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The *in vitro* evaluation of solithromycin (CEM-101) against pathogens isolated in the United States and Europe (2009)

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Summary *Objectives:* Solithromycin (formerly CEM-101) is a novel fluoroketolide with potent activity against bacterial pathogens that are susceptible or resistant to other MLS_B-ketolide agents. The objective of this study was to assess the activity of solithromycin and comparator antimicrobials against a large number and variety of contemporary clinical bacterial pathogens collected in the United States (USA) and Europe during 2009.
Method: During 2009, a total of 10,670 non-duplicated clinical isolates were collected from 52 medical centers located in the USA (27 centers; 6228 isolates) and Europe (25 centers; 4442 isolates). Susceptibility testing and interpretation were performed using CLSI reference methods.
Results: Among 1363 *Streptococcus pneumoniae* isolates, 99.9% of the strains displayed solithromycin MIC values at $\leq$0.5 mg/L, and 100% were inhibited at an MIC of 1 mg/L. Solithromycin demonstrated activity and potency against *Haemophilus influenzae* comparable to azithromycin (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L) and was very potent against all 313 *Moraxella catarrhalis* isolated (MIC_{50}, 0.06 mg/L and MIC_{90}, 0.12 mg/L). Against 4729 *Staphylococcus aureus* isolates, solithromycin (MIC_{50}, 0.06 mg/L and MIC_{90}, $>$4 mg/L) activity was greater against methicillin-susceptible isolates (MIC_{50}, 0.06 mg/L and MIC_{90}, 0.06 mg/L) compared to methicillin-resistant isolates (MIC_{50}, 0.06 mg/L and MIC_{90}, $>$4 mg/L). Solithromycin was very active against all 757 β-haemolytic streptococci (MIC_{50}, $\leq$0.03 mg/L and MIC_{90}, 0.06 mg/L) and 310 viridans group streptococci (MIC_{50}, $\leq$0.03 mg/L and MIC_{90}, 0.06 mg/L) evaluated.
Conclusion: This contemporary surveillance study utilizing clinical isolates shows that solithromycin exhibits favorable *in vitro* potency and spectrum of activity against bacterial pathogens most frequently isolated in community-acquired respiratory tract (CA-RTI) and skin and skin structure infections (SSSI).

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Introduction

Ketolides are semi-synthetic antimicrobial agents derived from erythromycin A, and were designed primarily to overcome macrolide-resistant streptococci including *Streptococcus pneumoniae*. Antimicrobial agents within this class possess a keto group at the C-3 position of the lactone ring, rather than L-cladinose, as seen in erythromycin A.[1] Telithromycin, the first ketolide licensed for clinical use, possesses an *in vitro* spectrum of activity that covers both typical and atypical/intracellular respiratory tract pathogens, including macrolide- and multidrug-resistant (MDR) *S. pneumoniae*.[2] Although telithromycin was approved by the United States (USA) Food and Drug Administration (FDA) in 2004 for treatment of mild to moderate community-acquired bacterial pneumonia (CABP), reports of serious hepatoxicity resulted in the USA-FDA issuing a public health advisory followed by a warning for telithromycin use in 2006.

Solithromycin (formerly OP-1068 and CEM-101) is the first fluoroketolide selected as a candidate for oral and/or parenteral therapy of CABP and skin and skin structure infections (SSSI). Initial screening *in vitro* studies indicated potency comparable or superior to telithromycin, erythromycin, azithromycin and clarithromycin, as well as activity against Gram-positive isolates having documented resistances to macrolides or lincosamides.[3–6] Solithromycin activity is generally focused against Gram-positive pathogens, but also possesses measurable activity against fastidious Gram-negative species (*Haemophilus* and *Moraxella* species), some Enterobacteriaceae (*Salmonella* spp., *Shigella* spp.), and pathogens causing various sexually transmitted diseases.[7,8]

In this study, we report solithromycin and comparator activities, measured by reference Clinical and Laboratory Standards Institute (CLSI) methods,[9,10] tested against 10,670 contemporary clinical isolates collected in USA and European medical centres during 2009.

