

Revised Abstract

Background: Solithromycin is a fourth-generation macrolide, the first fluoroketolide, undergoing Phase III clinical trials for the treatment of moderate to moderately-severe community-acquired bacterial pneumonia. This study evaluated the *in vitro* activity of solithromycin against *Streptococcus pneumoniae* (SP) collected in 2012-2013 from patients located in various European countries.

Methods: A total of 418 SP isolated from respiratory samples were collected from Europe. Isolates were tested in a central laboratory with MIC and susceptibility for solithromycin and comparators determined according to CLSI broth microdilution methodology and breakpoints. Provisional breakpoints of ≤ 1 (S), 2 (I) & ≥ 4 (R) were used for solithromycin. Susceptibility was analyzed for sub-sets of SP from European countries where $n \geq 30$.

Results: %S is shown in the Table (see Table 1, poster text). Solithromycin was fully active against all isolates. Penicillin susceptibility was only above 80% in Denmark and azithromycin susceptibility was only at this high level in Denmark and Russia. Overall antibiotic susceptibility was particularly low in Turkey.

Conclusions: Solithromycin showed very good activity against antimicrobial-resistant isolates, despite low susceptibility to azithromycin and penicillin in most countries and multi-drug resistance in Turkey. These data positively support the continued development of solithromycin for the treatment of respiratory infections caused by SP.

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 gonorrhoea. 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 favorable safety profile [1]. This study evaluated the *in vitro* activity of solithromycin against pneumococci isolated from different European countries during 2012-2013.

Materials & Methods

- A total of 418 pneumococcal isolates from Europe 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 followed the guidelines of CLSI published in 2014 [3]. Provisional solithromycin breakpoints of ≤ 1 (susceptible), 2 (intermediate) & ≥ 4 (resistant) were used in the analysis.
- 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].

Results

- Summary percent susceptibility data for solithromycin and comparators by country is shown in Table 1. Summary MIC data for solithromycin against *S. pneumoniae* from different European countries is shown in Table 2.
- Cumulative MIC distribution for solithromycin, amoxicillin/clavulanic acid, ceftriaxone, azithromycin and levofloxacin against pneumococci from combined European isolates is shown in Figure 1.
- Susceptibility data for antimicrobial agents with lower susceptibility is shown in Figure 2.

Table 1: Summary Percent Susceptibility data for solithromycin and comparators against Pneumococci by country.*

Drug (%S)	Belgium (n=53)	Denmark (n=30)	France (n=58)	Germany (n=42)	Italy (n=55)	Russia (n=70)	Spain (n=70)	Turkey (n=33)
Solithromycin	100	100	100	100	100	100	100	100
Azithromycin	77.4	93.3	65.5	73.8	56.4	84.3	70	42.4
Amox/Clav	98.1	100	100	100	92.9	96.4	94.3	71.4
Ceftriaxone	83	93.3	74.1	78.6	67.3	90.0	75.7	42.4
Penicillin	75.5	86.7	56.9	71.4	63.6	75.7	48.6	30.3
Ceftriaxone	98.1	100	96.6	92.9	92.7	92.9	90.0	63.6
Levofloxacin	100	100	100	97.6	96.4	97.1	95.7	90.9

* only countries for which $n \geq 30$ were analyzed; values in bold represent percent susceptibility >90

Table 2: Summary MIC Data ($\mu\text{g/ml}$) for Solithromycin Against Pneumococci from Different European Countries ($n \geq 30$ isolates).

Country	MIC ₅₀	MIC ₉₀	MIN MIC	MAX MIC
Belgium (53)	0.008	0.03	$<= 0.001$	0.12
Denmark (30)	0.008	0.015	0.004	0.015
France (58)	0.008	0.06	0.002	0.5
Germany (42)	0.008	0.06	0.008	0.5
Italy (55)	0.008	0.06	0.004	0.5
Russia (70)	0.008	0.015	0.002	0.5
Spain (70)	0.008	0.06	0.004	0.5
Turkey (33)	0.015	0.25	0.004	0.5

MIN MIC, minimum MIC; MAX MIC, maximum MIC

Figure 1: Cumulative Percentage MIC Distribution for Solithromycin, and Selected Comparators against 418 Pneumococci from Europe.

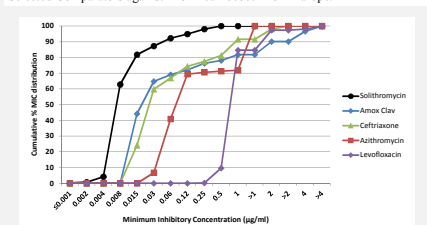


Figure 2: Susceptibility of Pneumococci from Different European Countries with Susceptibility $\leq 95\%$: Amoxicillin/Clavulanic acid, Azithromycin, Ceftriaxone, Clindamycin, Levofloxacin and Penicillin.



Conclusions

- Effective and safe oral antibiotics are essential to the successful treatment of CABP.
- However, low susceptibility was observed to oral antibiotics such as azithromycin, clindamycin and penicillin in most countries and amoxicillin clavulanic acid in Spain and Turkey – with multi-drug resistance in this country.
- On the other hand, all pneumococci were susceptible to solithromycin (MIC ≤ 0.5 $\mu\text{g/ml}$), irrespective of resistance to other agents.
- Levofloxacin was also very active against the pneumococci (with lower susceptibility in Turkey) but this oral agent is associated with several adverse events [1].
- Taken together, the MIC₉₀ for solithromycin was <0.06 $\mu\text{g/ml}$ with a maximum MIC of 0.5 $\mu\text{g/ml}$.
- Using provisional solithromycin breakpoints of ≤ 1 (susceptible), 2 (intermediate) & ≥ 4 (resistant), 100% of pneumococci from all countries were susceptible to solithromycin.
- These data positively support the continued development of solithromycin as a safe oral agent for the treatment of respiratory infections caused by *S. pneumoniae*.

References

- Oldach D, Clark K, Schranz J, Das A, Craft JC, Scott D, Jamieson BD, Fernandes P. 2013. Randomized, double-blind, multicenter phase 2 study comparing the efficacy and safety of oral solithromycin (CEM-101) to those of oral levofloxacin in the treatment of patients with community-acquired bacterial pneumonia. *Antimicrob Agents Chemother.* 57:2526-34.
- Clinical and Laboratory Standards Institute. 2012. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standards – Eighth Edition. CLSI document M07-A9. Wayne, PA.
- Clinical and Laboratory Standards Institute. 2014. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Second Informational Supplement. CLSI Document M100-S24. Wayne, PA.

Acknowledgement This study was sponsored by a grant from Cempra Pharmaceuticals.