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Activities of Omadacycline and Comparator Agents against *Staphylococcus aureus* Isolates from a Surveillance Program Conducted in North America and Europe

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ABSTRACT Omadacycline is a new broad-spectrum aminomethylcycline in late-stage clinical development for acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia as a once-daily formulation taken orally or intravenously. In this study, omadacycline and comparator agents were tested against 502 isolates of *Staphylococcus aureus* selected from a 2014 global surveillance program, and the results were compared with those for 7,740 isolates from a 2010 surveillance program. For the 2014 isolates, testing was completed on 252 isolates from Europe and 250 isolates from North America. Each set of isolates was composed of ~100 hospital-acquired methicillin-resistant *Staphylococcus aureus* (HA-MRSA) isolates (isolated >48 h after hospital admission), 100 community-acquired MRSA (CA-MRSA) isolates (isolated <48 h after hospital admission), and 50 methicillin-susceptible *S. aureus* (MSSA) isolates. The omadacycline MIC_{50} and MIC_{90} for all *S. aureus* collected during 2014 was 0.12 and 0.12 μg/ml, respectively. The MIC_{90} values were identical for MRSA, HA-MRSA, and CA-MRSA (0.12 μg/ml). The MIC_{90} values for isolates from 2010 for *S. aureus*, MRSA, and CA-MRSA were 0.25 μg/ml (0.5 μg/ml for HA-MRSA; 87.8% were at ≤0.25 μg/ml). All 2014 and 2010 MRSA isolates were susceptible to vancomycin, and ≥99.8% were susceptible to daptomycin, linezolid, and tigecycline. The activity of omadacycline was similar for North American and European isolates, including MRSA (CA-MRSA or HA-MRSA). There was no evidence for emerging resistance to omadacycline between 2010 and 2014. The potent activity of omadacycline against *S. aureus* indicates that omadacycline merits further study in serious infections where multidrug resistance may be a concern.

KEYWORDS omadacycline, *S. aureus*, aminomethylcycline

Received 10 November 2016 **Returned for modification** 29 November 2016 **Accepted** 14 December 2016

Accepted manuscript posted online 19 December 2016

Citation Pfaller MA, Rhomberg PR, Huband MD, Flamm RK. 2017. Activities of omadacycline and comparator agents against *Staphylococcus aureus* isolates from a surveillance program conducted in North America and Europe. Antimicrob Agents Chemother 61:e02411-16. https://doi.org/10.1128/AAC.02411-16.

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Staphylococcus aureus is a leading cause of community-acquired (CA) and hospital-acquired (HA) infections (1, 2). In addition to CA- and HA- methicillin-resistant *S. aureus* (MRSA), *S. aureus* is well known to acquire resistance to classes of antibacterial agents that include the tetracyclines, fluoroquinolones, and macrolides, often in combination with methicillin resistance (2). These resistant phenotypes are of great concern internationally and have stimulated the development of new agents with activity against resistant strains of *S. aureus* (3–7).

Omadacycline is a semisynthetic derivative of minocycline and the first member of the novel class of aminomethylcyclines (7–10). Similar to the older tetracyclines (doxycycline, minocycline, and tetracycline), omadacycline binds to the 30S ribosomal subunit of target Gram-positive and Gram-negative bacteria with the resultant inhibition of protein synthesis (5, 8, 9). Omadacycline exhibits excellent potency against MRSA and methicillin-susceptible *S. aureus* (MSSA) and maintains activity in the presence of

TABLE 1 Cumulative frequency distribution of omadacycline MIC results for *S. aureus* for Europe and North America