Materials and methods

Bacterial isolates

Over 10,000 non-duplicated isolates were collected prospectively from 52 medical centers located in the USA (27 centers from 21 states; 6228 isolates) and Europe (22 centers from 13 countries; 4442 isolates). European countries (number of centres) were: Belgium (1), France (5), Germany (3), Ireland (1), Israel (1), Poland (1), Spain (2), Sweden (2), Switzerland (1), Turkey (2), and United Kingdom (2). These isolates were recovered consecutively from patients with respiratory tract infections (RTI), bloodstream infections (BSI), or skin and skin structure infections (SSSI) and only one strain per patient episode defined as being clinically significant was included. The isolate distribution by age group was as follows (age group, % of isolates): ≤2 years, 10.1%; 3–18 years, 9.4%; 19–64 years, 44.6%; ≥65 years, 29.7%; patient age unknown, 6.2%. Isolates were identified by the submitting laboratories and confirmed by JMI Laboratories (North Liberty, Iowa, USA) using standard bacteriologic algorithms and methodologies, including the use of Vitek 2 Identification Systems (bioMerieux, Hazelwood, Missouri, USA) and 16S rRNA sequencing, where needed.

Susceptibility testing

Susceptibility testing was performed as per the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method[9] utilizing validated broth microdilution trays produced by TREK Diagnostics (Cleveland, Ohio, USA). Three media types were used: cation-adjusted Mueller-Hinton broth, cation-adjusted Mueller-Hinton broth with 2.5–5% lysed horse blood (for testing streptococci) and Haemophilus Test Medium (HTM). Quality control (QC) ranges for solithromycin were as recently published.[11] QC ranges and interpretive criteria for comparator compounds were those published by CLSI.[10] Tested QC strains included *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *S. pneumoniae* ATCC 49619 and *Haemophilus influenzae* ATCC 49247 and 49677. All QC results were within published limits. Depending upon the species, the following comparison antimicrobial agents were tested: amoxicillin/clavulanate, azithromycin, ceftriaxone, cefuroxime, clarithromycin, clindamycin, daptomycin, erythromycin, levofloxacin, linezolid, oxacillin, penicillin, quinupristin/dalfopristin, teicoplanin, telithromycin, tetracycline, trimethoprim/sulfamethoxazole (TMP/SMX), and vancomycin.

Results

A total of 10,670 isolates were evaluated and MIC distributions of organism groups analyzed are listed in Table 1. Solithromycin spectrum of activity and percent susceptible/resistant (where available) of comparator antimicrobial agents are shown in Table 2. The following summarizes these findings by species or organism group.

S. pneumoniae

Among 1363 *S. pneumoniae* isolates, 99.9% of the strains displayed solithromycin MIC values of ≤0.5 mg/L, and all were inhibited at an MIC of 1 mg/L (the current CLSI breakpoint for telithromycin). Two strains had solithromycin MICs at 1 mg/L. These strains, collected in two European countries (France and Ireland), also had telithromycin MICs at 1 mg/L and were non-susceptible to other macrolides, with the isolate from France also being resistant to clindamycin. Solithromycin was observed to be the most active antimicrobial agent with a MIC_{90} of 0.12 mg/L against all *S. pneumoniae* ($n = 1390$) and also against the subset of respiratory tract isolates ($n = 990$). Telithromycin susceptibility rates were >99.0% in both the USA and Europe. When tested against telithromycin non-susceptible strains, solithromycin showed at least equal MIC values, but in most cases solithromycin MIC results were two- to four-fold lower (Table 2). Solithromycin exhibited slightly reduced activity against penicillin-resistant *S. pneumoniae* when compared to penicillin-susceptible strains (MIC_{50} 0.015 and 0.06–0.12 mg/L, respectively), regardless of the CLSI penicillin breakpoint used (parenteral versus oral). Penicillin-resistant strains also showed higher resistance rates to

Table 1 MIC frequency distributions of solithromycin when tested against bacterial pathogens recovered as part of the global surveillance program for 2009.

