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In vitro Activity of Omadacycline and Comparators against Staphylococci, Streptococci, and Enterococci (including resistant organism subsets) from Patients in European Medical Centres during 2016: Results from the SENTRY Antimicrobial Surveillance Program

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REVISED ABSTRACT

Background: Omadacycline is a broad-spectrum aminomethylcycline antibacterial in late-stage clinical development for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP). Omadacycline has demonstrated potent *in vitro* activity against gram-positive and -negative bacterial pathogens commonly associated with skin and skin structure infections (SSSI) and respiratory tract infections (RTI). In addition, omadacycline remains highly active against isolates expressing common tetracycline-, penicillin-, fluoroquinolone-, and macrolide-resistance mechanisms. The *in vitro* susceptibility results for omadacycline and comparator agents tested against gram-positive bacterial clinical isolates collected from patients in European medical centres participating in the SENTRY surveillance program during 2016 are presented.

Methods: A total of 4,499 clinically significant gram-positive isolates that include 2,572 staphylococci, 1,355 streptococci, and 572 enterococci representing multiple infection types were collected during 2016 and included only one isolate/patient/infection episode. A central monitoring laboratory confirmed isolate identifications using standard bacteriologic algorithms, matrix-assisted laser desorption/ionization-time of flight mass spectrometry, and/or molecular characterization. Susceptibility testing was performed according to reference (CLSI) broth microdilution methodology, and results were interpreted per EUCAST breakpoints.

Results: Omadacycline demonstrated potent *in vitro* activity against *Staphylococcus aureus* (SA; n=2,165) with $MIC_{50/90}$ values of 0.12/0.25 mg/L. Overall, methicillin resistance in SA (MRSA) was 23.9%. Omadacycline ($MIC_{50/90}$ 0.12/0.25 mg/L) and tigecycline ($MIC_{50/90}$ 0.12/0.12 mg/L; 100.0% susceptible) were the most potent antimicrobials tested against MRSA whereas susceptibility to clindamycin (76.4%), erythromycin (41.1%), levofloxacin (30.1%), and tetracycline (81.1%) was reduced. Omadacycline was also highly active against coagulase-negative staphylococci (CoNS, n=407; $MIC_{50/90}$ 0.12/0.5 mg/L) that included methicillin-resistant strains (n=275; $MIC_{50/90}$ 0.12/0.5 mg/L) in which susceptibility to clindamycin (65.8%), erythromycin (18.9%), levofloxacin (32.1%), and tetracycline (73.1%) was also reduced.

Streptococci including *S. pneumoniae* (n=709; $MIC_{50/90}$ 0.06/0.12 mg/L), β-haemolytic streptococci (n=425; $MIC_{50/90}$ 0.06/0.12 mg/L), and viridans group streptococci (n=221; $MIC_{50/90}$ 0.06/0.12 mg/L) were inhibited by low levels of omadacycline. Penicillin resistance in *S. pneumoniae* (PRSP) was 11.1%. All PRSP isolates were inhibited by ≤0.12 mg/L of omadacycline whereas resistance to ceftriaxone (7.7%), erythromycin (71.8%), and tetracycline (65.4%) was high. All β-haemolytic streptococci were susceptible to tigecycline, penicillin, linezolid, daptomycin, and vancomycin; however, resistance to levofloxacin (98.8% susceptible), erythromycin (78.9% susceptible), clindamycin (88.7% susceptible), and tetracycline (58.3% susceptible) occurred.

Omadacycline exhibited potent *in vitro* activity against both *Enterococcus faecalis* (n=349; $MIC_{50/90}$ 0.12/0.25 mg/L) and *E. faecium* (n=223; $MIC_{50/90}$ 0.06/0.12 mg/L) that included vancomycin-resistant isolates. Vancomycin resistance rates were 0.0% and 19.7% against *E. faecalis* and *E. faecium*, respectively.

