Gram-positive organisms (these times were longer than those for telithromycin). No antagonism was found in synergy analyses, with enhanced inhibition being most noted for combinations with CEM-101 and ceftriaxone, gentamicin, and trimethoprim-sulfamethoxazole. Overall, this new antimicrobial agent (CEM-101) showed good antimicrobial characteristics compared with those of the agents in its class and exhibited measured parameter values similar or superior to those of utilized comparators, indicating that CEM-101 warrants further clinical evaluation.

Increased antimicrobial resistance among Gram-positive pathogens is occurring worldwide (1). Infections caused by 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 (1, 14). Therefore, new oral and/or parenteral antimicrobial agents with activities 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* (10, 23). Ketolides have a keto group at the C-3 position of the lactone ring rather than L-cladinose, which is found in erythromycin (10). Telithromycin was the first ketolide approved for clinical use, and while this antimicrobial agent performs well *in vitro* against Gram-positive bacterial strains and some fastidious Gram-negative bacterial strains (*Haemophilus influenzae*, *Moraxella catarrhalis*), issues with hepatotoxicity and other adverse events have been documented (2, 8, 22, 23). Telithromycin often lacks activity against strains with constitutive macrolide-lincosamide-streptogramin B ($cMLS_B$) resistance and is capable of inducing *erm* methylase genes within a narrow concentration range (10).

CEM-101 is a new fluoroketolide that displays activity against many pathogens that cause respiratory tract infections, uncomplicated skin and skin structure infections (SSSIs), and urogenital infections (8, 21). 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* (8, 21). Preliminary *in vitro* studies have shown that CEM-101 demonstrates activity comparable or superior to the activities of telithromycin, erythromycin, azithromycin, and clarithromycin (8).

The purpose of the study described here was to further investigate the potential *in vitro* activity of CEM-101 against a collection of isolates, including strains with reduced susceptibilities to macrolides that carry distinct resistance mechanisms.

MATERIALS AND METHODS

Bacterial isolates. Isolates were selected for passaging, single-step mutation, postantibiotic effect (PAE), and timed-killing studies on the basis of their MIC profiles and molecular characteristics, as defined in Table 1. Erythromycin resistance induction testing included 81 clinical isolates from surveillance initiatives displaying an erythromycin-resistant, clindamycin-susceptible phenotype. Selected organisms (D-test positive) were screened by PCR molecular methods for mechanisms of macrolide resistance, as described previously (3). Forty clinical isolates were tested in minimum bactericidal concentration (MBC) studies, including 10 *S. pneumoniae* isolates; 10 *S. aureus* isolates; and 5 isolates each of beta-hemolytic streptococci, viridans group streptococci, coagulase-negative staphylococci (CoNS), and enterococci. Additionally, 22 clinical and ATCC strains, including 9 *S. aureus* strains, 6 beta-hemolytic streptococci, and 7 *S. pneumoniae* strains, were used for drug interaction (synergy) studies.

MBC and timed-killing tests. MIC and MBC determinations used Clinical and Laboratory Standards Institute (CLSI) procedures (MIC and MBC ranges, 0.008

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▽ Published ahead of print on 22 February 2010.