Organism group (no. tested)[a]	Number of isolates inhibited at MIC (mg/L):										
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	≥[a]
S. pneumoniae (1363)	1084	90	64	108	15	2	0	0	0	0	0
USA (796)	562	73	56	93	12	0	0	0	0	0	0
Europe (567)	522	17	8	15	3	2	0	0	0	0	0
H. influenzae (727)	0	0	7	6	134	411	154	8	2	1	4
USA (445)	0	0	6	3	71	235	119	6	2	1	2
Europe (282)	0	0	1	3	63	176	35	2	0	0	2
M. catarrhalis (313)	42	193	76	2	0	0	0	0	0	0	0
USA (198)	31	114	51	2	0	0	0	0	0	0	0
Europe (115)	11	79	25	0	0	0	0	0	0	0	0
S. aureus (4729)	581	3135	250	22	12	5	6	6	—	—	712
USA (2970)	306	1899	184	13	7	1	5	5	—	—	550
Europe (1759)	275	1236	66	9	5	4	1	1	—	—	162
Coagulase-negative staphylococci (862)	288	246	65	8	3	1	2	2	—	—	247
USA (329)	109	98	17	4	0	0	2	1	—	—	98
Europe (533)	179	148	48	4	3	1	0	1	—	—	149
Enterococci (1609)	527	78	49	46	94	276	440	85	—	—	14
USA (872)	296	53	38	33	30	123	235	53	—	—	11
Europe (737)	231	25	11	13	64	153	205	32	—	—	3
Beta-haemolytic streptococci (757)	668	58	18	7	6	0	0	0	—	—	14
USA (446)	385	46	11	3	1	0	0	0	—	—	11
Europe (311)	283	12	7	4	5	0	0	0	—	—	3
Viridans group streptococci (310)	266	30	9	3	1	0	0	0	—	—	14
USA (172)	141	19	9	1	1	0	0	0	—	—	11
Europe (138)	125	11	0	2	0	0	0	0	—	—	3

[a] ≥off-scale results.

other non-β-lactam compounds, such as tetracycline and fluoroquinolones (data not shown). Comparison of geographic regions showed that *S. pneumoniae* isolated in Europe were considerably more susceptible to macrolides (erythromycin susceptibility 74.1%) compared to strains from the USA (58.9%); however, clindamycin susceptibility was similar in both regions at 81.1% and 80.3%, respectively. Conversely, penicillin susceptibility (CLSI oral breakpoints) was higher in the USA (86.4%) than in Europe (71.4%). Overall tetracycline susceptibility was 76.4% and varied little between the USA (75.9%) and Europe (77.2%). TMP/SMX was more active against European isolates (76.9% susceptible) compared to isolates from the USA (65.3% susceptible). Levofloxacin susceptibility was 99.0% overall and varied little between Europe (99.1%) and the USA (98.9%).

H. influenzae

Against 726 *H. influenzae* isolates, solithromycin showed activity and potency comparable to azithromycin (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L) and was two- to eight-fold more potent than telithromycin and clarithromycin (MIC_{90}, 4 and 16 mg/L, respectively), see Table 2. Solithromycin was active against 99.0% of the isolates at ≤4 mg/L, whereas telithromycin was active against 98.5% of these strains at this same breakpoint concentration (≤4 mg/L).[10] Applying current CLSI breakpoints,[10] 71.5 and 99 of *H. influenzae* isolates were considered susceptible to clarithromycin and azithromycin, respectively. Solithromycin activity was not influenced by β-lactamase status having a $MIC_{50/90}$ of 1/2 mg/L for both β-lactamase positive and negative isolates (Table 2). Agents showing >99% susceptibility rates included levofloxacin, amoxicillin/clavulanate, ceftriaxone, cefuroxime and tetracycline. Solithromycin *in vitro* activity was unaffected by ampicillin MIC values and/or β-lactamase production (Table 2). However, the activity of this fluoroketolide was eight-fold less when this compound was tested against azithromycin-resistant strains (7 strains detected in this survey, data not shown). Telithromycin and clarithromycin also showed decreased activity against azithromycin-resistant strains. Susceptibility patterns of *H. influenzae* collected in USA and Europe were very similar and solithromycin activity was identical in both regions and overall (MIC_{50}, 1 mg/L and MIC_{90}, 2 mg/L; Table 1).

Moraxella catarrhalis

Solithromycin (MIC_{50}, 0.06 mg/L and MIC_{90}, 0.12 mg/L) demonstrated two-fold greater activity than telithromycin (MIC_{50}, 0.12 mg/L and MIC_{90}, 0.25 mg/L). Antimicrobial activity of solithromycin was very similar for all tested antimicrobial agents against isolates collected in Europe or the USA. All *M. catarrhalis* were inhibited at a solithromycin MIC of 0.25 mg/L.

Table 2 Activity of solithromycin and comparator antimicrobial agents against bacterial pathogens recovered as part of the global surveillance program for 2009.