Conclusions: Omadacycline demonstrated potent *in vitro* antibacterial activity against gram-positive bacterial pathogens commonly associated with SSSI and RTI infections, including *S. aureus* (including MRSA), *S. pneumoniae* (including PRSP), β-haemolytic streptococci, and enterococci (including vancomycin-resistant *E. faecium* isolates). These data support further omadacycline clinical evaluation studies, especially where these resistant pathogens are likely to occur.

INTRODUCTION

- Omadacycline is a broad-spectrum aminomethylcycline protein synthesis inhibitor in late-stage clinical development (oral and intravenous formulations) for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP)
- The spectrum of activity of omadacycline includes a broad range of gram-positive (staphylococci, streptococci, and enterococci) and gram-negative bacterial pathogens commonly associated with ABSSSI and CABP
- Omadacycline is highly active against bacterial clinical isolates expressing common tetracycline-, penicillin/oxacillin-, fluoroquinolone-, and macrolide-resistance mechanisms that include *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), enterococci, and streptococci (*Streptococcus pneumoniae*, viridans group, and β-haemolytic streptococci)
- The *in vitro* susceptibility results for omadacycline and comparator agents against 4,499 gram-positive bacterial clinical isolates collected from patients in European medical centres participating in a global surveillance program during 2016 are presented

MATERIALS AND METHODS

- A total of 4,499 (nonduplicate) gram-positive bacterial isolates were collected from patients with multiple infection types in 38 medical centres in 18 European countries and Israel during 2016 and included 2,165 *S. aureus*, 407 CoNS, 425 β-haemolytic streptococci, 221 viridans group streptococci, 349 *E. faecalis,* and 223 *E. faecium*. Only one isolate per patient/infection episode was included
- Bacterial isolates were initially identified by the submitting laboratories and confirmed by JMI Laboratories using a matrix-assisted laser desorption/ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany)
- Susceptibility testing was performed according to CLSI (M07-A10, 2015) reference broth microdilution methodology and results were interpreted using EUCAST (2017) breakpoint interpretive criteria. CLSI quality control (QC) reference strains (M100-S27, 2017) were tested concurrently and included *S. aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922 and ATCC 35218, *Klebsiella pneumoniae* ATCC 700603, and *Pseudomonas aeruginos* ATCC 27853

RESULTS

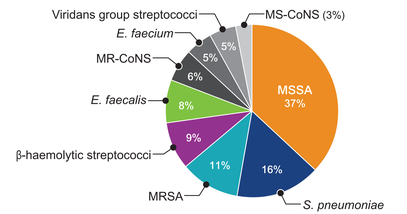
- Cumulative percent inhibition data for omadacycline against staphylococci, streptococci, and enterococci including the percentage of 2016 European gram-positive surveillance isolates by organism group are presented in Table 1 and Figure 1, respectively
- Omadacycline demonstrated potent *in vitro* activity against *S. aureus* isolates ($MIC_{50/90}$ 0.12/0.25 mg/L) and retained a high level of activity against isolates displaying tetracycline (doxycycline and tetracycline), fluoroquinolone (levofloxacin), macrolide (erythromycin), lincosamide (clindamycin), and/or oxacillin resistance phenotypes. Corresponding doxycycline, tetracycline, levofloxacin, erythromycin, clindamycin, and oxacillin resistance rates were 2.5%, 7.6%, 19.9%, 24.2%, 6.6%, and 23.9%, respectively (Table 2)
- Against MRSA, omadacycline (MIC_{50} 0.25 mg/L; highest MIC 2 mg/L) was comparable in activity to tigecycline (MIC_{50} 0.12 mg/L, highest MIC 0.5 mg/L) and ≥8-fold more potent than doxycycline and tetracycline (MIC_{50}, 2 and >8 mg/L, respectively; Table 2)

Table 1 Antimicrobial activity of omadacycline against 4,499 staphylococci, streptococci, and enterococci from patients in European medical centres during 2016