TABLE 1. Bacterial isolates used in this study

Isolate	Expt(s) performed	CEM-101 MIC range (μg/ml)	Characteristic(s)
S. aureus ATCC 29213	Passaging,[a] single-step mutation, postantibiotic effect, timed-killing, MBC, synergy	0.06–0.12	Macrolide susceptible
S. aureus NRS384	Passaging[b]	0.12	USA300-0114
S. aureus 004-573D	Passaging[b]	0.12	USA300[c]
S. aureus 117-472D	Passaging[b]	0.12	USA300[c]
S. aureus 024-11490A	Passaging[b]	0.12	USA300[c]
S. aureus 117-453D	Passaging[b]	0.12	USA300[c]
S. haemolyticus 064-4090A	Passaging[a]	0.12	*ermA*
S. epidermidis 095-2777A	Time-kill, MBC	0.12	Macrolide susceptible
E. faecalis ATCC 29212	Passaging,[a] single-step mutation, timed-killing	0.03	Macrolide susceptible
E. faecalis 061-6556A	Passaging[b]	0.06	Erythromycin susceptible
E. faecalis 067-6633A	Passaging[b]	2	*ermB*
Enterococcus faecium 067-1457A	Passaging[b]	0.06	Erythromycin susceptible
E. faecium 086-15387A	Passaging[b]	1	*ermB*
S. pneumoniae ATCC 49619	Passaging,[a] postantibiotic effect, timed-killing, MBC, synergy	0.008–0.015	Macrolide susceptible
S. pneumoniae 063-1085A	Passaging,[a] single-step mutation, MBC, synergy	0.015	Wild type
S. pneumoniae 075-241B	Passaging,[a] single-step mutation, timed-killing, MBC	0.015–0.03	*ermB*
S. pneumoniae 127-2273B	Passaging,[a] MBC, synergy	0.06	*mefA*
S. pyogenes 117-1612A	Passaging,[a] postantibiotic effect, timed-killing, MBC	0.015	Wild type
S. pyogenes 088-11708A	Timed-killing, MBC, synergy	0.06	Macrolide resistant, CEM-101 susceptible
S. mitis 051-4933A	Passaging[a]	0.12	*mefA*
S. mitis 112-1885A	Timed-killing, MBC	≤0.008	Macrolide susceptible
H. influenzae ATCC 49247	Postantibiotic effect	2	
M. catarrhalis 117-10142A	Postantibiotic effect	0.12	Wild type

[a] Passaging with CEM-101, telithromycin, clarithromycin, and azithromycin.
[b] Passaging with CEM-101 only.
[c] The pulsed-field gel electrophoresis profile was identical to that of *S. aureus* strain NRS384 (USA300-0114) from the Network on Antimicrobial Resistance in *Staphylococcus aureus*.

to 16 μg/ml) (17). The lowest concentration of a tested agent that killed ≥99.9% of the initial inoculum was defined as the MBC endpoint. Timed-killing bactericidal activity was performed for CEM-101, telithromycin, clarithromycin, and azithromycin by previously described methods (15–17). The compounds were tested at 2×, 4×, and 8× MIC; and colony count determinations were performed at 0, 2, 4, 8, and 24 h.

Single-step mutation studies. Fresh colonies from agar plates were emulsified in sterile broth to achieve a 4 McFarland turbidity standard (target concentration, 1.2×10^9 CFU/ml). An aliquot of the suspension was plated on agar plates containing 4×, 8×, and 16× the CEM-101 MIC for the isolate. Serial dilutions of the inoculum suspension were also plated on antimicrobial-free plates to determine the colony count (numbers of CFU/ml).

Passaging studies. Isolates were tested by reference broth microdilution methods according to CLSI guidelines (4). Azithromycin, clarithromycin, and telithromycin were tested as comparators. Passaging was performed by removing the entire content of the last well with growth in the MIC panel and placing it into broth medium to reach a 0.5 McFarland standard. A suspension (5×10^5 CFU/ml) was transferred for susceptibility testing, and this procedure was repeated through 7 passage days. The reversion of resistance was assessed by three consecutive passages performed on drug-free agar, and the final MIC was determined by a reference broth microdilution method (5). The significant development of resistant mutants was considered a ≥8-fold change in the initial MIC value (12).

Erythromycin resistance induction. D tests were performed according to the CLSI disk diffusion methodology (5). Erythromycin was used as the inducing agent; and clindamycin, telithromycin, and CEM-101 disks were placed around the erythromycin disk at distances of 12 and 15 mm for *Streptococcus* spp. and staphylococci, respectively. Quality control (QC) was performed according to CLSI guidelines by using strains *S. aureus* ATCC 25923, BAA-977, and BAA-976; *S. pneumoniae* ATCC 49619; *S. pyogenes* ATCC 19615; and *Streptococcus agalactiae* ATCC 12386. All QC results were within published limits.