Organism (no. of isolates)[a]	Yr	No. (cumulative %) of isolates inhibited by omadacycline MIC (μg/ml) of:									MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
		≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4		
S. aureus												
NA (250)	2014		2 (0.8)	125 (50.8)	102 (91.6)	3 (92.8)	7 (95.6)	11 (100.0)			0.06	0.12
NA (4,881)	2010		20 (0.4)	346 (7.5)	2,919 (67.3)	1247 (92.8)	215 (97.3)	101 (99.3)	29. (99.9)	4 (100.0)	0.12	0.25
EU (252)	2014		9 (3.6)	82 (36.1)	151 (96.0)	6 (98.4)	3 (99.6)	1 (100.0)			0.12	0.12
EU (2,859)	2010	2 (0.1)	21 (0.8)	243 (9.3)	1,752 (70.6)	696 (94.9)	134 (99.6)	8 (99.9)	3 (100.0)		0.12	0.25
MSSA												
NA (50)	2014			17 (34.0)	32 (98.0)	1 (100.0)					0.12	0.12
NA (2,373)	2010		14 (0.6)	178 (8.1)	1,457 (69.5)	628 (96.0)	82 (99.4)	11 (99.9)	3 (100.0)		0.12	0.25
EU (50)	2014		1 (2.0)	13 (28.0)	35 (98.0)	0 (98.0)	1 (100.0)				0.12	0.12
EU (2,109)	2010	2 (0.1)	15 (0.8)	204 (10.5)	1,333 (73.7)	461 (95.5)	90 (99.8)	3 (>99.9)	1 (100.0)		0.12	0.25
MRSA												
NA (200)	2014		2 (1.0)	108 (55.0)	70 (90.0)	2 (91.0)	7 (94.5)	11 (100.0)			0.06	0.12
NA (2,508)	2010		6 (0.2)	168 (6.9)	1,462 (65.2)	619 (89.9)	133 (95.2)	90 (98.8)	26 (99.8)	4 (100.0)	0.12	0.5
EU (202)	2014		8 (4.0)	69 (68.1)	116 (95.5)	6 (98.5)	2 (99.5)	1 (100.0)			0.12	0.12
EU (750)	2010		6 (0.8)	39 (6.0)	419 (61.9)	235 (93.2)	44 (99.1)	5 (99.7)	2 (100.0)		0.12	0.25
Hospital-acquired MRSA												
NA (101)	2014			45 (44.6)	44 (88.1)	0 (88.1)	6 (94.1)	6 (100.0)			0.12	0.5
NA (497)	2010			28 (5.6)	280 (62.0)	114 (84.9)	29 (90.7)	36 (98.0)	9 (99.8)	1 (100.0)	0.12	0.5
EU (102)	2014		5 (4.9)	35 (39.2)	55 (93.1)	4 (97.1)	2 (99.0)	1 (100.0)			0.12	0.12
EU (379)	2010		2 (0.5)	13 (4.0)	208 (58.8)	124 (91.6)	27 (98.7)	4 (99.7)	1 (100.0)		0.12	0.25
Community-acquired MRSA												
NA (99)	2014		2 (2.0)	63 (65.7)	26 (91.9)	2 (93.9)	1 (94.9)	5 (100.0)			0.12	0.25
NA (1,461)	2010		4 (0.3)	110 (7.8)	869 (67.3)	362 (92.1)	78 (97.4)	27 (99.2)	10 (99.9)	1 (100.0)	0.12	0.25
EU (100)	2014		3 (3.0)	34 (37.0)	61 (98.0)	2 (100.0)					0.12	0.12
EU (233)	2010		3 (1.3)	22 (10.7)	125 (64.4)	70 (94.4)	12 (99.6)	1 (100.0)			0.12	0.25

[a]Abbreviations: NA, North America; EU, Europe.

ribosomal protection (*tetM* in *S. aureus*) and efflux (*tetK* in *S. aureus*) tetracycline resistance genes. Also, this drug is not affected by mechanisms of resistance to other classes of antibacterial agents (8–10). Omadacycline has been shown to be noninferior to linezolid in a phase 3 study of the treatment of acute bacterial skin and skin structure infections (ABSSSI) (11) and is in phase 3 development for treatment of ABSSSI and community-acquired bacterial pneumonia (CABP) (7).

In the present study, we evaluated the *in vitro* activity of omadacycline and comparator agents against *S. aureus* that caused CA-MRSA and HA-MRSA infections in North America and Europe in a 2014 global surveillance program and compared the results with data collected in the 2010 SENTRY surveillance program. Tests followed Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution (BMD) methods (12, 13).

