

Revised Abstract

Objectives: Solithromycin is a fourth generation macrolide, the first fluoroketolide being developed in oral and intravenous formulations, that is currently undergoing Phase III clinical development for the treatment of community-acquired bacterial pneumonia. This study evaluated the prevalence of SCCmec types associated with MRSA causing respiratory infections in 2012-13 and the *in vitro* activity of solithromycin (SOL) and comparators against these isolates.

Methods: A total of 412 respiratory MRSA were evaluated from Europe (175), North America (169), Asia-Pacific (24) and the rest of the world (44). MRSA were re-identified in a central laboratory and SCCmec type determined by PCR [Mihairoiu et al *Antimicrob Agents Chemother* 2007 51:3374]. MIC for solithromycin and comparators was determined by CLSI broth microdilution methodology.

Results: The most common SCCmec was IV (199 MRSA, 48.3%), followed by II (112, 27.2%), III (52, 12.6%), I (37, 9.0%) and V (3, 0.7%). Nine MRSA (2.2%) were novel SCCmec types. MIC₅₀ for azithromycin (AZI), levofloxacin (LFX), SOL, trimethoprim-sulfamethoxazole (SXT) and tigecycline (TGC) against the major SCCmec types are shown in the Table. AZI and LFX were inactive against all MRSA irrespective of SCCmec. SXT and TGC were equally active against all MRSA. SOL was active against the most common SCCmec type IV and type III but not I or II.

SCCmec type	SOL	AZI	LFX	SXT	TGC
All (412)	16	>4	>2	<=0.5	0.25
IV (199)	0.12	>4	>2	<=0.5	0.12
II (112)	>32	>4	>2	<=0.5	0.25
III (52)	0.12	>4	>2	<=0.5	0.25
I (37)	>32	>4	>2	<=0.5	0.25

Conclusions: As SCCmec IV is linked with community-associated isolates of MRSA, whereas types I and II are associated with hospital-acquired MRSA, these data suggest that solithromycin may be suitable for the treatment of community-associated respiratory infections caused by MRSA.

Introduction

Solithromycin is a fourth generation macrolide, the first fluoroketolide being developed in oral and intravenous formulations, that is currently undergoing Phase III clinical development for the treatment of community-acquired bacterial pneumonia [1]. The staphylococcal cassette chromosome is a defining feature of MRSA, which are divided into several types. SCCmec Type I-III are characteristic of hospital-associated (HA)-MRSA while type IV is linked to community-associated-MRSA [2].

This study evaluated the prevalence of SCCmec types associated with 412 MRSA causing respiratory infections collected from various part of the world in 2012-13. *In vitro* activity of solithromycin and comparators against these isolates was determined and correlated with SCCmec types.

Materials & Methods

- A total of 412 respiratory MRSA were evaluated from Europe, North America, Asia-Pacific and the rest of the world (Table 1). Isolates were identified to the species level and minimum inhibitory concentrations (MICs) determined at a central testing laboratory (IHMA Europe, located in Epalinges, Switzerland).
- MICs were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method using panels prepared at IHMA [3].
- Quality controls were performed on each day of testing using appropriate ATCC control strains, following CLSI guidelines. Results were included in the analysis only when corresponding QC results were within the acceptable ranges [4].
- SCCmec type was determined by PCR as previously described [5].
- The 'D-test' to assess for inducible clindamycin-resistance was performed following the CLSI recommended method by broth microdilution (4 mg/L erythromycin & 0.5 mg/L clindamycin) [4].

Results

- The prevalence of SCCmec types associated with the 412 MRSA tested in this study is shown in Figures 1 and 2.
- Figure 3 shows the relationship between SCCmec type and macrolide-inducible resistance to clindamycin.
- Summary of MIC data for solithromycin and comparators against MRSA isolated from Europe, North-America, Asia-Pacific and the rest of the world is given in Table 2.
- The cumulative percentage MIC distributions for solithromycin are compared by world region and by SCCmec type in Figures 4 and 5.

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.
- Oster JA, French GL. 2010. Molecular epidemiology of community-associated methicillin-resistant *Staphylococcus aureus* in Europe. *Lancet Infect Dis* 10:227-239.
- Clinical 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. 2013. Performance Standards for Antimicrobial Susceptibility Testing: Twenty-third International Supplement. CLSI Document M100-S23. Wayne, PA.
- Milheiro C, Oliveira DC, de Lancastre H. 2007. Update to the multiplex PCR strategy for assignment of *mec* element types in *Staphylococcus aureus*. *Antimicrob Agents Chemother* 51:3374-7.

Acknowledgements

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

Region	No. MRSA Isolates
Europe	175
North-America	169
Asia	24
Rest of the world*	44
TOTAL	412

*Rest of the world = Africa, Latin America, Middle East

Figure 1: SCCmec types characterized from 412 MRSA isolates causing respiratory infection.

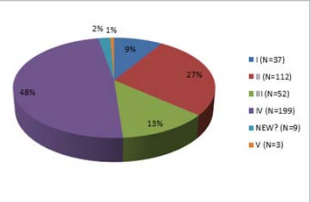


Figure 2: Percentage of SCCmec types characterized from MRSA causing respiratory infection in different regions of the world.

