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Activity of Solithromycin and Comparators against Respiratory Tract Pathogens Collected in the 2016 Global SENTRY Surveillance Program D SHORTRIDGE, JM STREIT, PR RHOMBERG, RK FLAMM JMI Laboratories, North Liberty, Iowa, USA

Amended Abstract

Introduction: Solithromycin (SOL) is a fluoroketolide being studied for treatment of community-acquired bacterial pneumonia (CABP) caused by pathogens including Streptococcus pneumoniae (SPN), Haemophilus influenzae (HI), Moraxella catarrhalis (MCAT), and Staphylococcus aureus (SA). In this study, the activity of SOL against 6,495 recent respiratory pathogens collected during 2016 from 94 hospitals in the United States (US), Europe (EU), Asia-Pacific (APAC), and Latin America (LAM), was determined as a part of the SENTRY surveillance program.

Methods: Isolates tested were composed of 1,145 SA, 2,129 SPN, 1,216 HI, 421 MCAT, and 1,584 beta-hemolytic streptococci (BHS) that included 749 S. pyogenes. More than 80% (5,283/6,495) of the isolates were from respiratory tract and bloodstream infections. Susceptibilities (S) to SOL and comparators were determined by the CLSI broth microdilution method in a central monitoring laboratory (JMI Laboratories). Other comparators tested included azithromycin (AZI) and telithromycin (TEL). CLSI (2017) interpretive criteria were used for AZI. TEL used CLSI criteria for SPN and HI and EUCAST (2017) criteria were used for BHS and MCAT.

Results: The SOL cumulative percentage MIC distribution and MIC_{50/90} values for respiratory pathogens are shown in the table. SOL inhibited all SPN isolates at ≤0.5 µg/mL, 64.3% were S to AZI (MIC_{50/90} 0.06/>32 µg/mL), and 99.9% were S to TEL (MIC_{50/90} 0.03/0.25 μ g/mL). All BHS isolates were inhibited by SOL at ≤1.0 μ g/mL, 73.2% were S to AZI (MIC_{50/90} 0.12/>32 µg/mL), and 97.7% had a TEL MIC ≤1.0 µg/mL (MIC_{50/90} 0.03/0.12 µg/mL). Activity for the 3 drugs against HI was similar; 98.9% had a SOL MIC $\leq 4.0 \ \mu g/mL$, 98.8% were S to AZI (MIC_{50/90} 0.5/1.0 $\mu g/mL$), and 98.4% were S to TEL (MIC_{50/90} 2.0/2.0 µg/mL). For SA, 89.0% had a SOL MIC ≤1.0 µg/mL, 59.4% were S to AZI (MIC_{50/90} 0.5/>32 μ g/mL), and 87.0% were S to TEL (MIC_{50/90} 0.12/ >32 µg/mL). All MCAT isolates were inhibited by ≤0.12 µg/mL of SOL or AZI, and ≤0.25 µg/mL for TEL.

Conclusions: SOL showed encouraging potency against SPN and BHS and was more potent than AZI. SOL had lower MIC_{50/90} values than TEL for SPN and BHS. For HI and MCAT, SOL had similar potency to AZI and TEL. These data support continued development of SOL as a treatment for community-acquired bacterial pneumonia.

MIC (µg/mL)				Cumulative % inhibited at SOL MIC:								
50%	90%	≤0.03	0.06	0.12	0.25	0.5	1.0	2.0	4.0	≥8.0		
800.0	0.12	81.2	87.3	93.1	99.2	100.0						
0.015	0.06	89.0	94.9	96.8	98.9	99.9	100.0					
1	2		0.0	0.5	1.3	16.4	74.5	97.7	98.9	100.0		
0.06	0.12	15.0	76.2	100.0								
0.03	16	61.4	86.9	88.1	88.6	88.9	89.0	89.0	89.3	100.0		
	50% 0.008 0.015 1 0.06 0.03	50% 90% 0.008 0.12 0.015 0.06 1 2 0.06 0.12 0.03 16	50%90% ≤ 0.03 0.008 0.12 81.2 0.015 0.06 89.0 1 2 0.06 0.12 15.0 0.03 16 61.4	50%90% ≤ 0.03 0.060.0080.1281.287.30.0150.0689.094.9120.00.060.1215.076.20.031661.486.9	50%90% ≤ 0.03 0.060.120.0080.1281.287.393.10.0150.0689.094.996.8120.00.50.060.1215.076.2100.00.031661.486.988.1	50%90% ≤ 0.03 0.060.120.250.0080.1281.287.393.199.20.0150.0689.094.996.898.9120.00.51.30.060.1215.076.2100.0—0.031661.486.988.188.6	50%90% ≤ 0.03 0.060.120.250.50.0080.1281.287.393.199.2100.00.0150.0689.094.996.898.999.9120.00.51.316.40.060.1215.076.2100.00.031661.486.988.188.688.9	50%90% ≤ 0.03 0.060.120.250.51.00.0080.1281.287.393.199.2100.0—0.0150.0689.094.996.898.999.9100.0120.00.51.316.474.50.060.1215.076.2100.0——0.031661.486.988.188.688.989.0	50%90% ≤ 0.03 0.060.120.250.51.02.00.0080.1281.287.393.199.2100.00.0150.0689.094.996.898.999.9100.0120.00.51.316.474.597.70.060.1215.076.2100.00.031661.486.988.188.688.989.089.0	50%90% ≤ 0.03 0.060.120.250.51.02.04.00.0080.1281.287.393.199.2100.00.0150.0689.094.996.898.999.9100.0120.00.51.316.474.597.798.90.060.1215.076.2100.00.031661.486.988.188.688.989.089.089.3		