Organism / organism group	No. of isolates at MIC (mg/L, cumulative %*											MIC_{50}	MIC_{90}
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>		
Staphylococcus aureus (2,165)	4	24	422	1,181	481	29	6	4					0.12	0.25
	<0.1	1.2	21.6	76.1	98.3	99.5	99.8	100.0						
MSSA (1,647)	1	19	379	897	339	12	0	0					0.12	0.25
	0.1	1.2	24.2	78.7	99.3	100.0								
MRSA (518)	0	5	43	284	142	14	6	4					0.12	0.25
	0.0	1.0	13.1	68.0	95.4	98.1	99.2	100.0						
Coagulase-negative staphylococci (407)	4	51	109	89	69	68	28	1	0	0	1		0.12	0.5
	1.0	13.5	40.3	62.2	79.7	96.3	103.2	103.5	103.5	103.5	103.7			
MS-CoNS (132)	4	25	49	28	9	12	5						0.06	0.5
	3.0	22.0	59.1	80.3	87.1	96.2	100.0							
MR-CoNS (275)	0	26	60	61	50	54	23	1					0.12	0.5
	0.0	9.5	31.3	53.5	71.6	91.3	99.6	100.0						
Streptococcus pneumoniae (709)	8	135	487	77	0	1							0.06	0.12
	1.1	20.2	88.9	99.7	99.7	99.9	100.0							
Penicillin-susceptible *Streptococcus pneumoniae* (≤0.06) (510)	7	110	349	43	0	1							0.06	0.06
	1.4	22.9	91.4	99.8	99.8	100.0								
Penicillin-intermediate *Streptococcus pneumoniae* (≥0.12 and ≤1) (121)	1	19	84	16	0	0							0.06	0.12
	0.8	16.5	80.0	93.2	93.2	93.2	100.0							
Penicillin-resistant *Streptococcus pneumoniae* (≥2) (78)	0	6	54	18									0.06	0.12
	0.0	7.7	76.9	100.0										
Viridans group streptococci (221)	8	50	112	36	12	3							0.06	0.12
	3.6	26.2	76.9	93.2	98.6	100.0								
β-haemolytic streptococci (425)	0	8	240	142	33	2							0.06	0.12
	0.0	1.9	58.4	91.8	99.5	100.0								
Streptococcus pyogenes (201)	0	4	153	31	3								0.06	0.12
	0.0	2.0	83.1	98.5	100.0									
Streptococcus agalactiae (126)	0	4	36	71	15	1							0.12	0.25
	0.0	3.2	31.0	87.3	99.2	100.0								
Other β-haemolytic streptococci (98)	0	0	42	40	15	1							0.12	0.25
	0.0	0.0	42.9	83.7	99.0	100.0								
Enterococcus faecalis (349)	0	10	94	145	87	12	1						0.12	0.25
	0.0	2.9	29.8	71.3	96.3	99.7	100.0							
Enterococcus faecium (223)	1	17	123	74	4	0	3	0	0	1			0.06	0.12
	0.4	8.1	63.2	96.4	98.2	98.2	99.6	99.6	99.6	100.0				
Vancomycin-susceptible *Enterococcus faecium* (179)	1	13	100	59	4	0	2						0.06	0.12
	0.6	7.8	63.7	96.6	98.9	98.9	100.0							
Vancomycin-nonsusceptible *Enterococcus faecium* (44)	0	4	23	15	0	0	1	0	0	1			0.06	0.12
	0.0	9.1	61.4	95.5	95.5	95.5	97.7	97.7	97.7	100.0				

* MIC_{50} values are underlined; MIC_{90} values are bold

Figure 1 Incidence of gram-positive pathogens from the omadacycline 2016 European surveillance program