PAE. The PAE values for CEM-101 and telithromycin were determined by established procedures (11). Both antimicrobial agents were tested against each isolate at 4× MIC. Colony count determinations were performed before antimicrobial exposure (time zero) and 1 or 2 h after antimicrobial exposure. After the antimicrobial agents were diluted (1:1,000), colony count determinations were performed every hour until turbidity was noted (up to 10 h postdilution) to determine the length of the PAE.

Drug interaction (synergy) studies. The activities of CEM-101 in combination with five agents (ceftriaxone, gentamicin, levofloxacin, trimethoprim-sulfamethoxazole, and vancomycin), each of which represents a distinct antimicrobial class, against the isolates were tested on checkerboard susceptibility panels. The drug interaction categories defined elsewhere (15) were used.

RESULTS AND DISCUSSION

MBC testing. CEM-101 was very active against the streptococci (MIC_{50}, ≤0.008 to 0.015 μg/ml) and the staphylococci (MIC_{50}, 0.06 to 0.12 μg/ml), being 2-fold more potent than telithromycin. In general, CEM-101 exhibited MBC/MIC ratios of ≤4 when it was tested against macrolide-susceptible streptococci and CoNS, indicating that it had bactericidal activity (Table 2). In contrast, *S. aureus* and enterococci showed elevated CEM-101 MBCs. All six macrolide-susceptible *S. pneumoniae* strains and two macrolide-resistant, clindamycin-susceptible *S. pneumoniae* strains had CEM-101 MBCs at or 2-fold higher than the MIC value. Conversely, two macrolide- and clindamycin-resistant *S. pneumoniae* strains exhibited elevated CEM-101 MBC/MIC ratios (≥32). The CEM-101 MBC/MIC ratios were generally elevated for *S. aureus* and were independent of the macrolide susceptibility pattern. The CEM-101 MBCs were not as high as those of telithromycin and remained ≤2 μg/ml for 3 of 10 *S. aureus* strains processed (Table 2).

These observations are in accordance with those from a study by Okamoto et al. (19), which showed that MBC/MIC ratios remained elevated for *S. aureus* strains, regardless of

TABLE 2. Distribution of isolates according to MBC/MIC ratios for CEM-101, telithromycin, clarithromycin, and azithromycin

Organism and antimicrobial agent (no. of isolates tested)	No. of strains with MBC/MIC ratio of:					
	1	2	4	8	16	≥32
S. pneumoniae (10)						
CEM-101	3	5	0	0	0	2
Telithromycin	2	6[a]	0	0	0	2
Clarithromycin	2	3	1	0	0	—[b]
Azithromycin	2	4	0	0	0	—[c]
Beta-hemolytic streptococci (5)						
CEM-101	0	1	2	0	0	2
Telithromycin	0	1	1	1	0	2
Clarithromycin	0	0	1	1	0	2[b]
Azithromycin	0	0	0	0	2	2[c]
Viridans group streptococci (5)						
CEM-101	3	0	1	0	0	1
Telithromycin	2	1	1	0	0	1
Clarithromycin	0	0	1	0	0	3[b]
Azithromycin	0	0	0	0	1	3[c]
S. aureus (10)						
CEM-101	1	0	0	0	1	8
Telithromycin	0	0	0	0	0	10
Clarithromycin	0	0	0	0	0	6[b]
Azithromycin	0	0	0	0	0	6[c]
Coagulase-negative staphylococci (5)						
CEM-101	1	1	0	3	0	0
Telithromycin	0	0	0	0	2	3
Clarithromycin	0	0	0	0	0	4[b]
Azithromycin	0	0	0	0	0	4[c]
Enterococcus spp. (5)						
CEM-101	0	0	0	0	0	5
Telithromycin	0	0	0	0	0	5
Clarithromycin	0	0	0	0	0	2[c]
Azithromycin	0	0	0	0	0	2[b]

[a] Includes six isolates with MICs of ≤0.008 μg/ml and an MBC of 0.015 μg/ml (off-scale comparisons).
[b] The MBC was not evaluated for isolates with resistance-level MIC results of ≥4 μg/ml.
[c] The MBC was not evaluated for isolates with resistance-level MIC results of ≥16 μg/ml.

their macrolide susceptibility pattern, when telithromycin was tested.