Introduction

- Solithromycin (SOL) is a fluoroketolide being studied for treatment of communityacquired bacterial pneumonia (CABP) caused by pathogens that include Streptococcus pneumoniae (SPN), beta-hemolytic streptococci (BHS), Haemophilus influenzae (HI), Moraxella catarrhalis (MCAT), and Staphylococcus aureus (SA)
- Ketolides have potent activity against respiratory pathogens, including macrolideresistant streptococci, HI, and MCAT
- In this study, the activity of SOL against 6,495 recent respiratory pathogens collected during 2016 from 94 hospitals in the United States (US), Europe (EU), Asia-Pacific (APAC), and Latin America (LAM) was determined as a part of the SENTRY Antimicrobial Surveillance Program
- SOL activity was compared to the ketolide comparator telithromycin (TEL) and macrolide comparator azithromycin (AZI)

- A total of 6,495 non-duplicated isolates were collected prospectively during 2016 from 94 medical centers located in the US (39 centers, 2,925 isolates), EU (34 centers, 2,451 isolates), APAC (11 centers, 674 isolates), and LAM (10 centers, 445 isolates)
- Isolates were recovered consecutively from patients with respiratory tract infections (RTI), bloodstream infections (BSI), skin and skin structure infections (SSSI), and other infection types; only 1 strain per patient episode that was defined as being clinically significant was included
- 81.3% (5,283/6,495) of the isolates were from respiratory tract and bloodstream infections
- Isolates were identified by the site and were confirmed by JMI Laboratories using standard biochemical tests, matrix-assisted laser desorption ionization-time of flight mass spectrometry, or DNA sequencing when required
- Susceptibilities (S) to SOL and comparators were determined by the CLSI broth microdilution method at JMI Laboratories
- Isolates tested were composed of 1,145 SA, 2,129 SPN, 1,216 HI, 421 MCAT, and 1,584 beta-hemolytic streptococci (BHS) that included 749 S. pyogenes
- Class comparators tested were macrolide (AZI) and ketolide (TEL)
- Other drugs tested included: clindamycin, erythromycin, penicillin, oxacillin, vancomycin, levofloxacin, trimethoprim/sulfamethoxazole, tetracycline, and ceftriaxone
- Interpretive criteria applied were CLSI M100-S27 (2017) and EUCAST v. 7.0 (2017) - TEL used CLSI criteria for SPN and HI and EUCAST (2017) criteria were used for BHS and MCAT.

Figure 1 Solithromycin cumulative percent of inhibition for respiratory pathogens



Materials and Methods

Results

• The activities of SOL and comparators are shown in Table 1, and the cumulative percent inhibition of the RTI pathogens for SOL are shown in Figure 1

- All SPN isolates were inhibited by SOL at ≤0.5 μ g/mL (MIC_{50/90},0.008/0.12 μ g/mL), 64.3% were S to AZI (MIC_{50/90} 0.06/>32 μ g/mL), and 99.9% were S to TEL (MIC_{50/90} 0.03/ 0.25 µg/mL) by CLŠĨ ŠPN S breakpoints of ≤0.5 and ≤1 for AZI and TEL respectively

SPN, Streptococcus pneumoniae; BHS, beta-haemolytic streptococci; HI, Haemophilus influenzae; MCAT, Moraxella catarrhalis; SA, Staphylococcus aureus

