Antimicrobial Activity of a New Fluoroketolide Solithromycin (CEM-101) Tested Against Fastidious Gram-negative Community-Acquired Bacterial Pneumonia Pathogens

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Abstract

Background: Solithromycin (CEM-101) is a novel fluoroketolide selected as a candidate for oral and parenteral therapy of community-acquired bacterial pneumonia (CABP). Solithromycin possesses potency against fastidious Gram-negative species including *H. influenzae* (HI) and *M. catarrhalis* (MCAT).

Methods: Solithromycin and 10 comparator agents were tested against 727 HI and 313 MCAT strains from USA and European medical centers during 2009 SENTRY Program surveillance. CLSI broth microdilution methods (M07-A8) were utilized to test isolates applying HTM (HI) or Mueller-Hinton (MCAT). Nitrocefin was used to detect β-lactamase production.

Results: Solithromycin showed comparable activity to azithromycin (AZ; both $MIC_{50/90}$, 1/2 µg/mL) and was two- to eight-fold more potent than telithromycin (TELI; MIC_{90}, 4 µg/mL) and clarithromycin (CLAR; MIC_{90}, 16 µg/mL) against HI and was active against 99.0% of the isolates at ≤4 µg/mL compared to TELI (98.5%). Solithromycin and other macrolides were eight-fold less active when tested against 7 AZ-resistant (R) strains. Solithromycin activity against MCAT ($MIC_{50/90}$, 0.06/0.12 µg/mL) was 2-fold greater than TELI ($MIC_{50/90}$, 0.12/0.25 µg/mL). All isolates were inhibited at a solithromycin MIC of 0.25 µg/mL. Solithromycin activity was unaffected by β-lactamase production (23.6% [HI] and >95% [MCAT]) and antimicrobial activity was similar for all tested agents against isolates from Europe or USA.

Conclusion: Solithromycin was two-fold more active than TELI against HI and MCAT and had activity similar to that of AZ against HI. β-lactam R did not influence solithromycin activity. The results of this study indicate solithromycin is a promising agent for treatment of CABP, including strains with R to currently used MLS_B class agents (Table 1).

Introduction

Solithromycin (CEM-101) is a potent, extended-spectrum fluoroketolide that is under clinical development for the treatment of bacterial pneumonia as well as for other indications. Both intravenous and oral formulations are advancing through Phase I/II clinical trials. Solithromycin has activity against the most common causes of community-acquired bacterial pneumonia (CABP), including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and atypical pathogens.

Resistance to macrolides is common among respiratory pathogens, particularly *S. pneumoniae*, and solithromycin has been developed to address this problem, as it retains activity against macrolide-resistant strains. Solithromycin has numerous favorable advantages over other macrolides and ketolides, including enhanced binding to targeted bacterial ribosomes, a longer post-antibiotic effect, and a lower rate of resistance development. In addition, safety data generated in Phase 1 trials have shown that solithromycin has excellent tolerability and a good safety margin, with limited adverse events when compared to telithromycin.

With the extensive healthcare costs associated with treating patients with CABP each year and the increasing amount of resistance to currently used antimicrobial agents (including macrolides), solithromycin could provide an effective alternative therapeutic option. In this investigation, the activity of solithromycin was compared to other agents (macrolides/ketolides and other classes) when tested against a large number of contemporary *H. influenzae* and *M. catarrhalis* isolates collected in the United States (USA) and Europe.

Materials and Methods

Bacterial Strain Collection: Consecutive and non-duplicate Gram-negative respiratory pathogens from patients with CABP were collected in the USA and Europe. Bacterial species included 727 isolates of *H. influenzae* and 313 isolates of *M. catarrhalis* that were forwarded from numerous medical centers enrolled in the SENTRY Antimicrobial Surveillance Program during 2009. Species identification was performed by the submitting laboratories with confirmation performed by the central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA).