Organism (no. tested)	Antimicrobial agent	MIC (mg/L)			% by category[a]
		50%	90%	Range	Susceptible/resistant
S. pneumoniae (1363)	Solithromycin	≤0.03	0.12	≤0.03–1	–/–
	Telithromycin	≤0.25	0.5	≤0.25–2	99.9/0.0
	Erythromycin	≤0.25	>2	≤0.25–>2	65.2/34.0
	Clindamycin	≤0.25	>2	≤0.25–>2	80.6/18.8
	Penicillin[b]	≤0.03	2	≤0.03–>4	90.2/1.2
	Penicillin[c]	≤0.03	2	≤0.03–>4	63.8/17.7
	Amoxicillin/clavulanate	≤1	4	≤1–16	88.6/8.7
	Ceftriaxone	≤0.25	1	≤0.25–8	90.4/1.2
	Cefuroxime	≤1	8	≤1–>8	74.6/22.8
	Tetracycline	≤2	>8	≤2–>8	76.4/23.0
	Levofloxacin	1	1	≤0.5–>4	99.0/0.8
	TMP/SMX[d]	≤0.5	>2	≤0.5–>2	70.1/21.5
S. aureus (4729)	Solithromycin	0.06	>4	≤0.03–>4	–/–
	Telithromycin	≤0.25	>2	≤0.25–>2	84.3/15.6
	Erythromycin	>2	>2	≤0.25–>2	49.1/50.2
	Clindamycin	≤0.25	>2	≤0.25–>2	83.9/15.8
	Oxacillin[e]	1	>2	≤0.25–>2	58.9/41.1
	Linezolid	2	2	≤0.06–>8	>99.9/<0.1
	Daptomycin	0.25	0.5	≤0.06–2	>99.9/–
	Vancomycin	1	1	≤0.12–2	100.0/0.0
	Tetracycline	≤2	≤2	≤2–>8	94.3/4.9
	Levofloxacin	≤0.5	>4	≤0.5–>4	64.6/34.8
	TMP/SMX	≤0.5	≤0.5	≤0.5–>2	98.7/1.3
MSSA[f] (2787)	Solithromycin	0.06	0.06	≤0.03–>4	0.06
	Telithromycin	≤0.25	≤0.25	≤0.25–>2	96.4/3.4
	Erythromycin	0.5	>2	≤0.25–>2	74.1/25.0
	Clindamycin	≤0.25	≤0.25	≤0.25–>2	96.2/3.6
	Linezolid	2	2	≤0.06–2	100.0/0.0
	Daptomycin	0.25	0.5	≤0.06–1	100.0/–
	Vancomycin	1	1	≤0.12–2	100.0/0.0
	Tetracycline	≤2	≤2	≤2–>8	95.3/3.8
	Levofloxacin	≤0.5	≤0.5	≤0.5–>4	92.3/7.2
	TMP/SMX	≤0.5	≤0.5	≤0.5–>2	99.2/0.8
MRSA[f] (1942)	Solithromycin	0.06	>4	≤0.03–>4	–/–
	Telithromycin	≤0.25	>2	≤0.25–>2	67.0/33.0
	Erythromycin	>2	>2	≤0.25–>2	13.2/86.4
	Clindamycin	≤0.25	>2	≤0.25–>2	66.3/33.4
	Linezolid	2	2	0.25–>8	99.9/0.1
	Daptomycin	0.5	0.5	0.12–2	99.9/–
	Vancomycin	1	1	0.25–2	100.0/0.0
	Tetracycline	≤2	≤2	≤2–>8	92.8/6.4
	Levofloxacin	>4	>4	≤0.5–>4	24.9/74.4
	TMP/SMX	≤0.5	≤0.5	≤0.5–>2	98.0/2.0
CoNS (862)	Solithromycin	0.06	>4	≤0.03–>4	–/–
	Telithromycin	≤0.25	>2	≤0.25–>2	70.4/29.5
	Erythromycin	>2	>2	≤0.25–>2	36.5/62.4
	Clindamycin	≤0.25	>2	≤0.25–>2	68.7/30.3
	Oxacillin[e]	>2	>2	≤0.25–>2	20.3/79.7
	Linezolid	1	1	≤0.06–>8	99.5/0.5
	Daptomycin	0.25	0.5	≤0.06–1	100.0/–
	Vancomycin	1	2	≤0.12–4	100.0/0.0
	Tetracycline	≤2	>8	≤2–>8	87.1/11.6
	Levofloxacin	4	>4	≤0.5–>4	43.5/54.2

(*continued on next page*)

Table 2 (*continued*)