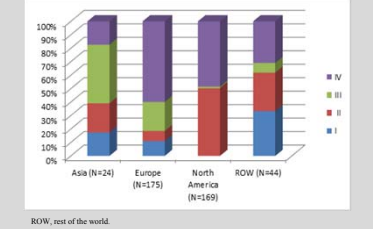


Figure 3: Percentage of macrolide-inducible resistance to clindamycin for different SCCmec types.

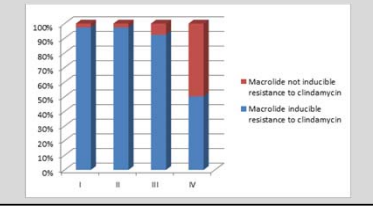


Table 2: Summary MIC data for solithromycin and comparators against 412 MRSA by SCCmec type.

Antimicrobial agent	SCCmec type (N)	MIC (mg/L)			
		50%	90%	MIN	MAX
Solithromycin	All (412)	16	>32	0.03	>32
	I (37)	>32	>32	0.06	>32
	II (112)	>32	>32	0.06	>32
	III (52)	0.12	>32	0.06	>32
	IV (199)	0.12	>32	0.03	>32
Azithromycin	All (412)	>4	>4	0.5	>4
	I (37)	>4	>4	1	>4
	II (112)	>4	>4	1	>4
	III (52)	>4	>4	0.5	>4
	IV (199)	>4	>4	0.5	>4
Daptomycin	All (412)	0.5	1	0.25	1
	I (37)	0.5	1	0.5	1
	II (112)	0.5	0.5	0.25	1
	III (52)	0.5	1	0.5	1
	IV (199)	0.5	1	0.25	1
Erythromycin	All (412)	>4	>4	0.25	>4
	I (37)	>4	>4	0.25	>4
	II (112)	>4	>4	1	>4
	III (52)	>4	>4	0.25	>4
	IV (199)	>4	>4	0.25	>4
Levofloxacin	All (412)	>2	>2	0.12	>2
	I (37)	>2	>2	0.25	>2
	II (112)	>2	>2	0.25	>2
	III (52)	>2	>2	0.25	>2
	IV (199)	>2	>2	0.12	>2
Linezolid	All (412)	2	2	<=0.5	>8
	I (37)	2	2	1	2
	II (112)	2	2	1	>8
	III (52)	2	2	1	4
	IV (199)	2	2	<=0.5	4
Telithromycin	All (412)	>2	>2	<=0.03	>2
	I (37)	>2	>2	0.12	>2
	II (112)	>2	>2	0.06	>2
	III (52)	0.25	>2	0.06	>2
	IV (199)	0.12	>2	<=0.03	>2
Tigecycline	All (412)	0.12	0.5	0.03	>2
	I (37)	0.25	0.5	0.12	1
	II (112)	0.25	0.5	0.03	>2
	III (52)	0.25	0.5	0.12	1
	IV (199)	0.12	0.5	0.06	0.5
Trimethoprim sulfamethoxazole	All (412)	<=0.5	1	<=0.5	>32
	I (37)	<=0.5	1	<=0.5	4
	II (112)	<=0.5	1	<=0.5	32
	III (52)	<=0.5	>32	<=0.5	>32
	IV (199)	<=0.5	<=0.5	<=0.5	>32
Vancomycin	All (412)	1	1	0.5	2
	I (37)	1	1	0.5	2
	II (112)	1	1	0.5	2
	III (52)	1	1	0.5	2
	IV (199)	1	1	0.5	2

Figure 4: Cumulative percentage MIC distribution for solithromycin against MRSA causing respiratory infection in different regions of the world.

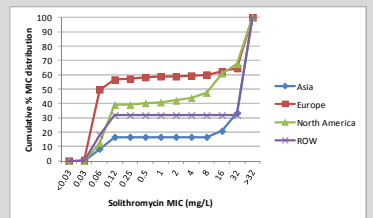
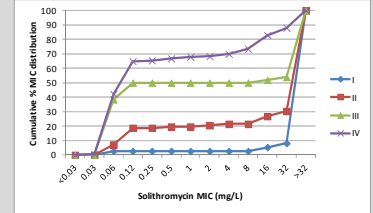


Figure 5: Cumulative percentage MIC distribution for solithromycin against MRSA causing respiratory infection with different SCCmec types.



Conclusions

- Solithromycin was active against the majority of MRSA with SCCmec IV (MIC 50% = 0.12 mg/L) which was the major SCCmec type in Europe and highly represented in isolates from North America.
- Solithromycin was also very active against SCCmec type III (MIC 50% = 0.12 mg/L) but not active against the majority of SCCmec type I and II (MIC 50% > 32 mg/L).
- Solithromycin was considerably more active against MRSA with SCCmec type III and IV than the macrolides.
- Daptomycin and vancomycin were equally active against all MRSA, whereas linezolid and tigecycline were less active against SCCmec type II and trimethoprim-sulfamethoxazole was less active against SCCmec type III MRSA. Azithromycin, erythromycin, and levofloxacin were inactive against most MRSA, irrespective of SCCmec type. Telithromycin showed a similar pattern of activity to that seen with solithromycin.
- SCCmec type IV was less associated with macrolide-inducible resistance to clindamycin than type I, II and III.
- These data show that solithromycin could be a good alternative to treat community-associated MRSA, which are commonly SCCmec IV, and support the continued development of this antibiotic.