Timed-killing tests. CEM-101 showed bactericidal activity (reduction of the initial inoculum of ≥3 $\log_{10}$ CFU/ml in 24 h) against macrolide-susceptible strains *S. aureus* ATCC 29213, *Staphylococcus epidermidis*, *S. pneumoniae* ATCC 49619, *S. pyogenes* (8× MIC only), and viridans group streptococci and a macrolide-resistant *S. pyogenes* strain (Table 3). Overall, CEM-101 produced a higher level of reduction in the numbers of CFU/ml and more rapid killing than telithromycin or clarithromycin and azithromycin. A tendency toward higher levels of killing and more rapid killing was also noted with increased concentrations of CEM-101, indicating that it has concentration-dependent killing activity, similar to other ketolides and unlike the macrolide compounds, which show time-dependent killing activity (25). In previous studies, telithromycin displayed a slower bacteriostatic effect against *S. pyogenes* than against *S. pneumoniae* (18). Conversely, in the present study, CEM-101 and telithromycin showed similar killing patterns when the results for the two *S. pyogenes* isolates and wild-type *S. pneumoniae* strain evaluated were compared. Previous studies have also concluded that at concentrations of 2× to 10× MIC, telithromycin and cethromycin (also a ketolide) are mainly bacteriostatic against *S. aureus* (25). Noteworthy in our study was the finding that CEM-101 is bactericidal at 2×, 4×, and 8× the MICs for the *S. aureus* and *S. epidermidis* strains tested.

Resistance development studies. The emergence of resistant mutants was not observed in the single-step mutational studies. The isolates tested included one isolate each of wild-type *Enterococcus faecium*, *S. aureus*, and *S. pneumoniae* as well as one *ermB*-carrying *S. pneumoniae* isolate. Strains were exposed to 4×, 8×, and 16× CEM-101 MIC, with no mutant colonies being detected. The mutation rates by organism were as follows: *E. faecium*, $< 4.0 \times 10^{-9}$; *S. aureus*, $< 6.0 \times 10^{-9}$; and *S. pneumoniae* $< 1.4 \times 10^{-9}$ and $< 6.5 \times 10^{-8}$ for the wild-type strain and the *ermB*-harboring strain, respectively.

Telithromycin-resistant single-step mutants were detected in previous studies that tested macrolide-susceptible and -resistant *S. pneumoniae* isolates, and resistance rates of 1.5×10^{-8} to 2.0×10^{-7} were noted for macrolide-susceptible strains, whereas mutational resistance rates of 1.1×10^{-7} to $> 1.0 \times 10^{-3}$ were observed for *mefE*- and *ermB*-carrying isolates (12). Noteworthy in our study was the lack of detection of mutants resistant to CEM-101, regardless of the macrolide susceptibility patterns of the strains tested. *S. pneumoniae* mutants resistant to clarithromycin and erythromycin have occurred in shorter time periods than mutants resistant to the ketolides when the isolates were tested by multistep resistance selection (12).