Susceptibility Test Methods: All isolates were tested for susceptibility by reference broth microdilution methods using the Clinical Laboratory Standards Institute recommendations (CLSI; M07-A8, 2009). Susceptibility testing was performed using validated broth microdilution panels manufactured by TREK Diagnostics Systems (Cleveland, Ohio, USA). *H. influenzae* isolates were tested in Haemophilus Test Media, and *M. catarrhalis* isolates were tested in cation-adjusted Mueller-Hinton broth. Validation of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of quality control strains, including *H. influenzae* ATCC 49247 and *Staphylococcus aureus* ATCC 29213 (M100-S20-U, 2010). Categorical interpretation of comparator MIC values was performed according to CLSI (M100-S20-U, 2010) and EUCAST criteria, when available.

Results

- *H. influenzae* MIC values for solithromycin were two-fold lower than that of telithromycin comparing both the MIC_{50} (1 versus 2 µg/mL) and MIC_{90} (2 versus 4 µg/mL) values for these agents, respectively (Tables 1 and 2). A total of 99.0% of isolates were inhibited by solithromycin at ≤4 µg/mL, the telithromycin FDA and CLSI breakpoint.
- Against all *H. influenzae* isolates (20.6% β-lactamase positive; Table 2), solithromycin showed activity and potency comparable to azithromycin (MIC_{50}, 1 µg/mL and MIC_{90}, 2 µg/mL) and was eight-fold more potent than clarithromycin (MIC_{90}, 16 µg/mL).
- Solithromycin activity was unaffected by ampicillin MIC values and/or β-lactamase production among *H. influenzae* (Table 2). However, the activity of this fluoroketolide was eight-fold less when this compound was tested against 11 azithromycin-resistant strains detected in this survey. Telithromycin and clarithromycin also showed decreased activity against azithromycin-resistant strains.
- Susceptibility patterns of *H. influenzae* collected in each of the geographic regions analyzed were very similar and solithromycin activity (MIC_{50}, 1 µg/mL and MIC_{90}, 2 µg/mL) was identical for North American and European strains (data not shown).
- Applying current CLSI breakpoints, 71.5, 98.5, and 99.0 % of *H. influenzae* isolates were generally considered susceptible to clarithromycin, telithromycin, and azithromycin, respectively (Table 2). In contrast, using EUCAST breakpoint criteria, only 0.8% of the isolates were categorized as susceptible to telithromycin; the vast majority of the isolates were categorized as intermediate to telithromycin and macrolides.
- Antimicrobial activity was very similar for all tested antimicrobial agents against *M. catarrhalis* isolates, which had a 96.2% β-lactamase production rate, collected in Europe or the USA; and all isolates were inhibited at a solithromycin MIC of ≤0.25 µg/mL (Table 1).
- Solithromycin (MIC_{50}, 0.06 µg/mL and MIC_{90}, 0.12 µg/mL) demonstrated activity two-fold greater than telithromycin and erythromycin (MIC_{50}, 0.12 µg/mL and MIC_{90}, 0.25 µg/mL) against *M. catarrhalis* isolates (Table 3).

Table 2. Antimicrobial activity of solithromycin and comparator antimicrobial agents when tested against 727 strains of *Haemophilus influenzae* (all regions).