RESULTS AND DISCUSSION

Activity of omadacycline against *S. aureus*: Europe versus North America. Identical omadacycline $MIC_{50/90}$ values were exhibited by North American and European MSSA isolates from 2010 (0.12/0.25 μg/ml) and 2014 (0.12/0.12 μg/ml) (Table 1). The MIC_{90} values for MRSA from Europe and North America were similar in 2010 (0.25 and 0.5 μg/ml [89.9% ≤0.25 μg/ml], respectively) and were identical (0.12 μg/ml) in 2014 (Table 1). The MIC_{90} values for HA-MRSA were higher in North America (0.5 μg/ml [84.9% ≤0.25 μg/ml] in 2010; 0.5 μg/ml [88.1% ≤0.25 μg/ml] in 2014) than in Europe (0.25 μg/ml in 2010; 0.12 μg/ml in 2014), whereas MIC_{90} values for CA-MRSA were identical in Europe and North America in 2010 (0.25 μg/ml) and 2014 (0.12 μg/ml) (Table 1). Although isolates with MIC values of 2 and 4 μg/ml were observed in the 2010 survey, none were detected in the 2014 survey, supporting a lack of emerging resistance to this agent.

Susceptibility of European and North American MRSA isolates to comparator agents. *S. aureus* isolates from Europe and North America exhibited high levels of

TABLE 2 Activity of omadacycline and comparator antimicrobial agents tested against isolates from North America and Europe

Organism group and antimicrobial agent	North America			Europe		
	MIC range	$MIC_{50/90}$	%S[a]	MIC range	$MIC_{50/90}$	%S[a]
MRSA[b]						
Omadacycline	0.03 to 4	0.12/0.5		0.03 to 2	0.12/0.25	
Tigecycline[c]	≤0.03 to 1	0.12/0.25	>99.9[c]	≤0.03 to 0.5	0.06/0.25	100.0[c]
Doxycycline	≤0.06 to >8	0.12/0.5	98.4	≤0.06 to >8	0.12/4	94.1
Tetracycline	≤0.25 to >8	≤0.25/1	95.2	≤0.25 to >8	≤0.25/>8	83.7
Levofloxacin	≤0.5 to >4	4/>4	30.2	0.5 to >4	>4/>4	13.1
Erythromycin	≤0.25 to >4	>4/>4	10.5	≤0.25 to >4	>4/>4	34.5
Clindamycin	≤0.25 to >2	≤0.25/>2	69.2	≤0.25 to >2	≤0.25 to >2	70.4
Linezolid	≤0.12 to 8	1/1	>99.9	≤0.12 to 2	1/1	100.0
Daptomycin	≤0.06 to 2	0.25/0.5	99.9	0.12 to 2	0.25/0.5	99.9
Vancomycin	0.25 to 2	1/1	100.00	≤0.12 to 2	1/1	100.0
Gentamicin	≤1 to >8	≤1/≤1	96.1	≤1 to >8	≤1/>8	79.2
Trimethoprim-sulfamethoxazole	≤0.5 to >4	≤0.5/≤0.5	97.7	≤0.5 to >4	≤0.5/≤0.5	98.3
Hospital-acquired MRSA[d]						
Omadacycline	0.06 to 4	0.06 to 4		0.03 to 2	0.12/0.25	
Tigecycline[c]	≤0.03 to 0.5	0.12/0.25	100.0[c]	≤0.03 to 0.5	0.12/0.25	100.0[c]
Doxycycline	≤0.06 to >8	0.12/1	98.1	≤0.06 to >8	0.12/4	91.4
Tetracycline	≤0.25 to >8	≤0.25/2	94.3	≤0.25 to >8	≤0.25/>8	79.0
Levofloxacin	≤0.5 to >4	>4/>4	20.6	≤0.5 to >4	>4/>4	12.3
Erythromycin	≤0.25 to >4	>4/>4	10.7	≤0.25 to >4	>4/>4	32.5
Clindamycin	≤0.25 to >2	≤0.25/>2	59.2	≤0.25 to >2	≤0.25/>2	65.2
Linezolid	0.25 to 8	1/1	99.8	≤0.12 to 2	1/1	100.0
Daptomycin	0.12 to 1	0.25/0.5	100.0	0.12 to 2	0.25/0.5	99.8
Vancomycin	0.5 to 2	1/1	100.0	≤0.12 to 2	1/1	100.0
Gentamicin	≤1 to >8	≤1/≤1	94.7	≤1 to >8	≤1/>8	70.4
Trimethoprim-sulfamethoxazole	≤0.5 to >4	≤0.5/≤0.5	96.8	≤0.5 to >4	≤0.5/≤0.5	97.9
Community-acquired MRSA[e]						
Omadacycline	0.03 to 4	0.12/0.25		0.03 to 1	0.12/0.25	
Tigecycline[c]	≤0.03 to 1	0.12/0.25	99.9[c]	≤0.03 to 0.5	0.06/0.25	100.0[c]
Doxycycline	≤0.06 to >8	0.12/0.25	98.8	≤0.06 to >8	0.12/0.5	96.7
Tetracycline	≤0.25 to >8	≤0.25/0.5	95.5	≤0.25 to >8	≤0.25/>8	87.7
Levofloxacin	≤0.5 to >4	4/>4	34.0	≤0.5 to >4	>4/>4	14.6
Erythromycin	≤0.25 to >4	>4/>4	10.8	≤0.25 to >4	>4/>4	35.4
Clindamycin	≤0.25 to >2	≤0.25/>2	73.1	0.25 to >2	≤0.25/>2	≤75.5
Linezolid	≤0.12 to 4	1/1	100.0	0.25 to 2	1/1	100.0
Daptomycin	≤0.06 to 2	0.25/0.5	99.8	0.12 to 1	0.25/0.5	100.0
Vancomycin	0.25 to 2	1/1	100.0	0.25 to 2	1/1	100.0
Teicoplanin	≤1 to 4	≤1/≤1	100.0	≤1 to 2	≤1/≤1	100.0
Gentamicin	≤1 to >8	≤1/≤1	96.7	≤1 to >8	≤1/>8	88.0
Trimethoprim-sulfamethoxazole	≤0.5 to >4	≤0.5/≤0.5	98.0	≤0.5 to >4	≤0.5/≤0.5	98.6

