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Short Communication

Surveillance of omadacycline activity tested against clinical isolates from the United States and Europe: Results from the SENTRY Antimicrobial Surveillance Programme, 2017

Michael D. Huband[a,*], Michael A. Pfaller[a,b], Dee Shortridge[a], Robert K. Flamm[a]

[a] JMI Laboratories, North Liberty, IA, USA
[b] University of Iowa, Iowa City, IA, USA

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ABSTRACT

Objectives: Omadacycline is an aminomethylcycline antibacterial (oral and intravenous once-daily formulation) that recently (October 2018) received United States Food and Drug Administration (FDA) approval for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) and community-acquired bacterial pneumonia (CABP) against selected organism groups. This study tested omadacycline and comparators against 14 000 non-duplicate bacterial isolates that were prospectively collected during 2017 from medical centres in Europe (EUR; 7000 isolates) and the United States (USA; 7000 isolates).
Methods: Omadacycline was tested by broth microdilution following Clinical and Laboratory Standards Institute M07-A11 (2018) methods.
Results: A total of 98.7% of *Staphylococcus aureus* isolates were susceptible to omadacycline ($MIC_{50/90}$, 0.12/0.25 mg/L; ABSSSI breakpoints) including 96.5% of methicillin-resistant *Staphylococcus aureus* (MRSA), 99.8% of methicillin-susceptible *Staphylococcus aureus*, and 93.9% of tetracycline-resistant strains. Omadacycline activity was similar for *Streptococcus pneumoniae* ($MIC_{50/90}$ 0.06/0.12 mg/L; 98.6% susceptible [CABP breakpoints]), *Streptococcus anginosus* group ($MIC_{50/90}$ 0.06/0.06 mg/L; 100.0% susceptible [ABSSSI breakpoints]), and *Streptococcus pyogenes* ($MIC_{50/90}$ 0.06/0.12 mg/L; 97.7% susceptible [ABSSSI breakpoints]). Omadacycline demonstrated activity against *Enterobacter cloacae* species complex isolates ($MIC_{50/90}$, 2/4 mg/L; 91.2% susceptible [ABSSSI breakpoints]), *Klebsiella pneumoniae* ($MIC_{50/90}$, 2/8 mg/L; 87.5% susceptible [CABP and ABSSSI breakpoints]), and inhibited 99.1% of *Escherichia coli* ($MIC_{50/90}$, 0.5/2 mg/L) isolates at $\leq$ 4 mg/L. Omadacycline was active against *Haemophilus influenzae* ($MIC_{50/90}$, 0.5/1 mg/L; 99.8% susceptible [CABP breakpoints]), including all β-lactamase positive isolates, and inhibited 100.0% of *Moraxella catarrhalis* isolates at $\leq$ 0.25 mg/L.
Conclusions: The potent activity of omadacycline against Gram-positive and Gram-negative bacteria indicates that omadacycline merits further study in serious infections in which multidrug resistance and mixed Gram-positive and Gram-negative infections may be of concern.

1. Introduction

Tetracyclines are broad-spectrum agents with activity against clinically important Gram-positive cocci (GPC) and Gram-negative bacilli (GNB) [1]. Omadacycline is a semisynthetic derivative of minocycline and the first member of the novel class of aminomethylcyclines [2–4]. Omadacycline remains active against bacterial strains expressing both ribosomal protection and tetracycline specific efflux resistance genes [3–5]. In addition to having activity against tetracycline-resistant bacterial isolates, omadacycline has potent activity against difficult-to-treat pathogens such as methicillin-resistant *Staphylococcus aureus* (*S. aureus*) (MRSA), vancomycin-resistant enterococci (VRE), and Enterobacteriaceae strains that produce a wide array of extended-spectrum β-lactamases (ESBLs) and carbapenem-resistant Enterobacteriaceae (CRE) isolates as well as multidrug-resistant (resistant to three or more classes of agents) strains of *Acinetobacter* spp. and *Stenotrophomonas maltophilia* (*S. maltophilia*) [5].

Omadacycline has been granted qualified infectious disease product designations by the United States Food and Drug Administration (FDA) for the treatment of community-acquired

* Corresponding author at: JMI Laboratories, Inc., 345 Beaver Kreek Centre, Suite A, North Liberty, IA, 52317, USA.
E-mail address: michael-huband@jmilabs.com (M.D. Huband).

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bacterial pneumonia (CABP), acute bacterial skin and skin structure infections (ABSSSIs), and complicated (cUTIs) and uncomplicated (uUTIs) urinary tract infections. Omadacycline recently received FDA approval (October 2018), including breakpoint interpretive criteria for ABSSSI and CABP against selected organism groups (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm622612.htm). Phase 2 studies of omadacycline for the oral and intravenous treatment of acute pyelonephritis in adults (NCTC03757234) and oral treatment of acute cystitis in women (NCTC03425396) are ongoing [5].

