Activity of Solithromycin and comparators against Streptococci isolated from Respiratory Samples Collected in 2012-2013

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Revised Abstract

Background: Solithromycin is a fourth-generation macrolide, the first fluoroketolide that is under development in oral and intravenous formulations in Phase 3 clinical trials for the treatment of moderate to moderately–severe community-acquired bacterial pneumonia. This study evaluated the *in vitro* activity of solithromycin against respiratory streptococcal isolates collected in Europe, Asia-Pacific and North America during 2012-2013.

Methods: A total of 1,070 streptococci, 927 *S. pneumoniae* and 143 *S. pyogenes*, were collected from Europe, Asia-Pacific and North America. Isolates were tested in a central laboratory with MIC and susceptibility for solithromycin and comparators determined according to CLSI broth microdilution methodology and breakpoints[3]. Provisional susceptible, intermediate and resistant breakpoints of 1, 2 and 4 mg/L were used for solithromycin against *S. pneumoniae*.

Results: MIC_{90} (mg/L) and percent susceptible (%S) data are shown in the Table:

S. pneumoniae		SOL	A/C	AZT	CTX	CLI	ERY	LVX	MOX	PEN	TEL	VAN
Europe (n=418)	MIC_{90}	0.06	2	>1	1	>0.5	>0.5	2	0.25	2	0.12	0.5
	%S	100	90	71	92	77	72	97	98	63	100	100
Asia-Pacific (129)	MIC_{90}	0.5	4	>1	2	>0.5	>0.5	2	0.25	4	0.5	0.5
	%S	100	85	29	77	42	29	98	99	51	99	100
North America (380)	MIC_{90}	0.25	2	>1	1	>0.5	>0.5	1	0.25	2	0.5	0.5
	%S	100	90	56	91	80	57	100	100	59	99	100
S. pyogenes		SOL	A/C	AZT	CTX	CLI	ERY	LVX	MOX	PEN	TEL	VAN
Europe (83)	MIC_{90}	0.03	0.03	1	0.03	0.06	0.25	2	0.25	≤0.06	0.06	0.5
	%S	NB	NB	89	100	96	90	100	NB	100	NB	100
Asia-Pacific (24)	MIC_{90}	0.5	0.03	>1	0.03	>0.5	>0.5	2	0.25	≤0.06	>2	0.5
	%S	NB	NB	33	100	54	33	96	NB	100	NB	100
North America (36)	MIC_{90}	0.06	0.03	>1	0.03	0.12	>0.5	2	0.5	≤0.06	0.03	0.5
	%S	NB	NB	83	100	97	81	97	NB	97	NB	100

A/C, amoxicillin/clavulanic acid; AZT, azithromycin; CTX, ceftriaxone; CLI, clindamycin; ERY, erythromycin; LVX, levofloxacin; MOX, moxifloxacin; PEN, penicillin; SOL, solithromycin; TEL, telithromycin; VAN, vancomycin; NB, no breakpoints available

Conclusions: Solithromycin showed very good activity against isolates from the different regions with MIC_{90} ranging from 0.06-0.5 mg/L to 0.03-0.5 mg/L, for pneumococci and *S. pyogenes*, respectively. These data positively support the continued development of solithromycin for the treatment of respiratory infections caused by streptococci.

Introduction

Solithromycin is a fluoroketolide available in both oral and intravenous formulations. It is being developed for the treatment of community-acquired bacterial pneumonia (CABP) and urethritis. Solithromycin is currently undergoing Phase 3 clinical trials for the treatment of moderate to moderately-severe CABP. Phase 2 clinical trial data showed solithromycin to be equivalent to levofloxacin in efficacy and to have a more favourable safety profile [1].

This study evaluated the *in vitro* activity of solithromycin against more than 1000 respiratory streptococcal isolates collected in Europe, Asia-Pacific and North America during 2012-2013.

Materials & Methods

- A total of 927 *S. pneumoniae* and 143 *S. pyogenes* were tested from Europe, Asia-pacific and North America (Table 1). Isolates were identified to the species level and MICs determined at a central testing laboratory (IHMA Europe, located in Epalinges, Switzerland).
- Minimum inhibitory concentrations (MICs) were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method using panels prepared at IHMA [2].
- MIC interpretive criteria mainly followed published guidelines of CLSI published in 2013 [3], but for tigecycline FDA breakpoints were used [4]. Provisional breakpoints of 1, 2 and 4 mg/L were used for solithromycin against *S. pneumoniae*.
- Quality controls were performed on each day of testing using appropriate ATCC control strains, following CLSI and manufacturer guidelines. Results were included in the analysis only when corresponding QC results were within the acceptable ranges [3].

References

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Acknowledgements

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Results

Summary of MIC and susceptibility data for solithromycin and comparators against *S. pneumoniae* and *S. pyogenes* isolated from Europe, North America and Asia-Pacific are given in Tables 2 and 3. The cumulative percentage MIC distributions for solithromycin are compared for each species by world region in Figures 1 and 2.

