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In Vitro Activity of Omadacycline and Comparators against Gram-Positive and -Negative Isolates Collected from Patients in United States Medical Centers (2018): SENTRY Surveillance Program Results

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INTRODUCTION

- Omadacycline is a new aminomethylcycline antibacterial (oral and intravenous formulations) approved in October 2018 by the United States Food and Drug Administration (FDA) for the treatment of adults with acute bacterial skin and skin structure infections (ABSSSIs) and community-acquired bacterial pneumonia (CABP) caused by indicated pathogens
- Omadacycline is currently in phase 2 clinical trials for treatment of uncomplicated urinary tract infections (uUTIs; NCT03425396) and acute pyelonephritis (NCT03757234)
- Omadacycline is highly active against gram-positive (staphylococci, streptococci, and enterococci) and gram-negative bacterial pathogens often associated with ABSSSIs, CABP, and UTIs

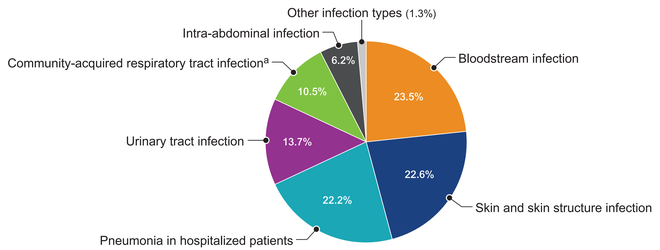
MATERIALS AND METHODS

- Gram-positive and gram-negative bacterial clinical isolates (n=7,000) were collected from patients in 31 medical centers located in the United States and included all 9 US census divisions
- Isolates were collected from patients with bloodstream infection (BSI), skin and skin structure infection (SSSI), pneumonia in hospitalized patients (PIHP), urinary tract infection (UTI), community-acquired respiratory tract infection (CARTI), intra-abdominal infection (IAI), and other infection types; 1 isolate was collected per patient/infection episode (Figure 1)
- Bacterial identifications were performed by the submitting laboratories and confirmed by JMI Laboratories using matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany)
- Broth microdilution susceptibility testing was performed according to Clinical and Laboratory Standards Institute Guidelines (CLSI; M07, 2018), and results were interpreted using CLSI M100 (2019) and FDA breakpoint interpretive criteria

RESULTS

- Omadacycline was highly active against *Staphylococcus aureus* isolates (97.8% susceptible [S]; ABSSSI FDA breakpoint criteria) including methicillin-susceptible *S. aureus* (MSSA; 98.2%S; CABP FDA breakpoint criteria), and methicillin-resistant *S. aureus* (MRSA; 95.2%S; ABSSSI FDA breakpoint criteria) (Table 1)
  - Omadacycline ($MIC_{50/90}$, 0.12/0.25 mg/L) was active against *S. aureus* isolates displaying resistance (R) to other antibacterial classes including: tetracycline, levofloxacin, erythromycin, clindamycin, and oxacillin (corresponding resistance rates were 3.5%, 32.2%, 50.9%, 13.4%, and 41.5%) (Table 2)
- 95.7% (22/23) of *Staphylococcus lugdunensis* isolates were susceptible to omadacycline ($MIC_{50/90}$, 0.06/0.12 mg/L) and 87.7% of all coagulase-negative staphylococci were inhibited by ≤0.5 mg/L of omadacycline (Table 1)
- *Enterococcus faecalis* ($MIC_{50/90}$, 0.12/0.25 mg/L) isolates were 98.2% susceptible (ABSSSI FDA breakpoint criteria) to omadacycline and 98.0% of *Enterococcus faecium* ($MIC_{50/90}$, 0.06/0.12 mg/L) isolates (including vancomycin-nonsusceptible strains) were inhibited by ≤0.25 mg/L of omadacycline (Table 1)
- 97.6% of *Streptococcus pneumoniae* isolates, including 93.9% of penicillin-R and 91.2% of tetracycline-R strains were susceptible (CABP FDA breakpoint criteria) to omadacycline ($MIC_{50/90}$, 0.06–0.12/0.12 mg/L) (Tables 1-2)
- β-hemolytic streptococci ($MIC_{50/90}$, 0.12/0.25 mg/L) including *Streptococcus pyogenes* ($MIC_{50/90}$, 0.12/0.12 mg/L; 96.7%S, ABSSSI FDA breakpoint criteria) were susceptible to low concentrations of omadacycline (Table 1)
- 95.7% of viridans group streptococci and all *Streptococcus anginosus* group isolates (100.0%S; ABSSSI FDA breakpoint criteria) were inhibited by ≤0.12 mg/L of omadacycline (Table 1)
- *Enterobacter cloacae* species complex (93.4%S; ABSSSI FDA breakpoint criteria) and *Klebsiella pneumoniae* (91.0%S; ABSSSI and CABP FDA breakpoint criteria) isolates were susceptible to omadacycline ($MIC_{50/90}$, 2/4 mg/L) (Table 1)
  - Similarly, 99.5% of *Escherichia coli* isolates and 99.0% of extended-spectrum β-lactamase (ESBL)-phenotype *E. coli* isolates were inhibited by ≤4 mg/L of omadacycline
- Omadacycline inhibited 88.3% of *Acinetobacter baumannii* isolates and 72.4% of *Stenotrophomonas maltophilia* isolates at ≤4 mg/L (Table 1) in which comparator agent susceptibilities were low (data not shown)
- 99.7% of *Haemophilus influenzae* isolates and 96.7% of *Haemophilus parainfluenzae* isolates were susceptible (CABP FDA breakpoint criteria) to omadacycline (Table 1)
- A total of 99.7% (341/342) of omadacycline quality control (QC) values obtained were within CLSI-approved QC ranges for the reference strains tested
  - A single omadacycline MIC value against *Staphylococcus aureus* ATCC 29213 was above the acceptable QC range and was addressed according to CLSI guidelines