Organism (no. tested)	Antimicrobial agent	MIC (mg/L)			% by category[a]
		50%	90%	Range	Susceptible/resistant
	TMP/SMX	≤0.5	>2	≤0.5—>2	61.2/38.8
Enterococci (1609)	Solithromycin	1	2	≤0.03—>4	—/—
	Telithromycin	2	>2	≤0.25—>2	—/—
	Erythromycin	>2	>2	≤0.25—>2	7.9/70.0
	Ampicillin	2	>16	≤1—>16	64.5/35.5
	Quinupristin/dalfopristin	>2	>2	≤0.25—>2	30.3/63.1
	Linezolid	1	2	0.25—>8	99.4/0.6
	Daptomycin	1	2	≤0.06—>8	99.9/—
	Vancomycin	1	>16	0.25—>16	76.9/22.2
	Teicoplanin	≤2	>16	≤2—>16	79.5/19.3
	Levofloxacin	>4	>4	≤0.5—>4	47.2/51.0
	TMP/SMX	1	>2	≤0.5—>2	—/—
E. faecalis (966)	Solithromycin	0.06	2	≤0.03—>4	—/—
	Telithromycin	≤0.25	>2	≤0.25—>2	—/—
	Erythromycin	>2	>2	≤0.25—>2	8.9/58.0
	Ampicillin	≤1	2	≤1—>16	99.9/0.1
	Quinupristin/dalfopristin	>2	>2	0.5—>2	0.3/95.8
	Linezolid	2	2	0.25—2	100.0/0.0
	Daptomycin	1	2	≤0.06—8	99.9/—
	Vancomycin	1	2	0.25—>16	97.2/2.6
	Teicoplanin	≤2	≤2	≤2—>16	98.1/1.9
	Levofloxacin	2	>4	≤0.5—>4	67.5/31.9
	TMP/SMX	≤0.5	>2	≤0.5—>2	—/—
E. faecium (581)	Solithromycin	2	4	≤0.03—>4	—/—
	Telithromycin	>2	>2	≤0.25—>2	—/—
	Erythromycin	>2	>2	≤0.25—>2	3.3/92.3
	Ampicillin	>16	>16	≤1—>16	4.8/95.2
	Quinupristin/dalfopristin	1	>2	≤0.25—>2	81.9/11.4
	Linezolid	1	2	0.5—>8	98.5/1.5
	Daptomycin	2	4	0.12—>8	99.8/—
	Vancomycin	>16	>16	0.25—>16	42.7/56.5
	Teicoplanin	16	>16	≤2—>16	47.2/49.7
	Levofloxacin	>4	>4	1—>4	10.5/86.7
	TMP/SMX	>2	>2	≤0.5—>2	—/—
β-haemolytic streptococci (757)[g]	Solithromycin	≤0.03	0.06	≤0.03—0.5	—/—
	Telithromycin	≤0.25	≤0.25	≤0.25—>2	—/—
	Erythromycin	≤0.25	>2	≤0.25—>2	74.1/24.3
	Clindamycin	≤0.25	>2	≤0.25—>2	87.6/11.8
	Linezolid	1	1	≤0.06—2	100.0/—
	Penicillin	0.03	0.06	≤0.015—0.12	100.0/—
	Daptomycin	0.12	0.25	≤0.06—0.5	100.0/—
	Vancomycin	0.5	0.5	≤0.12—1	100.0/—
	Levofloxacin	≤0.5	1	≤0.5—>4	98.9/0.9
	TMP/SMX	≤0.5	≤0.5	≤0.5—>2	—/—
Viridans group streptococci (310)[h]	Solithromycin	≤0.03	0.06	≤0.03—1	—/—
	Telithromycin	≤0.25	≤0.25	≤0.25—>2	—/—
	Erythromycin	≤0.25	>2	≤0.25—>2	54.2/43.5
	Clindamycin	≤0.25	0.5	≤0.25—>2	88.4/9.7
	Linezolid	1	1	0.12—2	100.0/—
	Penicillin	0.06	1	≤0.015—32	76.5/3.5
	Daptomycin	0.25	1	≤0.06—2	99.7/—
	Vancomycin	0.5	1	≤0.12—1	100.0/—
	Levofloxacin	1	2	≤0.5—>4	94.5/3.9
	TMP/SMX	≤0.5	>2	≤0.5—>2	—/—

Table 2 (*continued*)