Table 1: Number of isolates investigated and region of origin.

Region	*Streptococcus pneumoniae*	*Streptococcus pyogenes*
Europe	418	83
North-America	380	36
Asia-Pacific	129	24
TOTAL	927	143

Figure 1: Cumulative percentage MIC distribution for solithromycin and azithromycin against *S. pneumoniae* from different regions of the world.

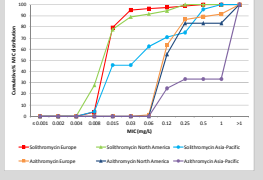

Figure 2: Cumulative percentage MIC distribution for solithromycin and azithromycin against *S. pyogenes* from different regions of the world.

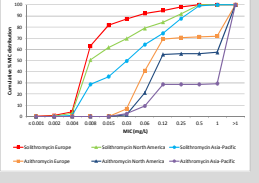

Table 2: Summary MIC and susceptibility data for solithromycin and comparators against 927 *S. pneumoniae*.

Antimicrobial agents	Region	Percentage:			MIC (mg/L):			
		Susceptible	Intermediate	Resistant	50%	90%	MIN	MAX
Solithromycin[a]	Europe (418)	100	0.0	0.0	0.008	0.06	≤ 0.001	0.5
	North America (380)	100	0.0	0.0	0.008	0.25	0.002	0.5
	Asia-Pacific (129)	100	0.0	0.0	0.06	0.5	0.004	1
Amoxicillin Clavulanic Acid	Europe (418)	90.2	6.5	3.4	0.03	2	≤ 0.015	> 4
	North America (380)	90.3	3.4	6.3	0.03	2	≤ 0.015	> 4
	Asia-Pacific (129)	84.5	7.0	8.5	0.06	4	≤ 0.015	> 4
Azithromycin	Europe (418)	71.3	0.7	28.0	0.12	> 1	≤ 0.03	> 1
	North America (380)	56.3	1.1	42.6	0.12	> 1	≤ 0.03	> 1
	Asia-Pacific (129)	28.7	0.8	70.5	> 1	> 1	≤ 0.03	> 1
Ceftriaxone	Europe (418)	91.6	6.5	1.9	0.03	1	≤ 0.015	> 2
	North America (380)	91.3	7.9	0.8	0.03	1	≤ 0.015	> 2
	Asia-Pacific (129)	76.7	17.8	5.4	0.12	2	≤ 0.015	> 2
Clindamycin	Europe (418)	77.0	0.5	22.5	0.03	> 0.5	≤ 0.015	> 0.5
	North America (380)	79.7	0.3	20.0	0.06	> 0.5	≤ 0.015	> 0.5
	Asia-Pacific (129)	41.9	0.8	57.4	> 0.5	> 0.5	≤ 0.015	> 0.5
Erythromycin	Europe (418)	72.3	0.5	27.3	≤ 0.06	> 0.5	≤ 0.06	> 0.5
	North America (380)	56.8	0.0	43.2	≤ 0.06	> 0.5	≤ 0.06	> 0.5
	Asia-Pacific (129)	29.5	0.0	70.5	> 0.5	> 0.5	≤ 0.06	> 0.5
Levofloxacin	Europe (418)	97.4	0.7	1.9	1	2	≤ 0.25	> 4
	North America (380)	99.7	0.0	0.3	1	1	0.5	> 4
	Asia-Pacific (129)	98.5	0.0	1.6	1	2	0.5	> 4
Moxifloxacin	Europe (418)	98.3	0.5	1.2	0.12	0.25	≤ 0.03	> 2
	North America (380)	99.7	0.0	0.3	0.12	0.25	0.06	> 2
	Asia-Pacific (129)	99.2	0.0	0.8	0.12	0.25	0.06	> 2
Penicillin	Europe (418)	63.4	20.6	16.0	≤ 0.06	2	≤ 0.06	> 4
	North America (380)	59.5	28.7	11.8	≤ 0.06	2	≤ 0.06	> 4
	Asia-Pacific (129)	51.2	20.2	28.7	≤ 0.06	4	≤ 0.06	> 4
Telithromycin	Europe (418)	100	0.0	0.0	0.008	0.12	≤ 0.002	1
	North America (380)	99.5	0.5	0.0	0.015	0.5	0.004	2
	Asia-Pacific (129)	99.2	0.8	0.0	0.06	0.5	0.008	2
Tigecycline	Europe (418)	95.2	0.0	4.8	0.03	0.06	0.015	0.25
	North America (380)	75.8	0.0	24.2	0.06	0.12	0.015	> 0.5
	Asia-Pacific (129)	72.1	0.0	27.9	0.06	0.12	0.015	0.5
Vancomycin	Europe (418)	100	0.0	0.0	0.25	0.5	0.12	1
	North America (380)	100	0.0	0.0	0.25	0.5	0.06	0.5
	Asia-Pacific (129)	100	0.0	0.0	0.25	0.5	0.12	0.5

[a]Provisional breakpoints of ≤1 (S), 2 (I) and 4 (R) mg/L were used for solithromycin.

