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In Vitro Activity of Omadacycline and Comparators against Recent Gram-Positive and -Negative Clinical Isolates Collected in 2018 from Patients in European Medical Centres: SENTRY Surveillance Program Results

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INTRODUCTION

- Omadacycline is a broad-spectrum aminomethylcycline antibacterial approved in October 2018 by the United States Food and Drug Administration (FDA) for treatment of adults with acute bacterial skin and skin structure infections (ABSSSIs) and community-acquired bacterial pneumonia (CABP)
- Omadacycline is currently in phase 2 clinical trials for treatment of uncomplicated urinary tract infections (uUTIs; NCT03425396) and acute pyelonephritis (NCT03757234)
- Omadacycline demonstrates potent *in vitro* activity against a broad range of gram-positive (staphylococci, streptococci, and enterococci) and gram-negative bacterial pathogens commonly associated with ABSSSIs, CABP, and UTIs
- Bacterial isolates expressing common tetracycline-, penicillin-, fluoroquinolone-, and macrolide-resistance mechanisms are susceptible (S) to omadacycline

MATERIALS AND METHODS

- A total of 7,000 gram-positive and gram-negative bacterial clinical isolates were collected from patients in 38 medical centres in 18 European countries during 2018
- Isolates were collected from patients with bloodstream infection (BSI; 27.9%), skin and skin structure infection (SSSI; 22.2%), pneumonia in hospitalized patients (PIHP; 19.9%), UTI (12.1%), intra-abdominal infection (IAI; 5.3%), community-acquired respiratory tract infection (CARTI; 9.8%), and other infection types (2.8%); only 1 isolate per patient/infection episode was included
- Bacterial isolates were 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 Clinical and Laboratory Standards Institute guidelines
- Quality control (QC) ranges for reference compounds and bacterial strains were those approved or published by the CLSI (M100, 2019)

RESULTS

- In this study, 99.7% (329/330) of omadacycline QC values obtained were within CLSI published ranges
- During the omadacycline 2018 surveillance program, 27.9% of isolates collected were from patients with BSI, 22.2% from SSSI, 19.9% from PIHP, 12.1% from UTI, 9.8% from CARTI, 5.3% from IAI, and 2.8% from other infection types
- Omadacycline demonstrated potent *in vitro* activity against *Staphylococcus aureus* (99.7%S; ABSSSI FDA-breakpoint criteria) including methicillin-susceptible *S. aureus* (MSSA; 99.5%S; CABP FDA-breakpoint criteria), and methicillin-resistant *S. aureus* (MRSA; 98.9%S; ABSSSI FDA-breakpoint criteria) isolates with $MIC_{50/90}$ values of 0.12/0.25 mg/L (Table 1)
- Omadacycline was active against *S. aureus* isolates displaying resistance to other antibacterials including: tetracycline, levofloxacin, erythromycin, clindamycin, and/or oxacillin (Table 2)
- Omadacycline ($MIC_{50/90}$, 0.12/0.5 mg/L) inhibited 93.5% of all CoNS at ≤0.5 mg/L (Table 1)
  - All *Staphylococcus lugdunensis* isolates were S (100.0%S; ABSSSI FDA-breakpoint criteria) to omadacycline
- 98.8% of *Enterococcus faecalis* isolates (including vancomycin non-susceptible strains) were susceptible (ABSSSI FDA-breakpoint criteria) to omadacycline ($MIC_{50/90}$ 0.12/0.25 mg/L) (Table 1)
- *Streptococcus pneumoniae* isolates (including penicillin- and tetracycline-R strains) were inhibited by low concentrations of omadacycline ($MIC_{50/90}$, 0.06/0.12 mg/L; 98.6%S, CABP FDA-breakpoint criteria) (Tables 1 and 2)
- β-haemolytic streptococci including *Streptococcus agalactiae* ($MIC_{50/90}$ 0.12/0.25 mg/L) and *Streptococcus pyogenes* ($MIC_{50/90}$ 0.06/0.12 mg/L; 100.0%S, ABSSSI FDA-breakpoint criteria) were susceptible to low concentrations of omadacycline (Table 1)
- 95.3% of viridans group streptococci were inhibited by ≤0.12 mg/L of omadacycline (Table 1)
  - All *Streptococcus anginosus* group isolates (100.0%S; ABSSSI FDA-breakpoint criteria) were S to omadacycline ($MIC_{50/90}$, 0.06/0.06 mg/L)
- 90.4% of *Enterobacter cloacae* species complex (ABSSSI FDA-breakpoint criteria) and 85.1% of *Klebsiella pneumoniae* (ABSSSI and CABP FDA-breakpoint criteria) isolates were susceptible to omadacycline (Table 1)
  - Similarly, 99.2% of *Escherichia coli* isolates and 97.9% of extended-spectrum β-lactamase (ESBL)-phenotype *E. coli* isolates were inhibited by ≤4 mg/L of omadacycline
- Against non-fermenters, 86.4% of *A. baumannii* isolates were inhibited by ≤4 mg/L of omadacycline (Table 1), and comparator agent susceptibilities were low
  - Similarly, omadacycline inhibited 83.9% of *Stenotrophomonas maltophilia* isolates at ≤4 mg/L (Table 1)
- All *Haemophilus influenzae* isolates (100.0%S; CABP FDA-breakpoint criteria) and 88.2% of *Haemophilus parainfluenzae* (CABP FDA-breakpoint criteria) isolates were susceptible to omadacycline (Table 1)