Organism (no. tested)	Antimicrobial agent	MIC (mg/L) 50%	90%	Range	% by category[a] Susceptible/resistant
H. influenzae					
β-lactamase positive (150)	Solithromycin	1	2	0.12—>16	—/—
	Telithromycin	2	4	0.5—>8	98.0/2.0
	Clarithromycin	8	16	2—>32	62.7/9.3
	Azithromycin	1	4	≤0.5—>4	98.0/—
	Tetracycline	≤2	≤2	≤2—>8	96.7/3.3
	Amox/clav	≤1	2	≤1—8	99.3/0.7
	Cefuroxime	≤1	2	≤1—4	100.0/0.0
	Ceftriaxone	≤0.25	≤0.25	≤0.25	100.0/—
	Levofloxacin	≤0.5	≤0.5	≤0.5	100.0/—
	TMP/SMX	≤0.5	>2	≤0.5—>2	75.3/23.3
β-lactamase-negative (576)	Solithromycin	1	2	0.12—>16	—/—
	Telithromycin	2	4	0.12—>8	98.6/0.5
	Clarithromycin	8	16	≤0.25—>32	73.8/3.8
	Azithromycin	1	2	≤0.5—>4	99.3/—
	Tetracycline	≤2	≤2	≤2—>8	99.5/0.5
	Amox/clav	0.5	1	≤0.25—4	100.0/0.0
	Cefuroxime	≤1	2	≤1—>8	99.3/0.3
	Ceftriaxone	≤0.25	≤0.25	≤0.25—1	100.0/—
	Levofloxacin	≤0.5	≤0.5	≤0.5	100.0/—
	TMP/SMX	≤0.5	>2	≤0.5—>2	72.5/23.1
M. catarrhalis (313)	Solithromycin	0.06	0.12	≤0.008—0.25	—/—
	Telithromycin	0.12	0.25	≤0.06—0.25	—/—
	Erythromycin	0.12	0.25	≤0.06—0.5	—/—
	Ampicillin	≤1	2	≤1—8	—/—
	Amoxicillin/clavulanate	≤1	≤1	≤1—2	—/—
	Ceftriaxone	≤0.25	0.5	≤0.25—2	—/—
	Cefuroxime	≤1	2	≤1—>8	—/—
	Tetracycline	≤2	≤2	≤2—8	—/—
	Imipenem	≤0.12	≤0.12	≤0.12—0.25	—/—
	Levofloxacin	≤0.5	≤0.5	≤0.5—1	—/—
	TMP/SMX	≤0.5	≤0.5	≤0.5—>2	—/—

[a] Criteria as published by the CLSI.[9,10]
[b] Criteria as published by the CLSI[9,10] for 'Penicillin parenteral (non-meningitis)'.
[c] Criteria as published by the CLSI[9,10] for 'Penicillin (oral penicillin V)'.
[d] TMP/SMX = trimethoprim/sulfamethoxazole.
[e] Criteria as published by the CLSI,[9,10] β-lactam susceptibility should be directed by the oxacillin test results.
[f] MSSA = Methicillin-susceptible *S. aureus* and MRSA = methicillin-resistant *S. aureus*.
[g] Includes: *Streptococcus dysgalactiae* (18 isolates), Group A *Streptococcus* (264 isolates), Group B *Streptococcus* (371 isolates), Group C *Streptococcus* (29 isolates), Group F *Streptococcus* (8 isolates), and Group G *Streptococcus* (67 isolates).
[h] Includes: *Streptococcus anginosus* (22 isolates), *Streptococcus bovis* (21 isolates), *Streptococcus constellatus* (11 isolates), *Streptococcus equinus* (one isolate), *Streptococcus gallolyticus* (four isolates), *Streptococcus gordonii* (two isolates), *Streptococcus intermedius* (four isolates), *Streptococcus milleri* (six isolates), *Streptococcus mitis* (59 isolates), *Streptococcus mutans* (two isolates), *Streptococcus oralis* (17 isolates), *Streptococcus parasanguinis* (13 isolates), *Streptococcus salivarius* (22 isolates), *Streptococcus sanguinis* (15 isolates), *Streptococcus vestibularis* (one isolate), unspeciated *Streptococcus* (two isolates), unspeciated alpha-haemolytic streptococci (two isolates), and unspeciated viridans group streptococci (106 isolates).