- All BHS isolates were inhibited by ≤1.0 µg/mL of SOL, 73.2% were S to AZI (MIC_{50/90} 0.12/>32 μg/mL), and 94.9% S to TEL (EUCAST; MIC_{50/90} 0.03/0.12 μg/mL)
- SOL was the most active agent tested against SPN and BHS
- Activities for the macrolides and ketolides against HI were similar with 98.9% having a SOL MIC ≤4.0 µg/mL, 98.8% were S to AZI (MIC_{50/90} 0.5/1.0 µg/mL), and 98.4% were S to TEL (MIC_{50/90} 2.0/2.0 µg/mL)
- For SA, 89.0% had a SOL MIC ≤1.0 µg/mL, 59.4% were S to AZI (MIC_{50/90} 0.5/ >32 µg/mL), and 87.0% were S to TEL (MIC_{50/90} 0.12/>32 µg/mL)
- All MCAT isolates were inhibited by ≤0.12 µg/mL of SOL and AZI or by ≤0.25µg/mL of

Table 1 Activities of solithromycin and comparators

	MIC	MIC	0/ 0
Antimicrobial agent			%S
Staphylococcus aureus	(n=1,145)	10	
Solithromycin	0.03	16	50
Erythromycin	0.25	>8	59
Clindamycin	≤0.25	>2	86.9
Vancomycin	0.5	1	100
Linezolid	1	1	100
Oxacillin	0.5	>2	65.8
Penicillin	>2	>2	19.7
Tetracycline	≤0.5	≤0.5	94.1
Ceftriaxone	4	>8	65.8
Levofloxacin	0.25	>4	71
Trimethoprim-			
sulfamethoxazole	≤0.5	≤0.5	98.5
Azithromycin	0.5	>32	59.4
Telithromycin	0.12	>32	87
Streptococcus pneumor	<i>niae</i> (n=2,129)	
Solithromycin	800.0	0.12	
Amoxicillin-clavulanic			
acid	≤0.03	2	93.1
Erythromycin	0.06	>32	64.1
Clindamycin	≤0.25	>2	83
Vancomycin	0.25	0.5	100
Penicillin	0.03	2	65.6
Tetracycline	≤0.25	>8	77.9
Ceftriaxone	0.03	1	84.8
Levofloxacin	1	1	98.5
Trimethoprim-			00.0
sulfamethoxazole	0.25	>4	71
Azithromycin	0.20	>32	64.3
Clarithromycin	0.00	>2	64.3
Tolithromycin	0.00	0.25	04.5
ß haamalytic strantasas	0.05	0.23	33.3
P-naemorytic Streptococ	0.015	0.06	
	0.015	0.00	
Amoxiciliin-clavulanic	<0.02	0.00	00.0
	≤0.03	0.06	99.9
Erythromycin	0.03	>32	73.0
Clindamycin	≤0.25	>2	85.6
Vancomycin	0.25	0.5	100
Linezolid	1	1	100
Penicillin	0.015	0.06	99.9
letracycline	0.5	>8	55.6
Ceftriaxone	0.03	0.06	100
Levofloxacin	0.5	1	98.4
Trimethoprim-			
sulfamethoxazole	≤0.12	0.25	
Azithromycin	0.12	>32	73.2
Telithromycin	0.03	0.12	
Haemophilus influenzae	e (n=1,216)		
Solithromycin	1	2	
Ampicillin	1	>8	63.3
Amoxicillin-clavulanic			
acid	1	2	98.4
Tetracycline	0.5	1	99.1
Ceftriaxone	0.004	0.015	100
Levofloxacin	0.015	0.03	99.7
Trimethoprim-			
sulfamethoxazole	0.12	>4	65.1
Azithromvcin	0.5	1	98.8
Telithromycin	2	2	98.4
Moraxella catarrhalis (n	=421)	_	
Solithromycin	0.06	0.12	
Amoxicillin-clavulanic			
acid	0 12	0.25	100
Penicillin	>4	>4	
Tetracycline	0.25	0.5	99 5
Ceftriaxone	0.25	0.0	100
	0.20	0.0	100
Trimethonrim	0.00	0.00	100
sulfamathayazala	0 10	05	06 7
Δzithromyoin	0.12	0.0	30.7 100
Telithromycin	0.015	0.03	100

Criteria as published by CLSI [2017] and EUCAST [2017] Oxacillin nonsusceptible reported as resistant

Using oral breakpoints

Using meningitis breakpoints ^e Beta-lactamase positive reported resistant for penicillins without inhibitor

- A comparison of SOL and TEL activities against all SPN and macrolide-resistant SPN (erythromycin MIC ≥1) are shown in Figure 2
- Both ketolides have similar activity to SPN overall
- SOL (MIC_{50/90} 0.06/0.25 μ g/mL) is 2-fold more active than TEL (MIC_{50/90} 0.12/0.5 µg/mL) against macrolide-resistant strains



