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In Vitro Activity of Omadacycline Against resistant *Staphylococcus aureus*

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Abstract

Background: Omadacycline is the first aminomethylcycline in late stage clinical development for acute bacterial skin and skin structure infection (ABSSSI) as once-daily oral and IV formulations. In vitro bacterial activities against a collection of resistant *S. aureus* were investigated.

Materials/methods: The *in vitro* activity of **omadacycline (OMC)** was compared with that of doxycycline (DO), tigecycline (TI), linezolid (LI), ceftaroline (CE), levofloxacin (LE), moxifloxacin (MO), telithromycin (TE), azithromycin (AZ) and erythromycin (ER) against a total of 239 resistant *S. aureus*, by microdilution procedures (CLSI, M7-A12, M100-S25). The tested strains included *S. aureus* that were methicillin-resistant (*mec*A (150)), macrolide-resistant (*erm*A, B or C (50)) and ciprofloxacin-resistant (*gyr*A and *par*C (39)).

Results: Against methicillin-resistant (*mec*A genotype) *S. aureus*, the MIC of **OMC** ranged from 0.016 to 0.25 mg/L and **OMC** (MIC_{90} 0.25 mg/L) and TE (MIC_{90} 0.12 mg/L) were more active than TI (MIC_{90} 0.5 mg/L), DO (MIC_{90} 1 mg/L), CE (MIC_{90} 1 mg/L), LI (MIC_{90} 2 mg/L), MO (MIC_{90} 4 mg/L), LE (MIC90 ≥16 mg/L), AZ (MIC_{90} ≥16 mg/L) and ER (MIC_{90} ≥16 mg/L). **OMC** (MIC_{90} 0.25 mg/L) showed higher activity than TI (MIC_{90} 0.5 mg/L), DO (MIC_{90} 1 mg/L), CE (MIC_{90} 1 mg/L), LI (MIC_{90} 2 mg/L), MO (MIC_{90} 4 mg/L), LE (MIC_{90} 4 mg/L), TE (MIC_{90} 4 mg/L), AZ (MIC_{90} ≥16 mg/L) and **ER** (MIC_{90} ≥16 mg/L) against macrolide-resistant (*erm*A, B, C genotype) *S. aureus*. Against ciprofloxacin-resistant (*gyr*A and *par*C genotype) *S. aureus*, the MIC of **OMC** ranged from 0.06 to 0.25 mg/L and AZ (MIC_{90} ≥16 mg/L), ER (MIC_{90} ≥16 mg/L), LE (MIC_{90} ≥16 mg/L), LI (MIC_{90} 4 mg/L), CE (MIC_{90} 1 mg/L) and DO (MIC_{90} 1 mg/L) were less active than OMC (MIC_{90} 0.25 mg/L), TE (MIC_{90} 0.25 mg/L) and TI (MIC_{90} 0.5 mg/L).

Conclusions: The results of this study suggest that **OMC** may have use in infections caused by resistant *S. aureus* and highlights the potential utility of this oral and IV agent for the treatment of ABSSSI.

Introduction

Staphylococcus aureus is a frequent cause of serious bacterial infections worldwide. Acute bacterial skin and skin structure infections (ABSSSI) have increased in recent years, and *S. aureus* is the most frequent bacteria accounting for 45% of pathogens isolated from infectious sites. **Omadacycline** is the first aminomethylcycline to be developed as a once daily, oral and IV treatment of ABSSSI and Community-Acquired Bacterial Pneumonia (CABP). The Phase 3 development program has now been completed for these indications. **Omadacycline** has excellent activity against the primary pathogens associated with ABSSSI and CABP, including antibiotic resistant organisms, including *S. aureus*, β-hemolytic *streptococci*, *S. pneumoniae*, *H. influenzae*, *Legionella* and *C. pneumoniae*.

Objective

The goal of this study was to investigate the in vitro activity of **omadacycline** against resistant *Staphylococcus aureus*. We determined the minimum inhibitory concentration (MIC) of **omadacycline** and comparators (doxycycline, tigecycline, linezolid, ceftaroline, levofloxacin, moxifloxacin, telithromycin, azithromycin and erythromycin) against 239 resistant *S. aureus* including methicillin-resistant (*mec*A group), macrolide-resistant (*erm*A, B or C group) and ciprofloxacin-resistant (*gyr*A and *par*C group) strains, isolated from respiratory tract or blood cultures sources.