Figure 1 Site of infection incidence for omadacycline from the 2018 surveillance program in the United States



[a] Caused by *S. pneumoniae*, *H. influenzae*, *H. parainfluenzae*, or *M. catarrhalis*

Table 1 *In vitro* antimicrobial activity of omadacycline tested against the main organisms and organism groups included in the 2018 SENTRY Antimicrobial Surveillance Program in the United States

Organism/organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of: ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	> [a]	MIC_{50}	MIC_{90}
Staphylococcus aureus (1,724)[b]	1[b] 0.1	4 0.3	132 7.9	1,305 83.6	206 95.6	38 97.8	32[c] 99.7	4[c] 99.9	0 99.9	2 100.0				0.12	0.25
Methicillin-susceptible (1,009)[b]		0 0.0	3 0.3	66 6.8	781 84.2	141 98.2	14 99.6	3 99.9	1 100.0					0.12	0.25
Methicillin-resistant (715)[b]		1 0.1	1 0.3	66 9.5	524 82.8	65 91.9	24 95.2	29 99.3	3 99.7	0 99.7	2 100.0			0.12	0.25
Coagulase-negative staphylococci (171)		1 0.6	3 2.3	46 29.2	37 50.9	21 63.2	42 87.7	19 98.8	1 99.4	1 100.0				0.12	1
Staphylococcus lugdunensis (23)[b]		1 4.3	2 13.0	17 87.0	2 95.7	0 95.7	0 95.7	0 95.7	1 100.0					0.06	0.12
Enterococcus faecalis (218)[b]		2 0.9	8 4.6	94 47.7	81 84.9	29 98.2	2 99.1	2 100.0						0.12	0.25
Vancomycin-nonsusceptible (>4 mg/L) (5)[b]		1 20.0	0 20.0	1 40.0	3 100.0									0.12	
Enterococcus faecium (100)		1 1.0	6 7.0	45 52.0	43 95.0	3 98.0	2 100.0							0.06	0.12
Vancomycin-nonsusceptible (>4 mg/L) (73)		1 1.4	5 8.2	33 53.4	31 95.9	2 98.6	1 100.0							0.06	0.12
Streptococcus pneumoniae (449)[b]		3 0.7	40 9.6	250 65.3	145 97.6	11 100.0								0.06	0.12
Penicillin-resistant oral (≥2 mg/L; CLSI) (33)[b]		0 0.0	1 3.0	15 48.5	15 93.9	2 100.0								0.12	0.12
Tetracycline-resistant (≥4 mg/L; CLSI) (91)[b]		0 0.0	3 3.3	40 47.3	40 91.2	8 100.0								0.12	0.12
Viridans group streptococci (70)		7 10.0	10 24.3	26 61.4	24 95.7	2 98.6	1 100.0							0.06	0.12
Streptococcus anginosus group (23)[b]		7 30.4	6 56.5	7 87.0	3 100.0									0.03	0.12
β-hemolytic streptococci (283)			0 0.0	97 34.3	146 85.9	36 98.6	4 100.0							0.12	0.25
Streptococcus pyogenes (182)[b]			0 0.0	83 45.6	93 96.7	5 99.5	1 100.0							0.12	0.12
Streptococcus agalactiae (82)			0 0.0	13 15.9	40 64.6	28 98.8	1 100.0							0.12	0.25
Enterobacteriaceae (2,673)				1 <0.1	1 0.1	20 0.8	571 22.2	895 55.7	640 79.6	217 87.7	114 92.0	128 96.8	74 99.6	12 100.0	1	8