- Omadacycline and tigecycline were equally active against CoNS and MR-CoNS isolates with MIC_{90} values of 0.5 mg/L and 0.25 mg/L, respectively (Table 2). Doxycycline (MIC_{90}, 4 mg/L) and tetracycline (MIC_{90}, >8 mg/L) were 8- and ≥16-fold less active than omadacycline against MR-CoNS (Table 2)
- Doxycycline, tetracycline, levofloxacin, erythromycin, and clindamycin resistance rates in CoNS were 7.9%, 17.4%, 48.3%, 61.4%, and 23.1%, respectively, and increased to 10.5%, 22.2%, 67.9%, 79.6%, and 33.1%, respectively, in MR-CoNS (Table 2)
- *S. pneumoniae* isolates, including penicillin-resistant strains, were highly susceptible to omadacycline ($MIC_{50/90}$, 0.06/0.12 mg/L) and tigecycline ($MIC_{50/90}$, 0.03/0.06 mg/L), whereas 20.3% of *S. pneumoniae* isolates were resistant to tetracycline ($MIC_{50/90}$, ≤0.25/>8 mg/L; Table 2)
- Viridans group streptococci were inhibited by low levels of omadacycline ($MIC_{50/90}$, 0.06/0.12 mg/L) and tigecycline ($MIC_{50/90}$, 0.03/0.06 mg/L). Tetracycline ($MIC_{50/90}$, 0.5/>8 mg/L), ceftriaxone ($MIC_{50/90}$, 0.12/2 mg/L; 15.4% resistant), and clindamycin ($MIC_{50/90}$, ≤0.25/2 mg/L; 10.9% resistant) were considerably less active (Table 2)
- Omadacycline ($MIC_{50/90}$, 0.06/0.12 mg/L) and tigecycline ($MIC_{50/90}$, 0.06/0.06 mg/L) were also very active against β-haemolytic streptococci (*Streptococcus agalactiae*, *S. dysgalactiae*, and *S. pyogenes*). These isolates were very susceptible (100.0%) to all agents tested except for tetracycline (58.3% susceptible), clindamycin (88.7% susceptible), erythromycin (78.9% susceptible) and levofloxacin (98.8% susceptible; Table 2)
- Omadacycline was two-fold more active against *E. faecium* ($MIC_{50/90}$ 0.06/0.12 mg/L) compared to *E. faecalis* ($MIC_{50/90}$ 0.12/0.25 mg/L), and its activity was unchanged against *E. faecium* isolates displaying resistance to vancomycin (Tables 1 and 2)

Table 2 *In vitro* activity of omadacycline and comparator antimicrobials against staphylococci, streptococci, and enterococci from patients in European medical centres during 2016