Materials and Methods

Strains: A total of 239 resistant strains of *S. aureus* including: methicillin-resistant (*mec*A group (150)), macrolide-resistant (*erm*A, B or C group (50)) and ciprofloxacin-resistant (*gyr*A and *par*C group (39)) strains. Strains were collected mostly from respiratory tract or blood cultures sources, from 1995 to present and were identified by standard methods such as described by Versalovic et al[1]. Genomic DNA was isolated[4] and multiplex PCR were performed with primers specific for *mec* A, *erm* A, *erm* B and *erm* C[5] or for *gyr*A and *par*C[6].

Determination of MICs

MICs were determined using the CLSI broth medium microdilution method[2,3] using microdilution plating of the organisms onto a series of broth medium microplates of increasing concentrations from 0.004 mg/L to 16 mg/L. Cation supplemented Mueller-Hinton broth medium (M-H) supplemented by 2% NaCl was used as broth medium against *S. aureus* strains. *S. aureus* ATCC 29213 was included as quality control strain.

Results

Table 1 Susceptibility of resistant *Staphylococcus aureus*

Organism (no. tested)	Antibiotic	MIC (mg/L)		
		Range	50%	90%
Staphylococcus aureus all tested resistant strains (239 strains)	**Omadacycline**	**0.016-1**	**0.25**	**0.25**
	Doxycycline	0.06-≥16	0.5	1
	Tigecycline	0.25-2	0.5	0.5
	Linezolid	0.5-4	1	2
	Ceftaroline	0.06-2	0.5	2
	Levofloxacin	0.5-≥16	4	≥16
	Moxifloxacin	0.25-≥16	4	≥16
	Telithromycin	0.016-≥16	0.12	4
	Azithromycin	0.016-≥16	2	≥16
	Erythromycin	0.06-≥16	2	≥16
Staphylococcus aureus Methicillin-resistant (mec A genotype group) (150 strains)	**Omadacycline**	**0.16-1**	**0.25**	**0.25**
	Doxycycline	0.06-≥16	0.5	1
	Tigecycline	0.25-2	0.5	0.5
	Linezolid	0.5-4	1	2
	Ceftaroline	0.06-2	0.05	1
	Levofloxacin	1-≥16	4	≥16
	Moxifloxacin	0.25-≥16	2	4
	Telithromycin	0.016-≥16	0.06	0.12
	Azithromycin	1-≥16	2	≥16
	Erythromycin	0.5-≥16	1	≥16
Staphylococcus aureus Macrolide-resistant (erm A,B,C genotype group) (50 strains)	**Omadacycline**	**0.06-0.25**	**0.25**	**0.25**
	Doxycycline	0.25-1	1	1
	Tigecycline	0.25-1	0.5	0.5
	Linezolid	1--4	2	2
	Ceftaroline	0.12-2	1	1
	Levofloxacin	0.5-4	2	4
	Moxifloxacin	0.25-4	1	4
	Telithromycin	0.12-≥16	2	4
	Azithromycin	4-≥16	≥16	≥16
	Erythromycin	8-≥16	≥16	≥16
Staphylococcus aureus Ciprofloxacin- Resistant (gyrA & parC genotype group) (39 strains)	**Omadacycline**	**0.06-0.25**	**0.25**	**0.25**
	Doxycycline	0.5-1	1	1
	Tigecycline	0.25-0.5	0.5	0.5
	Linezolid	1--4	2	4
	Ceftaroline	0.06-1	0.5	1
	Levofloxacin	8-≥16	≥16	≥16
	Moxifloxacin	4-≥16	≥16	≥16
	Telithromycin	0.016-4	0.06	0.25
	Azithromycin	0.016-≥16	0.12	≥16
	Erythromycin	0.12-≥16	1	≥16

Results continued

Table 2 Frequency MIC distribution of omadacycline and comparators against *Staphylococcus aureus*