Table 3. Summary MIC and susceptibility data for solithromycin and comparators against 143 *S. pyogenes*.

Antimicrobial agents	Region	Percentage			MIC (mg/L)			
		Susceptible	Intermediate	Resistant	50%	90%	MIN	MAX
Solithromycin[a]	Europe (83)	100	0.0	0.0	0.015	0.03	0.008	0.5
	North America (36)	100	0.0	0.0	0.015	0.06	0.008	0.25
	Asia-Pacific (24)	100	0.0	0.0	0.06	0.5	0.008	1
Amoxicillin Clavulanic Acid	Europe (83)	NA	NA	NA	≤ 0.015	0.03	≤ 0.015	0.12
	North America (36)	NA	NA	NA	≤ 0.015	0.03	≤ 0.015	0.03
	Asia-Pacific (24)	NA	NA	NA	≤ 0.015	0.03	≤ 0.015	0.03
Azithromycin	Europe (83)	89.2	2.4	8.4	0.12	1	0.06	> 1
	North America (36)	83.3	0.0	16.7	0.12	> 1	0.12	> 1
	Asia-Pacific (24)	33.3	0.0	66.7	> 1	> 1	0.12	> 1
Ceftriaxone	Europe (83)	100	-	-	0.03	0.03	≤ 0.015	0.5
	North America (36)	100	-	-	0.03	0.03	≤ 0.015	0.03
	Asia-Pacific (24)	100	-	-	0.03	0.03	≤ 0.015	0.03
Clindamycin	Europe (83)	96.4	0.0	3.6	0.06	0.06	0.03	> 0.5
	North America (36)	97.2	2.8	0.0	0.06	0.12	0.03	0.5
	Asia-Pacific (24)	54.2	0.0	45.8	0.12	> 0.5	0.06	> 0.5
Erythromycin	Europe (83)	90.4	0.0	9.6	≤ 0.06	0.25	≤ 0.06	> 0.5
	North America (36)	80.6	0.0	19.4	≤ 0.06	> 0.5	≤ 0.06	> 0.5
	Asia-Pacific (24)	33.3	0.0	66.7	> 0.5	> 0.5	≤ 0.06	> 0.5
Levofloxacin	Europe (83)	100	0.0	0.0	1	2	0.5	2
	North America (36)	97.2	0.0	2.8	0.5	2	0.5	> 4
	Asia-Pacific (24)	95.8	0.0	4.2	1	2	≤ 0.25	> 4
Moxifloxacin	Europe (83)	NA	NA	NA	0.12	0.25	0.06	1
	North America (36)	NA	NA	NA	0.12	0.5	0.06	2
	Asia-Pacific (24)	NA	NA	NA	0.25	0.25	0.06	> 2
Penicillin	Europe (83)	98.8	-	-	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06
	North America (36)	97.2	-	-	≤ 0.06	≤ 0.06	≤ 0.06	0.25
	Asia-Pacific (24)	100	-	-	≤ 0.06	≤ 0.06	≤ 0.06	0.12
Telithromycin	Europe (83)	NA	NA	NA	0.015	0.06	0.015	> 2
	North America (36)	NA	NA	NA	0.015	0.03	0.015	0.5
	Asia-Pacific (24)	NA	NA	NA	0.12	> 2	0.015	> 2
Tigecycline	Europe (83)	100	-	-	0.06	0.06	0.03	0.12
	North America (36)	100	-	-	0.06	0.06	0.015	0.06
	Asia-Pacific (24)	100	-	-	0.06	0.12	0.03	0.25
Vancomycin	Europe (83)	100	-	-	0.25	0.5	0.25	0.5
	North America (36)	100	-	-	0.5	0.5	0.25	1
	Asia-Pacific (24)	100	-	-	0.25	0.5	0.25	0.5

[a]Provisional breakpoints of ≤1 (S), 2 (I) and 4 (R) mg/L were used for solithromycin. NA, breakpoints not available.

Conclusions

- Solithromycin showed very good activity against *S. pneumoniae* and *S. pyogenes* with $MIC_{90} \leq 0.5$ mg/L for all the regions of the world included in this study, Europe, North-America and Asia-Pacific.
- For both species, MIC_{90} Europe < MIC_{90} North America < MIC_{90} Asia-Pacific.
- Solithromycin was considerably more active than macrolides and penicillins against *S. pneumoniae* and more active than macrolides against *S. pyogenes.*
- Solithromycin was also more active than telithromycin.
- These data show that solithromycin could be a good alternative to treat respiratory infections caused by *S. pneumoniae* and *S. pyogenes* especially in regions of the world like Asia where there is a very high level of resistance to macrolides and penicillins and thus strongly support the continued development of this antibiotic.