

Revised Abstract

Background: Solithromycin is a fourth-generation macrolide, the first fluoro ketolide, 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.

Methods: A total of 996 SP isolated from respiratory samples were collected from Europe, Asia-Pacific, North America and other locations world-wide. Isolates were tested in a central laboratory with MIC and susceptibility to 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 and FDA breakpoints for tigecycline. Susceptibility was analyzed for sub-sets of SP resistant to azithromycin (AZI-R), clindamycin (CLI-R), penicillin (PEN-R), amoxicillin clavulanic acid (AMC-R), 3 drugs (MDR-3) or 4 drugs (MDR-4).

Results: %S is shown in the Table in the poster text (>90 %S in bold). Solithromycin was fully active against all isolates. Penicillin and azithromycin, in particular, were inactive against all resistant strains. AMC, CLI and ceftriaxone were also inactive against the MDR strains.

Conclusions: Solithromycin showed very good activity against antimicrobial-resistant isolates, including MDR strains. These data positively support the continued development of solithromycin for the treatment of respiratory infections caused by SP.

Introduction

Solithromycin is a fluoro ketolide 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 drug-resistant pneumococci isolated world-wide during 2012-2013.

Materials & Methods

- A total of 996 pneumococcal isolates from Europe, Asia-Pacific, North America and other locations world-wide were identified to 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

Figure 1: Summary of the Susceptibility of Azithromycin-Resistant Pneumococci to Solithromycin and Comparators

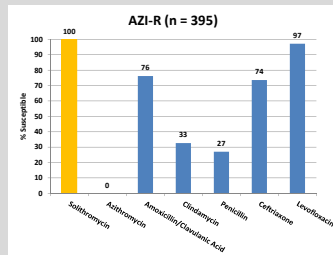


Figure 2: Summary of the Susceptibility of Clindamycin-Resistant Pneumococci to Solithromycin and Comparators

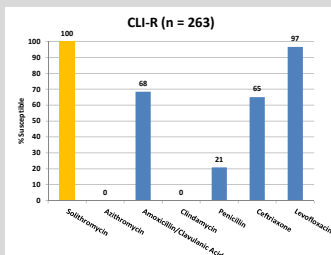


Figure 3: Summary of the Susceptibility of Penicillin-Resistant Pneumococci to Solithromycin and Comparators

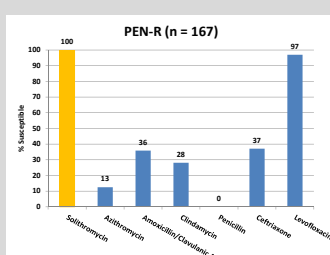


Figure 4: Summary of the Susceptibility of Amoxicillin Clavulanic Acid-Resistant Pneumococci to Solithromycin and Comparators

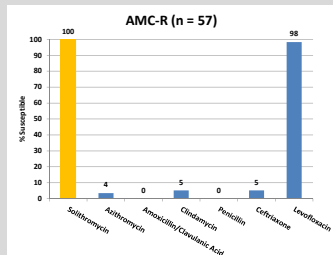


Figure 5: Summary of the Susceptibility of Multi-Drug Resistant Pneumococci (3 antibiotic classes) to Solithromycin and Comparators

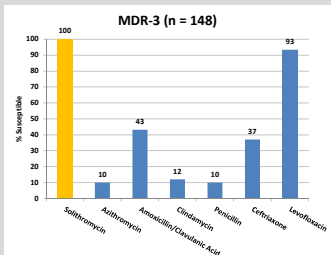


Figure 6: Summary of the Susceptibility of Multi-Drug Resistant Pneumococci (4 antibiotic classes) to Solithromycin and Comparators

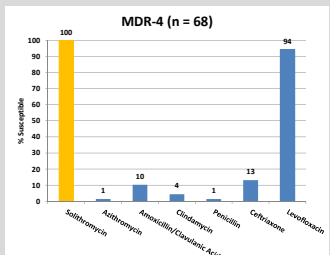


Table 1: Summary of the Susceptibility of Pneumococci in Different Resistance Groups to Solithromycin and Comparators

Drug (%Susceptible)	AZI-R (n=395)	CLI-R (n=263)	PEN-R (n=167)	AMC-R (n=57)	MDR-3 (n=148)	MDR-4 (n=68)
Solithromycin	100	100	100	100	100	100
Azithromycin	0.0	0.0	12.6	3.5	10.1	1.5
Amoxicillin/Clavulanic Acid	76.3	68.4	35.9	0.0	43.3	10.3
Clindamycin	32.7	0.0	28.1	5.3	12.2	4.4
Penicillin	27.1	20.9	0.0	0.0	10.1	1.5
Ceftriaxone	73.7	65.0	37.1	5.3	37.2	13.2
Levofloxacin	97.2	96.6	97.0	98.3	93.2	94.1

AZI-R, azithromycin-resistant; CLI-R, clindamycin-resistant; PEN-R, penicillin-resistant (oral/breakpoint); MDR-3, resistant to 3 antibiotic classes; MDR-4, resistant to 4 antibiotic classes.
All values in bold, >90 percent susceptible

A summary of the susceptibility of different resistance groups of *S. pneumoniae* to solithromycin and comparators is shown in Table 1.

Summary susceptibility data for solithromycin and comparators against azithromycin-resistant pneumococci, clindamycin-resistant pneumococci, penicillin-resistant pneumococci, amoxicillin/clavulanic acid-resistant pneumococci, multi-drug resistant pneumococci (3 antibiotic classes) and multi-drug resistant pneumococci (4 antibiotic classes) are shown in Figures 1 to 6.

Conclusions

- The IDSA/ATS recommends a third-generation cephalosporin (eg. ceftriaxone) plus a macrolide (eg. azithromycin) for the treatment of CABP.
- However, reduced susceptibility to both agents is associated with resistance to other non-related antibiotics (eg. only 13% of PEN-R pneumococci are susceptible to AZI & 65% of CLI-R pneumococci are susceptible to ceftriaxone).
- All antimicrobial-resistant strains were susceptible to solithromycin (MIC ≤ 0.5 $\mu\text{g/ml}$) but this was not the case for other oral agents, except levofloxacin.
- Although levofloxacin is active against resistant strains it is associated with several adverse events [1].
- Using provisional solithromycin breakpoints of ≤ 1 (susceptible), 2 (intermediate) & ≥ 4 (resistant), 100% of pneumococci were susceptible to solithromycin irrespective of their resistance phenotypes.
- 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 – Ninth 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.