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
H. influenzae					
All (727)					
Solithromycin	1	2	0.12 – >16	- / -	- / -
Telithromycin	2	4	0.12 – >8	98.5 / 0.8	0.4 / 0.8
Azithromycin	1	2	≤0.5 – >4	99.0 / -	99.0[b] / 1.0
Clarithromycin	8	16	≤0.25 – >32	71.5 / 5.0	0.8 / 0.8
Ampicillin	≤1	>16	≤1 – >16	79.0 / 20.4	79.0 / 21.0
Amoxicillin/clavulanate	≤1	≤1	≤1 – 8	99.7 / 0.3	90.5 / 9.5
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 1	100.0 / -	-[c] / -[c]
Cefuroxime	≤1	2	≤1 – >8	99.4 / 0.3	79.5 / 4.5
Tetracycline	≤2	≤2	≤2 – >8	98.9 / 1.1	98.9[b] / 1.1
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	73.0 / 23.3	73.0 / 25.2
Levofloxacin	≤0.5	≤0.5	≤0.5	100.0 / -	100.0 / 0.0
β-lactamase-positive (150)					
Solithromycin	1	2	0.12 – >16	- / -	- / -
Telithromycin	2	4	0.5 – >8	98.0 / 2.0	0.0 / 2.0
Azithromycin	1	4	≤0.5 – >4	98.0 / -	98.0[b] / 2.0
Clarithromycin	8	16	2 – >32	62.7 / 9.3	0.0 / 2.0
Amoxicillin/clavulanate	≤1	2	≤1 – 8	99.3 / 0.7	84.0 / 16.0
Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0 / -	-[c] / -[c]
Cefuroxime	≤1	2	≤1 – 4	100.0 / 0.0	79.3 / 1.3
Tetracycline	≤2	≤2	≤2 – >8	96.7 / 3.3	96.7[b] / 3.3
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	75.3 / 23.3	75.3 / 23.3
Levofloxacin	≤0.5	≤0.5	≤0.5	100.0 / -	100.0 / 0.0
β-lactamase-negative (577)					
Solithromycin	1	2	0.12 – >16	- / -	- / -
Telithromycin	2	4	0.12 – >8	98.6 / 0.5	0.5 / 0.5
Azithromycin	1	2	≤0.5 – >4	99.3 / -	99.3[b] / 0.7
Clarithromycin	8	16	≤0.25 – >32	73.8 / 3.8	1.0 / 0.5
Amoxicillin/clavulanate	≤1	≤1	≤1 – 8	99.8 / 0.2	92.2 / 7.8
Ceftriaxone	≤0.25	≤0.25	≤0.25 – 1	100.0 / -	-[c] / -[c]
Cefuroxime	≤1	2	≤1 – >8	99.3 / 0.3	79.5 / 5.4
Tetracycline	≤2	≤2	≤2 – >8	99.5 / 0.5	99.5[b] / 0.5
Trimethoprim/sulfamethoxazole	≤0.5	>2	≤0.5 – >2	72.5 / 23.1	72.5 / 25.6
Levofloxacin	≤0.5	≤0.5	≤0.5	100.0 / -	100.0 / 0.0

a. Criteria as published by the CLSI [2010a] and EUCAST [2010].
b. Includes susceptible and intermediate. Dilution range tested did not include EUCAST susceptible breakpoint.
c. Dilution range tested did not include EUCAST susceptible and resistant breakpoints.

Table 3. Antimicrobial activity of solithromycin and comparator antimicrobial agents when tested against 313 isolates of *Moraxella catarrhalis* (all regions).

Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S / %R	EUCAST[a] %S / %R
Solithromycin	0.06	0.12	≤0.008 – 0.25	- / -	- / -
Telithromycin	0.12	0.25	≤0.06 – 0.25	- / -	100.0 / 0.0
Erythromycin	0.12	0.25	≤0.06 – 0.5	100.0 / -	92.7 / 0.0
Amoxicillin/clavulanate	≤1	≤1	≤1 – 2	100.0 / 0.0	99.7 / 0.3
Ceftriaxone	≤0.25	0.5	≤0.25 – 2	100.0 / -	99.4 / 0.0
Cefuroxime	≤1	2	≤1 – >8	99.7 / 0.3	82.1 / 1.3
Tetracycline	≤2	≤2	≤2 – 8	99.7 / 0.3	99.7 / 0.3
Trimethoprim/sulfamethoxazole	≤0.5	≤0.5	≤0.5 – >2	91.7 / 3.2	91.7 / 4.8
Levofloxacin	≤0.5	≤0.5	≤0.5 – 1	100.0 / -	100.0 / 0.0

a. Criteria as published by the CLSI [2010b] and EUCAST [2010].

Table 1. Frequency distributions of solithromycin and telithromycin tested against *H. influenzae* and *M. catarrhalis* respiratory tract isolates from patients with CABP collected in 2009.