S. aureus

Against 4729 *S. aureus* isolates, solithromycin (MIC_{50}, 0.06 mg/L and MIC_{90}, >4 mg/L) appeared to have similar activity to telithromycin; however, a direct comparison of MIC_{50} was not possible because the concentration range tested for telithromycin did not extend below 0.25 mg/L. Solithromycin activity was greater against methicillin-susceptible *S. aureus* (MSSA; MIC_{50}, 0.06 mg/L and MIC_{90}, 0.06 mg/L) compared to methicillin-resistant *S. aureus* (MRSA; MIC_{50}, 0.06 mg/L and MIC_{90}, >4 mg/L). The activity of solithromycin against *S. aureus* in Europe was greater (MIC_{90}, 0.25 mg/L) than in the USA (MIC_{90}, >4 mg/L); however this can be explained by the higher MRSA rate in the USA (51.3%) compared to Europe (23.8%). Comparison of geographic regions showed that isolates from Europe were considerably more susceptible to macrolides (erythromycin; MSSA 82.9%, MRSA 31.7%) compared to the

USA (MSSA 65.9%, MRSA 8.1%%), however clindamycin susceptibility was similar in both regions (data not shown). Although fluoroquinolone susceptibility was most similar in MSSA from Europe (levofloxacin 94.7%) and the USA (90.0%), susceptibility was greater against MRSA from the USA (29.0%) than in Europe (10.0%). Overall tetracycline susceptibility was 94.3% (Table 2) and varied little between MSSA (95.3%) and MRSA (92.8%) or between the USA (95.0%) and Europe (93.0%). Susceptibility rates were high against all isolates for vancomycin (100.0%), daptomycin (>99.9%), linezolid (>99.9%), and TMP/SMX (98.7%).

Coagulase-negative staphylococci (CoNS)

The activity of solithromycin and telithromycin against CoNS was similar to that described above for *S. aureus*. Against all tested isolates, solithromycin activity was bimodal (MIC_{50}, 0.06 mg/L and MIC_{90}, >4 mg/L) with activity being higher against methicillin-susceptible (MS)-CoNS (MIC_{90}, 0.12 mg/L) than against methicillin-resistant (MR)-CoNS (MIC_{90}, >4 mg/mL) with similar results observed for the USA and Europe. Comparison of geographic regions showed that isolates from Europe and the USA were similar with regards to susceptibility to comparator antimicrobial agents. Against all isolates, macrolide (erythromycin) susceptibility was 36.5% (MS-CoNS 64.0%, MR-CoNs 29.5%), clindamycin susceptibility was 68.7% (MS-CoNS 95.4%, MR-CoNs 61.9%), fluoroquinolone (levofloxacin) susceptibility was 43.5% (MS-CoNS 88.6%, MR-CoNs 32.0%), tetracycline susceptibility was 87.1% (MS-CoNS 89.1%, MR-CoNs 86.6%), and TMP/SMX susceptibility was 61.2% (MS-CoNS 92.0%, MR-CoNs 53.4%). Susceptibility rates were very high when testing all isolates against vancomycin (99.1%), daptomycin (100.0%), and linezolid (99.5%).

Enterococci

Against 1609 enterococci, solithromycin (MIC_{50}, 1 mg/L and MIC_{90}, 2 g/L; Table 2) demonstrated activity two-fold higher than telithromycin (MIC_{50}, 2 mg/L and MIC_{90}, >2 mg/L). Antimicrobial activity was very similar for all tested antimicrobial agents against isolates collected in Europe or the USA. The activity of solithromycin was greater against vancomycin-susceptible enterococci (MIC_{50}, 0.12 mg/L) compared to vancomycin-non-susceptible enterococci (MIC_{50}, 2 mg/L; data not shown). Interestingly, solithromycin was more active against vancomycin-susceptible isolates from the USA (MIC_{50}, 0.12 mg/L) compared to Europe (MIC_{50}, 1 mg/L). Solithromycin was more active against *E. faecalis* (MIC_{50}, 0.06 mg/L and MIC_{90}, 2 mg/L) compared to *Enterococcus faecium* (MIC_{50}, 2 mg/L and MIC_{90}, 4 mg/L), see Table 2. Overall, 22.2% of enterococci (range by species 2.6—56.5%, Table 2) were resistant to vancomycin, 35.5% were resistant to ampicillin (generally *E. faecium*), 63.1% were resistant to quinupristin-dalfopristin (generally *E. faecalis*), and 51.0% were resistant to levofloxacin. Susceptibility rates were high against all isolates for daptomycin (99.9%), and linezolid (99.4%).

Beta-haemolytic streptococci (BHS)

Solithromycin was very active against all 757 BHS (MIC_{50}, ≤0.03 mg/L and MIC_{90}, 0.06 mg/L). Interestingly, telithromycin MIC range extended to >2 mg/L (7 isolates), whereas the solithromycin MIC range for this group was considerably lower at 0.06—0.5 mg/L. Erythromycin susceptibility was only 74.1% overall (Table 2), but higher in Europe (81.7%) than the USA (68.8%). Clindamycin susceptibility was 87.6% overall and similar for Europe and the USA. Many other comparator agents were very active against BHS.