[a]Criteria as published by CLSI (13).
[b]*n* = 2,708 North American and 952 European isolates.
[c]Tigecycline breakpoint from Tygacil package insert; Wyeth (revised December 2014) was used because no CLSI breakpoint was available.
[d]*n* = 617 North American and 486 European isolates.
[e]*n* = 1,861 North American and 424 European isolates.

susceptibility to daptomycin, linezolid, tigecycline, trimethoprim-sulfamethoxazole, and vancomycin (98% to 100%; data not shown). These agents remained highly active against MRSA from both regions (Table 2). Doxycycline and tetracycline were slightly more active against MRSA isolates from North America (98.4% and 95.2%, respectively) versus those from Europe (94.1% and 83.7%, respectively) (Table 2). Likewise, gentamicin susceptibility was higher for North American MRSA isolates (96.1%) than for European MRSA isolates (79.2%). Both regions had lower susceptibility for clindamycin, erythromycin, and levofloxacin.

Isolates of HA-MRSA and CA-MRSA from both regions were comparably susceptible to daptomycin, linezolid, tigecycline, trimethoprim-sulfamethoxazole, and vancomycin (Table 2). Whereas HA-MRSA and CA-MRSA isolates from North America and Europe showed reduced susceptibility to clindamycin, erythromycin, and levofloxacin, the European isolates of HA-MRSA were more susceptible than the North American isolates

to clindamycin (65.2% versus 59.2%) and erythromycin (32.5% versus 10.7%). Isolates of both HA-MRSA and CA-MRSA from North America were more susceptible to gentamicin and levofloxacin than those from Europe (Table 2).