	Number of strains inhibited at MIC in µg/mL (cumulative percentage):												
Organism group (no. tested)[a]	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>
H. influenzae (727)													
Solithromycin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.0)	6 (1.8)	134 (20.2)	411 (76.8)	154 (97.9)	8 (99.0)	2 (99.3)	1 (99.5)	4 (100.0)
Telithromycin	-[a]	-	-	0 (0.0)	3 (0.4)	5 (1.1)	30 (5.2)	277 (43.3)	316 (86.8)	85 (98.5)	5 (99.2)	6 (100.0)	
Azithromycin	-	-	-	-	-	-	74 (10.2)	354 (58.9)	242 (92.2)	50 (99.0)	-	-	7 (100.0)
M. catarrhalis (313)													
Solithromycin	9 (2.9)	2 (3.5)	31 (13.4)	193 (75.1)	76 (99.4)	2 (100.0)							
Telithromycin	-	-	-	77 (24.6)	204 (89.8)	32 (100.0)							

a. - = represent the dilutions that were not tested.

Conclusions

- When testing solithromycin (CEM-101) against *H. influenzae*, the activity was similar to that of azithromycin and greater than telithromycin. Furthermore, β-lactam resistance in *H. influenzae* did not influence this new fluoroketolide's activity.
- Against *M. catarrhalis*, solithromycin demonstrated two-fold greater potency than telithromycin.
- The results of the present study indicate that solithromycin is a promising agent for treatment of Gram-negative pathogens commonly causing CABP, especially those having resistances to currently utilized MLS_B agents including telithromycin.

References

1. Biedenbach DJ, Castanheira M, Jones RN (2010). Determination of CEM-101 activity tested against clinical isolates of *Neisseria meningitidis* from a worldwide collection. *Antimicrob Agents Chemother* 54: 4009-4011.
2. Clinical and Laboratory Standards Institute (2009). *M07-A8. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: eighth edition.* Wayne, PA: CLSI.
3. Clinical and Laboratory Standards Institute (2010a). *M100-S20-U. Performance standards for antimicrobial susceptibility testing: 20th informational supplement (June 2010 Update)*. Wayne, PA: CLSI.
4. Clinical and Laboratory Standards Institute (2010b). *M45-A2. Methods for antimicrobial dilution and disk susceptibility testing of infrequently isolated or fastidious bacteria; approved guideline: second edition.* Wayne, PA: CLSI.
5. EUCAST (2010). Breakpoint tables for interpretation of MICs and zone diameters. Version 1.1, April 2010. Available at: http://www.eucast.org/clinical_breakpoints/, June 10, 2010.
6. Farrell DJ, Castanheira M, Sader HS, Jones RN (2010). The in vitro evaluation of solithromycin (CEM-101) against pathogens isolated in the United States and Europe (2009). *J Infect In press*.
7. Farrell DJ, Sader HS, Castanheira M, Biedenbach DJ, Rhomberg PR, Jones RN (2010). Antimicrobial characterisation of CEM-101 activity against respiratory tract pathogens, including multidrug-resistant pneumococcal serogroup 19A isolates. *Int J Antimicrob Agents* 35: 537-543.
8. Jones RN, Ross JE, Rhomberg PR (2010). MIC quality control guidelines and disk diffusion test optimization for CEM-101, a novel fluoroketolide. *J Clin Microbiol* 48: 1470-1473.
9. Jones RN, Sader HS, Janacheck MJ, Moet GJ (2009). First year antimicrobial surveillance results for CEM-101, a novel fluoroketolide with potent activity against pathogens associated with community-acquired bacterial pneumonia. Abstr. F1-2035. *49th ICAAC, September 12-15, 2009*, San Francisco, CA, US
10. Putnam SD, Castanheira M, Moet GJ, Farrell DJ, Jones RN (2010). CEM-101, a novel fluoroketolide: antimicrobial activity against a diverse collection of Gram-positive and Gram-negative bacteria. *Diagn Microbiol Infect Dis* 66: 393-401.
11. Putnam SD, Sader HS, Farrell DJ, Biedenbach D, Castanheira M (2010). Antimicrobial characterization of CEM-101, a novel fluoroketolide: Activity against staphylococci and enterococci. *Int J Antimicrob Agents Accepted for publication*.
12. Woosley LN, Castanheira M, Jones RN (2010). CEM-101 activity against Gram-positive organisms. *Antimicrob Agents Chemother* 54: 2182-2187.