Organism (no. tested)	Antibiotic	Number of Strain(s) susceptible to MIC = mg/L									
		≤0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	≥16
Staphylococcus aureus all tested resistant strains (239 strains)	**Omadacycline**		**1**	**1**	**24**	**36**	**165**	**6**	**6**				
	Doxycycline				1		12	142	78			2	4
	Tigecycline						26	201	6	6			
	Linezolid							2	96	128	13		
	Ceftaroline				5	8	11	133	77	5			
	Levofloxacin							3	22	75	81	3	55
	Moxifloxacin						21	53	46	62	11	1	45
	Telithromycin		7	36	77	57	4	4	11	12	23	3	5
	Azithromycin		3	3	3	11	2	0	30	85	12	8	82
	Erythromycin				1	2	4	54	77		3	3	95
Staphylococcus aureus Methicillin-resistant (mec A group) (150 strains)	**Omadacycline**		**1**	**1**	**13**	**17**	**106**	**6**	**6**				
	Doxycycline				1		10	96	37			2	4
	Tigecycline						9	130	5	6			
	Linezolid							2	85	56	7		
	Ceftaroline				2	5	1	106	33	3			
	Levofloxacin								1	54	76	2	17
	Moxifloxacin						14	36	24	58	10	1	7
	Telithromycin		5	19	61	52	2	2	1	2	1	1	4
	Azithromycin								30	77	6		37
	Erythromycin								71		3	1	33
Staphylococcus aureus Macrolide-resistant (erm A,B,C group) (50 strains)	**Omadacycline**				**3**	**10**	**37**						
	Doxycycline						2	37	11				
	Tigecycline						9	40	1				
	Linezolid								6	41	3		
	Ceftaroline					1	1	6	40	2			
	Levofloxacin							3	21	21	5		
	Moxifloxacin						7	17	22	4			
	Telithromycin					1	2	2	10	10	22	2	1
	Azithromycin										4	8	38
	Erythromycin											2	48
Staphylococcus aureus Ciprofloxacin-Resistant (gyrA & parC group) (39 strains)	**Omadacycline**				**8**	**9**	**22**						
	Doxycycline							9	30				
	Tigecycline						8	31					
	Linezolid								5	31	3		
	Ceftaroline				3	2	9	21	4				
	Levofloxacin											1	38
	Moxifloxacin										1		38
	Telithromycin		2	17	16		4						
	Azithromycin		3	3	3	11	2			8	2		7
	Erythromycin				1	2	4	12	6				14

Discussion

- **Omadacycline** exhibits *in vitro* activity against resistant strains of *S. aureus*.
- **Omadacycline** demonstrated more consistent activity than other older tetracyclines, ketolides, macrolides, quinolones, oxazolidinone or third generation cephalosporins.
- Against all resistant strains of *S. aureus*, the activity of **omadacycline** (**MIC_{90} = 0.25 mg/L**) was more potent than other tested antibiotics.
- 95% (227/239) of the tested *S. aureus* were inhibited by a concentration of **≤0.25 mg/L** of **omadacycline** compared to respectively 76%, 10%, 10% and 5% inhibition in the case of telithromycin, tigecycline, ceftaroline and doxycycline.

Discussion

- MIC_{90} of **0.25 mg/L** was obtained against methicillin-resistant *S. aureus* (*mec*A genotype group) with **omadacycline** that was comparable to tigecycline and more potent than doxycycline, ceftaroline, linezolid and moxifloxacin.
  - 138 strains (92%), 139 strains (93%), 11 strains (7%), 9 strains (6%) and 8 strains (5%), showed a MIC **≤0.25 mg/L** to respectively **omadacycline**, telithromycin, doxycycline, tigecycline and ceftaroline.
- Against macrolide-resistant *S. aureus* (*ermA, B, C* genotype group) strains, **omadacycline** (**MIC_{90} = 0.25 mg/L**) was the most active agent and was more active than doxycycline, ceftaroline, linezolid, levofloxacin, moxifloxacin, telithromycin, azithromycin and erythromycin .
  - MIC of **≤0.25 mg/L** to **omadacycline** was obtained by 50 strains (100%) compared to respectively 9 strains (18%), 2 strains (4%) and 2 strains (4%) in the case of moxifloxacin, ceftaroline and tigecycline.
- Against ciprofloxacin-resistant *S. aureus* (*gyr*A and *par*C genotype group), MIC_{90} for **omadacycline** (**0.25 mg/L**) remained lower than doxycycline, ceftaroline and linezolid, and was comparable to telithromycin and tigecycline.
  - MIC_{90} ≥16 mg/L was observed with levofloxacin, moxifloxacin, azithromycin, and erythromycin.

Conclusion

Based on the *in vitro* results of this study, **omadacycline** exhibits potent *in vitro* activity against resistant *S. aureus* (MRSA and macrolide- or ciprofloxacin-resistant) and these results support completed clinical studies as a antimicrobial agent for the treatment of ABSSSI and CABP caused by *S. aureus* MRSA.

Acknowledgments

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