The data from this survey demonstrate that omadacycline remains highly active against clinical isolates of *S. aureus* over time (2010 to 2014) and across European and North American study sites. The activity of omadacycline was comparable for HA-MRSA and CA-MRSA from both regions as well. Omadacycline MIC values of 2 and 4 μg/ml were observed among North American MRSA isolates from 2010 but were not detected in isolates from 2014. Such isolates accounted for $<$1% of isolates tested in 2010, and whether they represent spurious results or strains with decreased susceptibility to omadacycline due to acquired resistance factors has not been determined to date. The fact that they were not detected in 2014 speaks against emerging resistance to this agent in both North America and Europe. Daptomycin, linezolid, tigecycline, trimethoprim-sulfamethoxazole, and vancomycin were all highly active against North American and European isolates of CA-MRSA and HA-MRSA and showed no decrease in susceptibility over time. Although doxycycline and tetracycline were quite active against North American isolates of MRSA (98.4% and 95.2%, respectively), these agents were less active against European strains (94.1% and 83.7%, respectively). Resistance to erythromycin, clindamycin, and levofloxacin was elevated among MRSA isolates from both regions, and resistance was generally higher for HA-MRSA than for CA-MRSA. These data build on those previously reported by Macone et al. (10) and indicate that omadacycline merits further study in serious *S. aureus* infections, including ABSSSI, CABP, and complicated urinary tract infection, where multidrug resistance may be a problem.

MATERIALS AND METHODS

Organism collection. A total of 102 HA-MRSA, 100 CA-MRSA, and 50 MSSA isolates from Europe and 101 HA-MRSA, 99 CA-MRSA, and 50 MSSA isolates from North America (2014 global surveillance program; total $n = 502$) were selected for testing. The isolates from 2014 were selected purely on the basis of the resistant phenotype for both North American and European isolates. *S. aureus* isolates were categorized as HA-MRSA if they were isolated $>$48 h after hospital admission and as CA-MRSA if they were isolated $<$48 h after hospital admission. The 2014 data were compared with the results from testing 7,740 *S. aureus* isolates from the 2010 global surveillance program.

Susceptibility testing. Comparator agents were tested in validated dry-form BMD panels manufactured by Thermo Fisher Scientific, Inc. (Cleveland, OH, USA) following CLSI methods (12). Omadacycline was tested in dry-form panels in 2010 and panels with fresh-frozen cation-adjusted Mueller-Hinton broth medium made at JMI Laboratories (North Liberty, IA, USA) for testing of the 2014 strains. Concurrent quality control (QC) testing was performed to ensure proper test conditions and procedures (12, 13). QC strains included *S. aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212 (13). All QC results were within published ranges. All 13 omadacycline MIC results for *S. aureus* ATCC 29213 were at 0.03 μg/ml, and all 12 results for *E. faecalis* ATCC 29212 were at 0.06 μg/ml (data not shown). CLSI interpretive criteria were used (13).

ACKNOWLEDGMENTS

We thank the following staff members at JMI Laboratories (North Liberty, IA, USA): L. Duncan, M. Janechek, J. Oberholser, J. Schuchert, and J. Streit for technical support and L. Flanigan for editorial assistance.

This study and manuscript were funded by Paratek Pharmaceuticals, Inc.

JMI Laboratories, Inc., received research and educational grants in 2014 to 2015 from Achaogen, Actavis, Actelion, Allergan, American Proficiency Institute (API), AmpliPhi, Anacor, Astellas, AstraZeneca, Basilea, BD, Cardeas, Cellceutix, CEM-102 Pharmaceuticals, Cempra, Cerexa, Cidara, CorMedix, Cubist, Debiopharm, Dipexium, Dong Wha, Durata, Enteris, Exela, Forest Research Institute, Furiex, Genentech, GSK, Helperby, ICPD, Janssen, Lannett, Longitude, Medpace, Meiji Seika Kasha, Melinta, Merck, Motif, Nabriva, Novartis, Paratek, Pfizer, Pocared, PTC Therapeutics, Rempex, Roche, Salvat, Scynexis, Seachaid, Shionogi, Tetraphase, The Medicines Co., Theravance, Thermo Fisher, VenatoRX, Vertex, Wockhardt, Zavante, and some other corporations. Some JMI employees are advisors/consultants for Allergan, Astellas, Cubist, Pfizer, Cempra, and Theravance.

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