TABLE 3. Summary of timed-killing curve results

Strain	Result for:			
	CEM-101	Telithromycin	Clarithromycin	Erythromycin
S. aureus ATCC 29213	Cidal at 2×, 4×, 8× MIC	Cidal at 8× MIC only	Cidal at 8× MIC only	Cidal at 8× MIC only
S. epidermidis 2777A	Cidal at 2×, 4×, 8× MIC	Static	Static	Static
E. faecalis ATCC 29212	Static	Static	Static	Static
S. pneumoniae ATCC 49619	Cidal at 2×, 4×, 8× MIC	Cidal at 2×, 4×, 8× MIC	Cidal at 2×, 4×, 8× MIC	Cidal at 2×, 4×, 8× MIC
S. pneumoniae 241B	Static	Static	NT[a]	NT
S. pyogenes 1612A	Cidal at 8× MIC only	Cidal at 8× MIC only	Cidal at 8× MIC only	Cidal at 8× MIC only
S. pyogenes 11708A	Cidal at 2×, 4×, 8× MIC	Cidal at 2×, 4×, 8× MIC	NT	NT
S. mitis 1885A	Cidal at 2×, 4×, 8× MIC	Cidal at 2×, 4×, 8× MIC	Cidal at 8× MIC only	Cidal at 4×, 8× MIC

[a] NT, not tested.

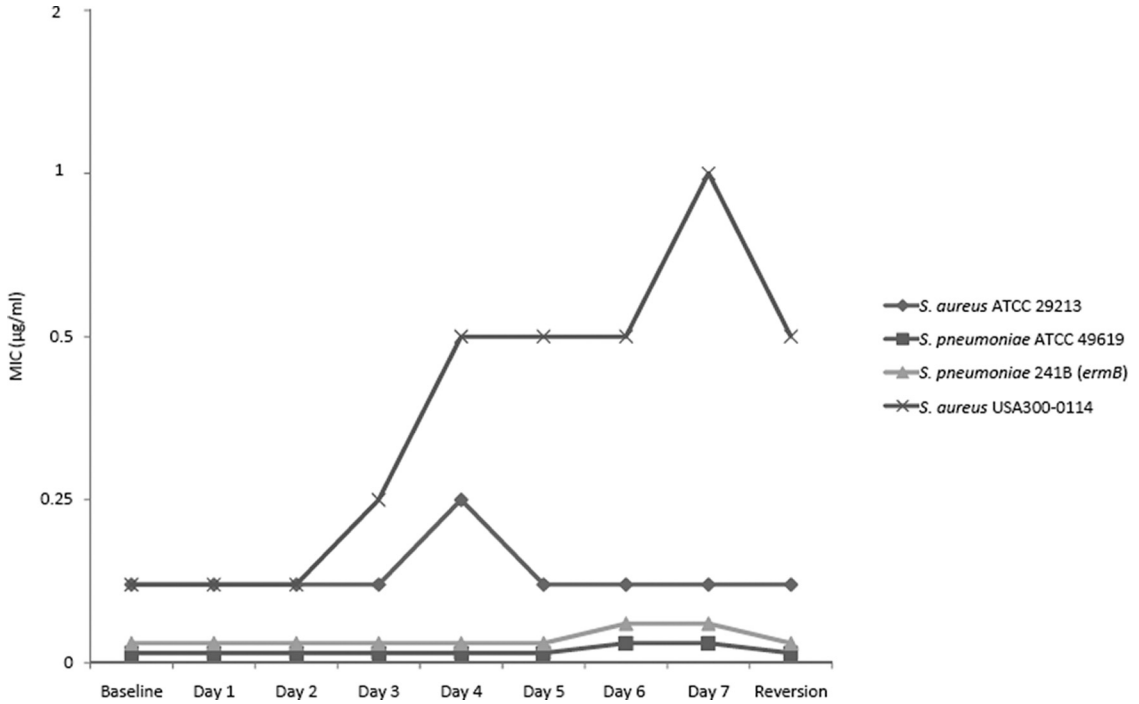

FIG. 1. CEM-101 passaging results for selected strains (7 days).