Organism (no. tested) and antimicrobial agent	MIC_{50}	MIC_{90}	Range	EUCAST*		
				%S	%I	%R
S. aureus (2,165)						
Omadacycline	0.12	0.25	≤0.015 – 2	—	—	—
Doxycycline	≤0.06	0.25	≤0.06 – >8	94.9	2.6	2.5
Tetracycline	≤0.5	≤0.5	≤0.5 – >8	92.3	0.1	7.6
Tigecycline	0.06	0.12	≤0.015 – 0.5	100.0		0.0
Oxacillin	0.5	>2	≤0.25 – >2	76.1		23.9
Levofloxacin	0.25	>4	≤0.03 – >4	80.1		19.9
Erythromycin	0.25	>8	≤0.06 – >8	74.5	1.4	24.2
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	93.3	<0.1	6.6
Linezolid	1	2	≤0.12 – 2	100.0		0.0
Daptomycin	0.5	0.5	≤0.12 – 1	100.0		0.0
Vancomycin	0.5	1	0.25 – 2	100.0		0.0
MRSA (518)						
Omadacycline	0.12	0.25	0.03 – 2	—	—	—
Doxycycline	≤0.06	2	≤0.06 – >8	87.3	4.4	8.3
Tetracycline	≤0.5	>8	≤0.5 – >8	81.1	0.2	18.7
Tigecycline	0.12	0.12	0.03 – 0.5	100.0		0.0
Levofloxacin	>4	>4	0.12 – >4	30.1		69.9
Erythromycin	>8	>8	≤0.06 – >8	41.1	1.5	57.3
Clindamycin	≤0.25	>2	≤0.25 – >2	76.4	0.0	23.6
Linezolid	1	1	0.25 – 2	100.0		0.0
Daptomycin	0.5	0.5	≤0.12 – 1	100.0		0.0
Vancomycin	0.5	1	0.25 – 2	100.0		0.0
CoNS^ (407)						
Omadacycline	0.12	0.5	≤0.015 – 2	—	—	—
Doxycycline	0.12	2	≤0.06 – >8	88.2	3.9	7.9
Tetracycline	≤0.5	>8	≤0.5 – >8	78.6	3.9	17.4
Tigecycline	0.06	0.25	≤0.015 – 0.5	100.0		0.0
Oxacillin	>2	>2	≤0.25 – >2	34.9		65.1
Levofloxacin	0.5	>4	0.06 – >4	51.7		48.3
Erythromycin	>8	>8	≤0.06 – >8	37.6	1.0	61.4
Clindamycin	≤0.25	>2	≤0.25 – >2	75.9	1.0	23.1
Linezolid	0.5	1	0.25 – >8	99.8		0.2
Daptomycin	0.5	0.5	≤0.12 – 2	99.8		0.2
Vancomycin	1	2	≤0.12 – 4	100.0		0.0
MR-CoNS (275)						
Omadacycline	0.12	0.5	0.03 – 2	—	—	—
Doxycycline	0.25	4	≤0.06 – >8	85.1	4.4	10.5
Tetracycline	≤0.5	>8	≤0.5 – >8	73.1	4.7	22.2
Tigecycline	0.12	0.25	≤0.015 – 0.5	100.0		0.0
Levofloxacin	4	>4	0.06 – >4	32.1		67.9
Erythromycin	>8	>8	≤0.06 – >8	18.9	1.5	79.6
Clindamycin	≤0.25	>2	≤0.25 – >2	65.8	1.1	33.1
Linezolid	0.5	1	0.25 – >8	99.6		0.4
Daptomycin	0.5	1	≤0.12 – 2	99.6		0.4
Vancomycin	1	2	0.25 – 4	100.0		0.0
S. pneumoniae (709)						
Omadacycline	0.06	0.12	≤0.015 – 1	—	—	—
Tetracycline	≤0.25	>8	≤0.25 – >8	79.3	0.4	20.3
Tigecycline	0.03	0.06	0.015 – 0.25	—	—	—
Penicillin	0.015	2	≤0.004 – >8	71.9		28.1^
				71.9	22.6	5.5^
Ceftriaxone	0.03	1	≤0.015 – >2	87.7	11.4	0.8
Levofloxacin	1	2	0.25 – >4	97.9		2.1
Azithromycin	0.06	>32	0.008 – >32	77.9	0.1	22.0
Erythromycin	0.03	>32	≤0.015 – >32	78.4	0.3	21.3
Clindamycin	≤0.25	>2	≤0.25 – >2	84.5		15.5
Linezolid	1	2	0.25 – 2	100.0	0.0	0.0
S. pneumoniae PRSP (78)						
Omadacycline	0.06	0.12	0.03 – 0.12	—	—	—
Tetracycline	>8	>8	≤0.25 – >8	34.6	0.0	65.4
Tigecycline	0.06	0.06	0.03 – 0.06	—	—	—
Penicillin	2	4	2 – >8	0.0		100.0^
				0.0	50.0	50.0^
Ceftriaxone	1	2	0.5 – >2	6.4	85.9	7.7
Levofloxacin	1	1	0.5 – 4	98.7		1.3
Azithromycin	>32	>32	0.03 – >32	28.2	0.0	71.8
Erythromycin	>32	>32	0.03 – >32	28.2	0.0	71.8
Clindamycin	>2	>2	≤0.25 – >2	44.9		55.1
Linezolid	1	1	0.25 – 2	100.0	0.0	0.0
Viridans group streptococci° (221)						
Omadacycline	0.06	0.12	≤0.015 – 0.5	—	—	—
Tetracycline	0.5	>8	≤0.25 – >8	—	—	—
Tigecycline	0.03	0.06	≤0.008 – 0.25	—	—	—
Penicillin	0.06	2	0.008 – >8	79.2	13.1	7.7
Ceftriaxone	0.12	2	≤0.015 – >2	84.6		15.4
Levofloxacin	1	2	0.25 – >4	—	—	—
Erythromycin	0.03	8	≤0.015 – >32	—	—	—
Clindamycin	≤0.25	2	≤0.25 – >2	89.1		10.9
Linezolid	1	1	0.12 – >4	—	—	—
Daptomycin	0.25	1	≤0.06 – 1	—	—	—
Vancomycin	0.5	0.5	0.25 – 1	100.0		0.0