Organism/organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of: ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	> [a]	MIC_{50}	MIC_{90}
Escherichia coli (1,161)			1 0.1	0 0.1	13 1.2	521 46.1	470 86.6	130 97.8	20 99.5	5 99.9	1 100.0			1	2
ESBL-phenotype (196)				0 0.0	1 0.5	51 26.5	87 70.9	46 94.4	9 99.0	1 99.5	1 100.0			1	2
Klebsiella pneumoniae (534)[a,e]			0 0.0	1 0.2	0 0.2	22 4.3	179 37.8	226 80.1	58 91.0	21 94.9	21 98.9	6 100.0		2	4
Non-ESBL-phenotype (446)[a,e]			0 0.0	1 0.2	0 0.2	19 4.5	165 41.5	205 87.4	31 94.4	11 96.9	12 99.6	2 100.0		2	4
ESBL-phenotype (88)[a,e]					0 0.0	3 3.4	14 19.3	21 43.2	27 73.9	10 85.2	9 95.5	4 100.0		4	16
Klebsiella oxytoca (125)					0 0.0	3 2.4	97 80.0	15 92.0	5 96.0	4 99.2	1 100.0			1	2
Enterobacter cloacae species complex (196)[a,f]					0 0.0	1 0.5	29 15.3	138 85.7	15 93.4	7 96.9	4 99.0	2 100.0		2	4
Ceftazidime-susceptible (≤4 mg/L) (145)[a,f]					0 0.0	1 0.7	26 18.6	108 93.1	7 97.9	2 99.3	0 99.3	1 100.0		2	2
Ceftazidime-nonsusceptible (>4 mg/L) (51)[a,f]						0 0.0	3 5.9	30 64.7	8 80.4	5 90.2	4 98.0	1 100.0		2	8
Citrobacter spp. (143)				0 0.0	1 0.7	18 13.3	63 57.3	40 85.3	9 91.6	8 97.2	3 99.3	1 100.0		1	4
Acinetobacter baumannii (77)			0 0.0	3 3.9	36 50.6	9 62.3	6 70.1	2 72.7	12 88.3	5 94.8	2 97.4	2 100.0		0.25	8
Stenotrophomonas maltophilia (98)					0 0.0	2 2.0	6 8.2	24 32.7	39 72.4	18 90.8	5 95.9	2 98.0	2 100.0	4	8
Haemophilus influenzae (297)[a]				1 0.3	9 3.4	147 52.9	123 94.3	16 99.7	1 100.0					0.5	1
Haemophilus parainfluenzae (30)[a]				0 0.0	2 6.7	8 33.3	10 66.7	9 96.7	1 100.0					1	2
Moraxella catarrhalis (119)				81 68.1	35 97.5	3 100.0								≤0.12	0.25

ESBL, extended-spectrum β-lactamase
[a] Criteria as published by the United States Food and Drug Administration (FDA) for acute bacterial skin and skin structure infection (ABSSSI).
[b] Green, susceptible according to FDA breakpoint interpretive criteria.
[c] Yellow, intermediate according to FDA breakpoint interpretive criteria.
[d] Red, resistant according to FDA breakpoint interpretive criteria.
[e] Criteria as published by the FDA for community-acquired bacterial pneumonia (CABP).
[f] FDA breakpoint interpretive criteria for *E. cloacae* (ABSSSI) applied to *E. cloacae* species complex isolates.