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

Organism (no. tested) / Antimicrobial agent	MIC_{50}	MIC_{90}	Range	EUCAST[a] or FDA[b] %S	%I	%R
***S. aureus* (1,393)**						
Omadacycline	0.12	0.25	≤0.015 to 2	99.7[c]	0.2	0.1
Tigecycline	0.12	0.12	0.03 to 0.5	100.0		0.0
Tetracycline	≤0.5	≤0.5	≤0.5 to >8	93.3	0.2	6.5
Oxacillin	0.5	>2	≤0.06 to >2	79.8		20.2
Levofloxacin	0.25	>4	0.06 to >4	82.1		17.9
Erythromycin	0.25	>8	≤0.06 to >8	76.9	1.2	21.9
Clindamycin	0.06	0.06	≤0.03 to >2	94.0	0.1	5.8
Linezolid	1	2	0.25 to 4	100.0		0.0
Vancomycin	1	1	0.25 to 2	100.0		0.0
***S. pneumoniae* (422)**						
Omadacycline	0.06	0.12	≤0.015 to 0.25	98.6[d]	1.4	0.0
Tigecycline	0.06	0.06	0.015 to 0.12			
Tetracycline	0.5	>4	0.12 to >4	78.2	0.5	21.3
Ceftriaxone	0.03	1	≤0.015 to >2	83.9	14.5	1.7
Levofloxacin	1	2	0.5 to >4	97.9		2.1
Erythromycin	0.03	>16	≤0.015 to >16	79.0	0.2	20.7
Clindamycin	≤0.25	>2	≤0.25 to >2	86.0		14.0
Linezolid	1	2	≤0.12 to 2	100.0	0.0	0.0
Vancomycin	0.25	0.5	≤0.06 to 0.5	100.0		0.0
Azithromycin	0.06	>4	≤0.03 to >4	77.5	0.2	22.3
Penicillin	0.03	2	≤0.008 to >4	72.3[e] 72.3[f]	22.0	27.7 5.7

[a] Criteria as published by EUCAST (2019).
[b] For *S. aureus*, using FDA breakpoint interpretive criteria for acute bacterial skin and skin structure infection and for *S. pneumoniae*, using FDA breakpoint interpretive criteria for community-acquired bacterial pneumonia.
[c] Using FDA breakpoint interpretive criteria for acute bacterial skin and skin structure infection.
[d] Using FDA breakpoint interpretive criteria for community-acquired bacterial pneumonia.
[e] Using meningitis breakpoints.
[f] Using non-meningitis breakpoints.

