

Revised Abstract

Background: Solithromycin is a fourth-generation oral and intravenous macrolide, the first fluoroketolide, that is currently undergoing Phase III clinical development for the treatment of community-acquired bacterial pneumonia. This study evaluated the *in vitro* activity of solithromycin against respiratory isolates of *Streptococcus pneumoniae* (SPN) and *S. pyogenes* (SPY) collected in Europe during 2012.

Methods: Hospitals in Belgium (N=3), Czech Republic (3), Denmark (1), France (5), Germany (7), Greece (2), Hungary (1), Italy (7), Netherlands (1), Portugal (2), Russia (4), Spain (6), Sweden (2) & Turkey (3) provided a total of 501 respiratory isolates. These were re-identified in a central laboratory with MIC and susceptibility for solithromycin and comparators determined according to CLSI broth microdilution methodology and breakpoints (except a susceptible breakpoint of ≤ 0.25 $\mu\text{g/ml}$ was used for tigecycline).

Results: Summary MIC ($\mu\text{g/ml}$) and percent susceptible (%S) data are shown in the Table:

	SPN (418)			SPY (83)		
	MIC ₅₀	MIC ₉₀	%S	MIC ₅₀	MIC ₉₀	%S
Solithromycin	0.008	0.06	NA	0.015	0.03	NA
Telithromycin	0.008	0.12	99.8	0.015	0.06	NA
Erythromycin	≤ 0.06	> 0.5	72.5	≤ 0.06	0.25	90.4
Azithromycin	0.12	> 1	71.5	0.12	1	89.2
Clindamycin	0.03	> 0.5	77.3	0.06	0.06	96.4
Amox-clav	0.03	2	90.0	≤ 0.015	0.03	NA
Ceftriaxone	0.03	1	91.1	0.03	0.03	100
Penicillin	≤ 0.06	2	62.9	≤ 0.06	≤ 0.06	100
Vancomycin	0.25	0.5	100.0	0.25	0.5	100
Levofloxacin	1	2	97.4	1	2	100
Moxifloxacin	0.12	0.25	98.3	0.12	0.25	NA
Tigecycline	0.03	0.06	100	0.06	0.06	100

NA=No breakpoint.

Conclusions: Solithromycin showed very good activity against SPN and SPY with MIC₅₀ of 0.008 and 0.015 $\mu\text{g/ml}$, respectively, and MIC₉₀ of 0.06 and 0.03 $\mu\text{g/ml}$, respectively. Solithromycin was considerably more active than the older macrolides. These data positively support the continued development of solithromycin for the treatment of respiratory infections caused by SPN and SPY.

Introduction

Solithromycin is a fourth-generation macrolide, the first fluoroketolide that is being developed in both oral and intravenous formulations. It is being developed for the treatment of community-acquired bacterial pneumonia. Published Phase 2 clinical trial data showed solithromycin to be equivalent to levofloxacin in efficacy and to have a more favorable safety profile [1]. Solithromycin is currently undergoing Phase 3 clinical trials.

This study evaluated the activity of solithromycin against recently circulating respiratory isolates of *Streptococcus pneumoniae* and *S. pyogenes* from European hospitals.

Materials & Methods

- A total of 418 *S. pneumoniae* and 83 *S. pyogenes* were tested from 47 sites located in various European countries (Table 1). These were collected from respiratory infections.
- Isolates were identified to the species level and MICs determined at a central testing laboratory (IHMA Europe, located in Epalinges, Switzerland). Organism collection, transport and development and management of a centralized database were also coordinated by IHMA.
- 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].
- 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

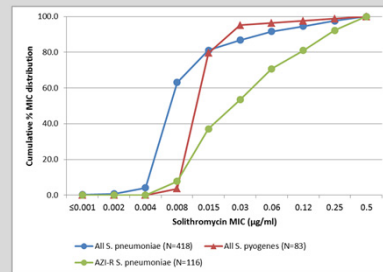
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Results

The cumulative percentage MIC distributions for solithromycin against the two streptococcal species and azithromycin-resistant *S. pneumoniae* are shown in Figure 1. These data for *S. pneumoniae* separated by penicillin susceptibility are shown in Figure 2. Summary MIC and susceptibility data for solithromycin and comparators are given in Tables 2 and 3.