CONCLUSIONS

- Omadacycline demonstrated potent *in vitro* activity against *S. aureus* (97.8%S; ABSSSI FDA breakpoint criteria) isolates from the United States including MSSA (98.2%S; CABP FDA breakpoint criteria), MRSA (95.2%S; ABSSSI FDA breakpoint criteria), and isolates displaying resistance to tetracycline, levofloxacin, erythromycin, and clindamycin
- *S. pneumoniae* (97.6%S; CABP FDA breakpoint criteria), *S. anginosus* group (100.0%S; ABSSSI FDA breakpoint criteria), and *S. pyogenes* (96.7%S; ABSSSI FDA breakpoint criteria) isolates were susceptible to low concentrations of omadacycline (MIC_{90}, 0.12 mg/L)
- Omadacycline was highly active against *E. faecalis* ($MIC_{50/90}$, 0.12/0.25 mg/L; 98.2%S; ABSSSI FDA breakpoint criteria) and *E. faecium* ($MIC_{50/90}$, 0.06/0.12 mg/L) isolates, including vancomycin-nonsusceptible isolates
- 93.4% of *E. cloacae* species complex (ABSSSI FDA breakpoint criteria) and 91.0% of *K. pneumoniae* (ABSSSI and CABP FDA breakpoint criteria) isolates were susceptible to omadacycline; 99.5% of *E. coli* isolates were inhibited by ≤4 mg/L of omadacycline
- Omadacycline inhibited 88.3% of *A. baumannii* and 72.4% of *S. maltophilia* isolates at ≤4 mg/L, which are pathogens that have few treatment options
- Omadacycline was active against *H. influenzae* (99.7%S; CABP FDA breakpoint criteria) and *H. parainfluenzae* (96.7%; CABP FDA breakpoint criteria) isolates
- Overall, omadacycline demonstrated potent *in vitro* activity against recent clinical isolates from the United States commonly associated with ABSSSI, CABP, and UTI
- These data support continued evaluation of omadacycline, especially in infections where drug-resistant pathogens are likely to be encountered

Table 2 *In vitro* activity of omadacycline and comparator agents against *Staphylococcus aureus* and *Streptococcus pneumoniae* isolates from patients in US medical centers during 2018

Organism (no. tested) antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI or FDA[a] %S	%I	%R
***S. aureus* (1,724)**						
Omadacycline	0.12	0.25	≤0.015 to 8	97.8 [b] 95.6 [c]	1.9 2.2	0.3 2.2
Tigecycline	0.12	0.12	≤0.015 to 2	99.9		
Doxycycline	≤0.06	0.25	≤0.06 to >8	98.3	1.5	0.2
Tetracycline	≤0.5	≤0.5	≤0.5 to >8	95.4	1.0	3.5
Oxacillin	0.5	>2	≤0.06 to >2	58.5		41.5
Levofloxacin	0.25	>4	0.06 to >4	67.5	0.3	32.2
Erythromycin	8	>8	≤0.06 to >8	44.3	4.8	50.9
Clindamycin	0.06	>2	≤0.03 to >2	86.5	0.1	13.4
Linezolid	1	2	≤0.12 to >8	99.9		0.1
Vancomycin	1	1	≤0.12 to 2	100.0	0.0	0.0
***S. pneumoniae* (449)**						
Omadacycline	0.06	0.12	≤0.015 to 0.25	97.6[c]	2.4	0.0
Tigecycline	0.06	0.12	0.015 to 0.25	86.9		
Tetracycline	0.25	>4	0.06 to >4	79.7	0.0	20.3
Ceftriaxone	0.03	1	≤0.015 to >2	89.1[d]	8.9	2.0
Levofloxacin	1	1	0.25 to >4	99.1	0.0	0.9
Erythromycin	0.06	>16	≤0.015 to >16	53.0	0.7	46.3
Clindamycin	≤0.25	>2	≤0.25 to >2	84.0	0.4	15.6
Linezolid	1	2	0.25 to 2	100.0		
Vancomycin	0.25	0.5	≤0.06 to 0.5	100.0		
Penicillin	0.03	1	≤0.008 to >4	64.6[e] 64.6[d]	28.1	7.3 35.4
Trimethoprim-sulfamethoxazole	0.25	>4	≤0.12 to >4	75.3	11.4	13.4

[a] Criteria as published by CLSI (2019) or FDA.
[b] Using FDA breakpoint interpretive criteria for acute bacterial skin and skin structure infection.
[c] Using FDA breakpoint interpretive criteria for community-acquired bacterial pneumonia.
[d] Using meningitis breakpoints.
[e] Using oral breakpoints.

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