Among the 18 isolates tested by multistep resistance selection, no significant variation (more than 1 $\log_2$ dilution) in the CEM-101 MIC values was observed for eight strains (44.4%). The remaining 10 strains exhibited modest increases in CEM-101 MIC values of 4- or 8-fold, with no reversion or only 2-fold decreases in the MIC after three subcultures (Fig. 1). A 4-fold increase in the CEM-101 MIC occurred for an *ermA*-carrying *Staphylococcus haemolyticus* strain and *S. pneumoniae* wild-type strain 1085A, whereas the incidence of mutants of both organisms resistant to telithromycin increased 8-fold. The *mefA*-carrying *Streptococcus mitis* strain showed 4-fold increases in the MIC values for CEM-101, telithromycin, and azithromycin, while the only agent to which the mutants were resistant was clarithromycin (8-fold increase). The activity of CEM-101 against five USA300-like strains was also tested, and 4- and 8-fold increases in the MICs were detected (three and two strains, respectively). Three of five USA300 strains displayed a 2-fold reversion. Overall, CEM-101 had resistance selection results less than or equivalent to those for telithromycin.

Erythromycin induction of resistance. Erythromycin induced clindamycin resistance in 21 of 31 (68%) *Staphylococcus* sp. strains (Table 4). Moreover, telithromycin and CEM-101 resistance was induced in all *Staphylococcus* spp. evaluated. Among the *S. aureus* strains with inducible clindamycin resistance (CEM-101 and telithromycin resistance was also inducible for these strains), 11 harbored *ermA* and 4 carried *ermC*. The CoNS isolates displayed induced resistance to all three agents and were found to carry *ermC*. All the staphylococcal isolates showing clindamycin-susceptible patterns (10 strains) harbored *mrsA*, which encodes an efflux resistance mechanism. Telithromycin inducibility was previously observed among *Staphylococcus* spp., and isolates harboring *ermA* and *ermC* were also clindamycin inducible (6).

Three patterns of resistance were noted among the beta-hemolytic streptococci: erythromycin-inducible resistance to all three agents tested (8 isolates), erythromycin-inducible resistance to clindamycin and telithromycin but not CEM-101 (7 isolates), and no inducible resistance to any of the three antimicrobial agents (5 isolates). Among the *S. pneumoniae* isolates, two distinct patterns were observed: no induction of resistance to any of the agents (14 isolates) or the complete induction of resistance to clindamycin, telithromycin, and CEM-101 (6 isolates). All *S. pneumoniae* strains with inducible resistance harbored *ermB*. A similar pattern of resistance was detected for the viridans group streptococci: four strains exhibited resistance to all three agents, while the remaining six isolates failed to show evidence of inducible resistance.

TABLE 4. Patterns of inducible CEM-101, telithromycin, and clindamycin resistance by erythromycin determined by a modified D-test method

Induced resistance to:			No. of occurrences	
Clindamycin	Telithromycin	CEM-101	Staphylococci (n = 31)	Streptococci (n = 50)
+	+	+	21	18
−	+	+	10	0
+	+	−	0	7
−	−	−	0	25

TABLE 5. CEM-101 drug interaction (synergy) results for five antimicrobial agents tested against *S. aureus*, *S. pyogenes*, and *S. pneumoniae*[a]

Agent used in combination with CEM-101	No. of isolates in the following interactive category:					
	Synergy		Additive	Indifferent	Antagonism	Indeterminate
	Complete	Partial				
Ceftriaxone	0	2	5	12	0	3
Gentamicin	2	2	4	14	0	0
Levofloxacin	0	0	3	19	0	0
Trimethoprim-sulfamethoxazole	0	2	4	16	0	0
Vancomycin	0	1	6	15	0	0

[a] Nine *S. aureus* strains, six *S. pyogenes* strains, and seven *S. pneumoniae* strains were tested.

The clinical usefulness of detecting induced telithromycin resistance is currently under evaluation, since studies analyzing beta-hemolytic streptococci and *S. pneumoniae* indicate that the results of that phenotypic test showed a poor correlation with the MIC values and/or the presence of the *erm* and *mef* genes (9, 20). This evaluation should be applied to CEM-101, since that fluoroketolide displayed resistance induction results similar to those noted for telithromycin.