Viridans group streptococci (VGS)

Solithromycin was very active against 310 VGS isolates (MIC_{50}, ≤0.03 mg/L and MIC_{90}, 0.06 mg/L), with the highest MIC at only 1 mg/L (Tables 1 and 2). Erythromycin susceptibility was only 54.2% overall and higher in Europe (64.5%) than the USA (45.9%). Clindamycin susceptibility was 88.4% overall and identical for Europe and the USA. Penicillin susceptibility was only 76.5% overall and similar in the two analyzed regions. Levofloxacin susceptibility was 94.5% overall and slightly higher in Europe (98.6%) than the USA (91.3%).

Discussion

Pathogens causing CABP are becoming increasingly difficult to treat empirically due to the development of antimicrobial resistances.[12] Important recent developments are the rapid progression of clonal multidrug-resistant *S. pneumoniae* (MDRSP) serotype 19A in the USA,[13,14] reports of macrolide resistance in *M. pneumoniae*,[15] and the increasing involvement of community-associated MRSA in severe necrotizing CABP.[16] In earlier investigations, solithromycin has demonstrated very potent activity against *S. pneumoniae*, including strains with defined macrolide resistance genotypes,[4] penicillin-resistant strains, and clonal serotype 19A MDR pneumococci.[6] Solithromycin has also demonstrated potent activity against *H. influenzae* and *M. catarrhalis*, regardless of β-lactamase status[6] and against *Mycoplasma pneumoniae*, including macrolide-resistant strains.[8] The present report provides contemporary 2009 clinical isolates to further support preliminary studies demonstrating solithromycin's potent activity against a large number of geographically diverse surveillance isolates of the major causative agents of CABP, i.e. *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*.

The great majority of SSSI's are monomicrobial and are caused by *S. aureus* and/or BHS such as *Streptococcus pyogenes*. These common community-acquired infections include simple abscesses, impetiginous lesions, furuncles, and cellulitis. They are usually confined to the superficial layers of the skin and do not disseminate into the bloodstream.[17] Current guidelines recommend incision and drainage and, if needed, for antimicrobial therapy the use of a semi-synthetic penicillin, first-generation or second-generation oral cephalosporin, a macrolide, or clindamycin.[18] Community-associated (CA) —MRSA (predominantly pulsed-field-type USA300) has been shown to be of higher prevalence than MSSA in patients presenting to emergency departments in the USA.[19] Similar infections in Europe are of lower but increasing prevalence and, although reports of USA300 are increasing in Europe, the most common strain detected is the European clone (ST80-IV).[20] In contrast to hospital-associated MRSA clones, CA-MRSA is typically resistant to only β-lactam agents and macrolides.

In this study, solithromycin was very active against MSSA ($MIC_{50/90}$, 0.06/0.06 mg/L) and most MRSA ($MIC_{50/90}$, 0.06/>4 mg/L). We have recently demonstrated that solithromycin was more potent against CA-MRSA ($MIC_{50/90}$, 0.12/0.12 mg/L; 30 isolates) than hospital-acquired-MRSA.[21] With an MIC_{90} of 0.06 mg/L the current data shows that solithromycin was very active against β-haemolytic streptococci (including 264 *S. pyogenes*, Table 2). Also, as seen previously, solithromycin was very active against BHS resistant to telithromycin.[6] Solithromycin, therefore, demonstrated high activity against the major pathogens causing SSSI (i.e. MSSA, CA-MRSA, and BHS). However, it will be important to monitor this clinical situation with ongoing resistance surveillance programs as, over the past 5 years, USA300 has been becoming increasingly resistant to multiple antimicrobial agents — including clindamycin and telithromycin.[22]

In summary, the data presented in this study demonstrates that solithromycin possesses favorable *in vitro* potency and spectrum of activity against contemporary bacterial pathogens most frequently causing CABP and SSSI in Europe and the USA. Solithromycin has a favorable *in vitro* profile compared to commonly prescribed antimicrobial agents such as macrolides, clindamycin, ketolide, oral β-lactams and the fluoroquinolones. As such, solithromycin is an important candidate for further clinical development as an oral or parenteral treatment of these infections. Continued antimicrobial resistance surveillance is warranted to monitor resistance trends.

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