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

Country (N sites)	<i>Streptococcus pneumoniae</i>	<i>Streptococcus pyogenes</i>
Belgium (3)	53	8
Czech Republic (3)	7	7
Denmark (1)	30	1
France (5)	58	8
Germany (7)	42	8
Greece (2)	3	3
Hungary (1)	4	15
Italy (7)	55	14
Netherlands (1)	1	16
Portugal (2)	70	1
Russia (4)	70	5
Spain (6)	70	2
Sweden (2)	97	4
Turkey (3)	33	4
TOTAL	418	83



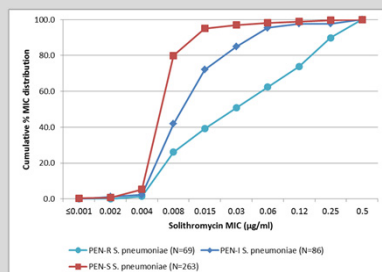
AZ-R, azithromycin-resistant

Figure 1: Cumulative percentage MIC distribution for solithromycin against *S. pyogenes*, all *S. pneumoniae* and azithromycin-resistant *S. pneumoniae*.

Table 2: Summary MIC and susceptibility data for solithromycin and comparators against 418 *S. pneumoniae*

Antimicrobial Agent	Percentage:			MIC ($\mu\text{g/ml}$):			
	SUS	INT	RES	MIC 50	MIC 90	MIN	MAX
Solithromycin	NA	NA	NA	0.008	0.06	≤ 0.001	0.5
Telithromycin	99.8	0.2	0	0.008	0.12	≤ 0.002	2
Erythromycin	72.5	0.5	27.0	≤ 0.06	> 0.5	≤ 0.06	> 0.5
Azithromycin	71.5	0.7	27.8	0.12	> 1	≤ 0.03	> 1
Clindamycin	77.3	0.5	22.2	0.03	> 0.5	≤ 0.015	> 0.5
Amoxicillin Clavulanic Acid	90.2	6.5	3.3	0.03	2	≤ 0.015	> 4
Ceftriaxone	91.1	6.5	2.4	0.03	1	≤ 0.015	> 4
Penicillin	62.9	20.8	16.3	≤ 0.06	2	≤ 0.06	> 4
Vancomycin	100	0	0	0.25	0.5	0.12	1
Levofloxacin	97.4	0.7	1.9	1	2	≤ 0.25	> 4
Moxifloxacin	98.3	0.3	1.4	0.12	0.25	≤ 0.03	> 2
Tigecycline	100	0	0	0.03	0.06	0.015	0.25

NA, breakpoints not available.



PEN-S, penicillin-susceptible; PEN-I, penicillin-intermediate; PEN-R, penicillin-susceptible.

Figure 2: Cumulative percentage MIC distribution for solithromycin against penicillin-susceptible, -intermediate, and -resistant *S. pneumoniae*.

Table 3: Summary MIC and susceptibility data for solithromycin and comparators against 83 *S. pyogenes*.

Antimicrobial Agent	Percentage:			MIC ($\mu\text{g/ml}$):			
	SUS	INT	RES	MIC 50	MIC 90	MIN	MAX
Solithromycin	NA	NA	NA	0.015	0.03	0.008	0.5
Telithromycin	NA	NA	NA	0.015	0.06	0.015	> 2
Erythromycin	90.4	0	9.6	≤ 0.06	0.25	≤ 0.06	> 0.5
Azithromycin	89.2	2.4	8.4	0.12	1	≤ 0.06	> 1
Clindamycin	96.4	0	3.6	0.06	0.06	0.03	> 0.5
Amoxicillin Clavulanic Acid	NA	NA	NA	≤ 0.015	0.03	≤ 0.015	0.12
Ceftriaxone	100	0	0	0.03	0.03	≤ 0.015	0.5
Penicillin	100	0	0	≤ 0.06	≤ 0.06	≤ 0.06	≤ 0.06
Vancomycin	100	0	0	0.25	0.5	0.25	0.5
Levofloxacin	100	0	0	1	2	0.5	2
Moxifloxacin	NA	NA	NA	0.12	0.25	0.06	1
Tigecycline	100	0	0	0.06	0.06	0.03	0.12

Conclusions

- Solithromycin showed very good activity against *S. pneumoniae* and *S. pyogenes* with all MICs 0.5 $\mu\text{g/ml}$ or less, including macrolide- and penicillin-resistant strains.
- Solithromycin was considerably more active than the older macrolides and was generally one dilution more active than telithromycin.
- Resistance to older macrolides was observed for 27 to 27.8% of *S. pneumoniae* and 8.4 to 9.6% of *S. pneumoniae* using CLSI breakpoints.
- These data positively support the continued development of solithromycin for the treatment of respiratory infections caused by *S. pneumoniae* and *S. pyogenes*.