* Criteria as published by EUCAST [2017].
^ Organisms include: *Staphylococcus capitis* (21), *S. caprae* (6), *S. cohnii* (3), *S. epidermidis* (221), *S. haemolyticus* (64), *S. hominis* (36), *S. lugdunensis* (32), *S. saprophyticus* (12), *S. simulans* (3), *S. warneri* (9)
‡ Using meningitis breakpoints
# Using nonmeningitis breakpoints
° Organisms include: *Streptococcus anginosus* (44), *S. anginosus* group (10), *S. australis* (2), *S. bovis* group (1), *S. constellatus* (10), *S. criistatus* (2), *S. equinus* (1), *S. gallolyticus* (18), *S. gordonii* (2), *S. infantis* (1), *S. intermedius* (1), *S. lutetiensis* (1), *S. mitis* group (53), *S. mitis/oralis* (2), *S. mutans* (2), *S. parasanguinis* (13), *S. salivarius* (2), *S. salivarius* group (4), *S. salivarius/vestibularis* (7), *S. sanguinis* (9), *S. vestibularis* (6)
¶ Organisms include: *Streptococcus agalactiae* (126), *S. canis* (2), *S. dysgalactiae* (96), *S. pyogenes* (201)
+ Uncomplicated UTI only

CONCLUSIONS

- Omadacycline was highly active against *S. aureus* ($MIC_{50/90}$ 0.12/0.25 mg/L) and CoNS ($MIC_{50/90}$ 0.12/0.5 mg/L) that included MRSA and MR-CoNS isolates from Europe as well as strains displaying resistance to tetracyclines (doxycycline and/or tetracycline), fluoroquinolones (levofloxacin), macrolides (erythromycin), and lincosamides (clindamycin)
- Streptococci, including *S. pneumoniae*, viridans group streptococci, and β-haemolytic streptococci, were inhibited by low levels of omadacycline ($MIC_{50/90}$ values of 0.06/0.12 mg/L)
- Omadacycline remained highly active against tetracycline-resistant *S. pneumoniae* (20.3% tetracycline-resistant) and β-haemolytic streptococci (41.5% tetracycline-resistant) isolates
- Omadacycline exhibited potent *in vitro* activity against *E. faecalis* ($MIC_{50/90}$ 0.12/0.25 mg/L) and vancomycin-susceptible and -resistant isolates of *E. faecium* ($MIC_{50/90}$ 0.06/0.12 mg/L). Tetracycline demonstrated little utility against *E. faecalis* and *E. faecium* isolates (MIC_{50} values >16 mg/L)
- Results of this surveillance study support the continued development of omadacycline in infections where resistant isolates of staphylococci, streptococci, and enterococci are likely to be found, including ABSSSI and CABP

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