Postantibiotic effect. The PAE results obtained with 4× MIC for CEM-101 and telithromycin were 2.3 and 2.6 h, respectively, for *S. aureus* ATCC 29213; 3.0 and 1.9 h, respectively, for *S. pneumoniae* ATCC 49619; 6.1 and 3.4 h, respectively, for *S. pyogenes* 1612A; 3.2 and 1.2 h, respectively, for *H. influenzae* ATCC 49247; and 6.3 and 4.0 h, respectively, for *M. catarrhalis* 10142A. All strains except *S. pneumoniae* and *H. influenzae* had an exposure time of 2 h; *S. pneumoniae* and *H. influenzae* were exposed for only 1 h. Overall, the PAE of CEM-101 was usually more extended (1 to 3 h longer) than that of telithromycin; both ketolide antimicrobial agents presented similar PAEs for *S. aureus*.

In general, the PAE values for the ketolides are usually improved compared to those for the macrolide comparators, and the ketolides have a theoretical maximum PAE against different isolates as the exposure concentration of ketolide increases (25). However, the results obtained in the present evaluation with 4× MIC were similar to those obtained in the study of Jacobs et al. (7), who reported telithromycin PAE values of 0.3 to 2.4 h for *S. aureus* and 1.5 to 3.8 h for *S. pneumoniae* at a higher level of exposure (10× MIC).

Drug interaction (synergy) studies. The vast majority of the results (76/110) showed indifferent MIC values for the codrugs in the presence of CEM-101 compared with the MIC values for the codrugs tested alone (Table 5). Three test combinations for CEM-101–ceftriaxone were not interpretable due to oxacillin resistance. Additive (22/110) and partial (7/110) synergies were also detected, whereas complete synergy with CEM-101 and gentamicin was observed for only two *S. pneumoniae* strains. More importantly, antagonistic effects were not detected, and since the majority of combinations displayed indifference, CEM-101 would likely not have a negative therapeutic effect when it is used in combination with these antimicrobial pairings for the treatment of *S. pneumoniae*, *S. aureus*, and *S. pyogenes* infections.

Due to the broad spectrum of activity covering Gram-positive cocci, atypical bacteria, intracellular pathogens, *H. influenzae*, and *M. catarrhalis* (azithromycin and clarithromycin only), macrolides have been widely used to treat upper and lower respiratory tract infections and as an alternative agent for use by patients allergic to β-lactams (24). However, emerging trends of resistance in Gram-positive pathogens and others organisms have created the need for new antimicrobial agents. Structural changes to macrolides have expanded their spectra of activity and potencies and have given origin to the ketolide group (25). CEM-101, a new fluoroketolide, has shown *in vitro* activity against macrolide-susceptible and -resistant strains and has proven to be at least 2-fold more potent than telithromycin in our studies. Earlier studies with pneumococci and *S. pyogenes* found that CEM-101 has a MIC value 4-fold lower than that of telithromycin, regardless of the macrolide susceptibility pattern (13). Additionally, CEM-101 has shown potency 2-fold greater than that of telithromycin against evolving multidrug-resistant serogroup 19A pneumococcal strains (6a).

The results of the timed-killing experiments reported here demonstrated that CEM-101 reduces the colony counts (in CFU/ml) to a greater extent and displays more rapid killing than telithromycin. Single-step mutational studies did not detect mutants resistant to CEM-101, and the rates of resistance to this new ketolide were equivalent to those to telithromycin when isolates were selected for resistance in multistep mutational studies. Similar results were also obtained with CEM-101 and telithromycin when they were used to test for erythromycin resistance induction. Furthermore, CEM-101 displayed superiority over telithromycin, as it had PAEs 1 to 3 h longer and proved to have no negative therapeutic effect with the codrug combinations tested (Table 5) in our synergy studies. With telithromycin proving to be less potent in multiple studies and having safety issues, CEM-101 appears to be a promising option for the treatment of community-acquired bacterial pneumonia (CABP) and complicated SSSIs.

ACKNOWLEDGMENTS

We thank Paul R. Rhomberg, Douglas J. Biedenbach, and Gary J. Moet for their excellent technical support during this study.

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