Figure 2 Comparison of the cumulative percent inhibition for solithromycin and telithromycin against S. pneumoniae and erythromycin-resistant S. pneumoniae



Table 2 Solithromycin MIC distribution for respiratory tract infection pathogens by continent

Organism/ continent	<0 002	0 004	0 008	0 015	0.03	0.06	0 12	0 25	0.5	1	2	4	8	16	32	>32	Total
Haemophilus		01001			0100	0100	UTTE	0120					•				Total
influenzae							6	10		183	282	15	3	3	1	6	1216
Asia-Pacific							Ŭ	3	15	56	29	2	Ū	Ŭ	•	Ŭ	105
Furope							4	Ũ	57	268	90	4	1	1	1	1	427
Latin America							•	1	11	25	8	1	1		•		47
US							2	6	100	358	155	8	1	2		5	637
Moraxella							_	Ū				Ū		_		U	
catarrhalis		2	21		40	258	100										421
Asia-Pacific			2		4	28	19										53
Europe			9		11	128	45										193
Latin America			1		3	16											20
US		2	9		22	86	36										155
Staphylococcus																	
aureus	1	1	1	20	680	292	14	5	4	1		3	5	10	48	60	1145
Asia-Pacific		1		1	79	20	2						1	1	10	8	123
Europe		-	1	12	264	102	1		1					2	4	13	400
Latin America	1		-	2	120	57	6	3	-			1		4	13	10	217
US				5	217	113	5	2	3	1		2	4	3	21	29	405
Streptococcus				-		-	-							-		-	
agalactiae		1	80	309	46	79	14	19	7	2							557
Asia-Pacific			6	49	5		2	2	1								65
Europe		1	26	99	5	17	5	5	1	1							160
Latin America			5	18	4		1	1									29
US			43	143	32	62	6	11	5	1							303
Streptococcus																	
dysgalactiae		1	7	212	35	5	4	3	7								274
Asia-Pacific			1	29	6	5	2	1	1								45
Europe			3	98	19		1	1	2								124
Latin America			2	6	2												10
US	1		1	79	8		1	1	4								95
Streptococcus																	
pneumoniae	9	121	1066	382	150	130	124	131	16								2129
Asia-Pacific	1	7	74	45	19	13	6	19	4								188
Europe	4	73	528	176	40	24	21	26	5								897
Latin America		1	49	26	7	2	3	6									94
US	4	40	415	135	84	91	94	80	7								950
Streptococcus																	
pyogenes		3	317	379	17	10	11	11	1								749
Asia-Pacific			29	56	3	2		4									94
Europe		2	83	143	6	4	6	4									248
Latin America		1	16	10	1												28
US			189	170	7	4	5	3	1								379

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- The SPN macrolide resistance rates varied for the regions studied with the US macrolide (erythromcyin) resistance rate of 46.3%, and was 22.0% for EU, 47.7% for APAC and 31.9% for LAM
- SPN susceptibility to AZI was 53.3% in US, 77.7% in EU, 54.3% in APAC and 68.1% in LAM
- SOL MIC distributions for each region (US, Europe, Asia-Pacific, and Latin America) are shown in Table 2
- Little variation existed in SOL MIC distribution between regions
- Overall rates of streptococci with SOL MICs $\geq 1 \mu g/mL$ were very low with only 2 BHS having an MIC of 1 µg/mL, 1 from the US and 1 from EU (no streptococci had a SOL MIC > 1 µg/mL)
- No SPN had an MIC ≥1 μ g/mL
- Only 13 of 1,216 HI had MICs >4 µg/mL, and these isolates also had elevated MICs to TEL
- These unusual resistant isolates were from the US (8), EU (4), and Latin America (1)
- The number of SA isolates with SOL MICs ≥1 µg/mL was lowest in EU (4.8%); rates were similar (12.9–16.3%) in the US, APAC, and LAM

Conclusions

- SOL was the most potent agent tested against SPN
- SOL was very active against macrolide resistant SPN (MICs ≤0.5 µg/mL)
- Macrolide resistance rates for SPN were the highest in APAC (47.7%) and the US (46.3%)
- SOL had lower MIC_{50/90} values than TEL for SPN and BHS
- For HI and MCAT, SOL had similar potency to AZI and TEL
- The number of HI isolates with MICs >4 μ g/mL was only 1.1% (13/1,216)
- No MCAT isolates had an elevated SOL MIC
- There was little variation in solithromycin susceptibility by region for the countries studied
- These data support continued development of SOL as a treatment for communityacquired bacterial pneumonia

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