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

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 (1,393)[a]	2[b] 0.1	6 0.6	110 8.5	1,062 84.7	195 98.7	14 99.7	3[c] 99.9	1[c] 100.0						0.12	0.25
Methicillin-susceptible (1,112)[e]	2 0.2	6 0.7	92 9.0	867 87.0	139 99.5	5 99.9	1 100.0							0.12	0.25
Methicillin-resistant (281)[a]		0 0.0	18 6.4	195 75.8	56 95.7	9 98.9	2 99.6	1 100.0						0.12	0.25
Coagulase-negative staphylococci (170)	2 1.2	9 6.5	46 33.5	36 54.7	26 70.0	40 93.5	10 99.4	1 100.0						0.12	0.5
Staphylococcus lugdunensis (16)[a]	2 12.5	4 37.5	9 93.8	1 100.0										0.06	0.06
Enterococcus faecalis (255)[a]	0 0.0	10 3.9	92 40.0	116 85.5	34 98.8	3 100.0								0.12	0.25
Vancomycin-susceptible (≤4 mg/L) (252)[a]	0 0.0	10 4.0	92 40.5	113 85.3	34 98.8	3 100.0								0.12	0.25
Vancomycin-nonsusceptible (>4 mg/L) (3)[a]			0 0.0	3 100.0										0.12	
Enterococcus faecium (143)	0 0.0	12 8.4	66 54.5	61 97.2	3 99.3	1 100.0								0.06	0.12
Streptococcus pneumoniae (422)[e]	3 0.7	63 15.6	247 74.2	103 98.6	6 100.0									0.06	0.12
Viridans group streptococci (86)	4 4.7	12 18.6	48 74.4	18 95.3	4 100.0									0.06	0.12
Streptococcus anginosus group (36)[a]	4 11.1	5 25.0	24 91.7	3 100.0										0.06	0.06
β-haemolytic streptococci (241)	0 0.0	1 0.4	68 28.6	128 81.7	32 95.0	11 99.6	1 100.0							0.12	0.25
Streptococcus pyogenes (101)[a]		0 0.0	55 54.5	46 100.0										0.06	0.12
Streptococcus agalactiae (75)		0 0.0	7 9.3	40 62.7	23 93.3	5 100.0								0.12	0.25
Enterobacteriaceae (3,017)			2 0.1	0 0.1	35 1.2	682 23.8	942 55.1	645 76.4	322 87.1	144 91.9	153 97.0	72 99.3	20 100.0	1	8
Escherichia coli (1,466)			2 0.1	0 0.1	32 2.3	641 46.0	517 81.3	201 95.0	61 99.2	10 99.9	2 100.0			1	2
ESBL-phenotype (333)				0 0.0	4 1.2	96 30.0	131 69.4	68 89.8	27 97.9	6 99.7	1 100.0			1	4
Klebsiella pneumoniae (646)[a,e]					0 0.0	10 1.5	211 34.2	210 66.7	119 85.1	52 93.2	36 98.8	6 99.7	2 100.0	2	8
Non-ESBL-phenotype (315)[a,e]					0 0.0	4 1.3	146 47.6	132 89.5	16 94.6	8 97.1	9 100.0			2	4
ESBL-phenotype (331)[a,e]					0 0.0	6 1.8	65 21.5	78 45.0	103 76.1	44 89.4	27 97.6	6 99.4	2 100.0	4	16
Klebsiella oxytoca (113)					0 0.0	4 3.5	88 81.4	11 91.2	8 98.2	2 100.0				1	2
Enterobacter cloacae species complex (230)[a]					0 0.0	2 0.9	37 17.0	139 77.4	30 90.4	13 96.1	7 99.1	2 100.0		2	4
Ceftazidime-susceptible (≤4 mg/L) (145)[a]					0 0.0	2 1.4	30 22.1	98 89.7	13 98.6	1 99.3	1 100.0			2	4
Ceftazidime-nonsusceptible (>4 mg/L) (85)[a,f]						0 0.0	7 8.2	41 56.5	17 76.5	12 90.6	6 97.6	2 100.0		2	8
Other *Enterobacter* spp. (56)						0 0.0	29 51.8	24 94.6	1 96.4	0 96.4	2 100.0			1	2
Citrobacter spp. (87)					0 0.0	21 24.1	39 69.0	20 92.0	4 96.6	1 97.7	2 100.0			1	2
Acinetobacter baumannii (147)			2 1.4	5 4.8	17 16.3	17 27.9	16 38.8	20 52.4	50 86.4	17 98.0	3 100.0			2	8
Stenotrophomonas maltophilia (62)						0 0.0	5 8.1	19 38.7	28 83.9	4 90.3	6 100.0			4	8
Haemophilus influenzae (230)[e]				0 0.0	8 3.5	131 60.4	80 95.2	11 100.0						0.5	1
Haemophilus parainfluenzae (17)[e]					0 0.0	4 23.5	6 58.8	5 88.2	2 100.0					1	4
Moraxella catarrhalis (144)				82 56.9	62 100.0									≤0.12	0.25

[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 was highly active against *S. aureus* (99.7%S; ABSSSI FDA-breakpoint criteria) isolates from Europe that included MSSA (99.5%S; CABP FDA-breakpoint criteria), and MRSA (98.9%S; ABSSSI FDA-breakpoint criteria) isolates displaying resistance to tetracycline, levofloxacin, erythromycin, and clindamycin
- Streptococci, including *S. pneumoniae*, *S. anginosus* group, and *S. pyogenes*, isolates were inhibited by low concentrations of omadacycline (MIC_{90}, 0.06-0.12 mg/L; 98.6%-100.0%S)
- Omadacycline exhibited potent activity against *E. faecalis* ($MIC_{50/90}$, 0.12/0.25 mg/L; 98.8%S; ABSSSI FDA breakpoint criteria)
- Against Enterobacteriaceae, 90.4% of *Enterobacter cloacae* species complex (ABSSSI FDA-breakpoint criteria) and 85.1% of *Klebsiella pneumoniae* (ABSSSI and CABP FDA-breakpoint criteria) isolates were susceptible to omadacycline and 99.2% of *E. coli* isolates and 97.9% of ESBL-phenotype *E. coli* isolates were inhibited by ≤4 mg/L of omadacycline
- Non-fermenters, including *A. baumannii* and *S. maltophilia,* were inhibited by ≤4 mg/L of omadacycline (86.4% and 83.9%, respectively) where few treatment options currently exist
- Omadacycline was active against fastidious organism groups, including 100.0% of *H. influenzae* isolates (CABP FDA-breakpoint criteria)
- These data support continued development of omadacycline in infections where R gram-positive and gram-negative isolates are likely to be found

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