The current study evaluated the antimicrobial activities of omadacycline and comparator agents tested against 14 000 isolates of GPC and GNB collected in 2017 from individual medical centres in the United States (USA) and Europe (EUR) as part of the SENTRY Antimicrobial Surveillance Programme. Evaluations of resistant subsets for most of the pathogen groups were included in the analysis.

2. Materials and methods

2.1. Organisms

A total of 14 000 non-duplicate bacterial isolates were prospectively collected from medical centres located in the USA (31 sites, 21 states and nine USA census divisions, 7000 isolates) and EUR (38 sites, 17 countries, 7000 isolates) for the 2017 SENTRY Antimicrobial Surveillance Programme. All organisms were isolated from hospitalised patients with bloodstream (3619 isolates), community-acquired respiratory tract infections (1582 isolates), hospital-associated respiratory tract infections (2844 isolates), ABSSSIs (3177 isolates), intra-abdominal infections (853 isolates), cUTIs (1636 isolates), and other types of infection (289 isolates). Isolates were identified to the species level at each participating medical centre and confirmed by the monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA) using standard biochemical algorithms or matrix-assisted laser desorption ionisation-time of flight mass spectrometry (Bruker, Billerica, Massachusetts, USA), when necessary.

2.2. Antimicrobial susceptibility testing

The MIC values were determined using the reference Clinical and Laboratory Standards Institute (CLSI) broth microdilution method [6]. Quality control (QC) and interpretation of results were performed in accordance with CLSI M100 and European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2019 guidelines [7,8]. *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* were grouped as ESBL screen-positive (SP) phenotype based on the CLSI screening criteria for potential ESBL production (ie, MIC $\geq$ 2 mg/L of ceftazidime, ceftriaxone, or aztreonam) [7]. Although other β-lactamases, such as AmpC and KPC, may also produce 'ESBL-SP phenotypes', these strains were grouped together because they demonstrate resistance to various broad-spectrum β-lactam compounds. *Enterobacter cloacae* (*E. cloacae*) species complex (SC) isolates were classified as ceftazidime-susceptible (MIC $\leq$ 4 mg/L) and ceftazidime-nonsusceptible (MIC > 4 mg/L). Other resistant phenotypes included MRSA (oxacillin MIC $\geq$ 4 mg/L or cefoxitin MIC $\geq$ 8 mg/L), vancomycin-nonsusceptible enterococci (MIC > 4 mg/L), tetracycline-resistant Enterobacteriaceae, *Acinetobacter baumannii* (*A. baumannii*) staphylococci, enterococci (all MIC values $\geq$ 16 mg/L), *Streptococcus pneumoniae* (*S. pneumoniae*) (MIC $\geq$ 4 mg/L), and macrolide-resistant *S. pneumoniae* (erythromycin MIC $\geq$ 1 mg/L and/or azithromycin MIC $\geq$ 2 mg/L). The QC strains were tested concurrently and included *E. coli* ATCC 25922 and ATCC 35218, *S. aureus* ATCC 29213, *Pseudomonas aeruginosa* (*P. aeruginosa*) ATCC 27853, *Enterococcus faecalis* (*E. faecalis*) ATCC 29212, and *S. pneumoniae* ATCC 49619. All QC results were within published ranges.

3. Results

3.1. Number of organisms and key resistance phenotypes

The 14 000 tested isolates included: 2684 *S. aureus*; 373 coagulase-negative staphylococci (CoNS) (including 19 *Staphylococcus capitis*, 208 *Staphylococcus epidermidis*, 41 *Staphylococcus haemolyticus*, 35 *Staphylococcus hominis*, 48 *S. lugdunensis*, and 22 other CoNS); 427 *E. faecalis*; 218 *Enterococcus faecium* (*E. faecium*) isolates; 968 *S. pneumoniae*; 132 Viridans streptococci; 50 *Streptococcus anginosus* (*S. anginosus*) group; 651 β-haemolytic streptococci (BHS) (including 299 *Streptococcus pyogenes* (*S. pyogenes*), 261 *Streptococcus agalactiae*, and 91 other BHS); 5993 Enterobacteriaceae (including 2581 *E. coli*, 1269 *Klebsiella pneumoniae* (*K. pneumoniae*), 278 *Klebsiella oxytoca*, 488 *E. cloacae* SC, 253 *Citrobacter* spp., 360 *Proteus mirabilis*, 221 indole-positive *Proteus* spp., and 273 *Serratia marcescens*); 227 *A. baumannii-calcoaceticus* SC; 1276 *P. aeruginosa*; 129 *S. maltophilia*; 556 *Haemophilus influenzae*; six *Haemophilus parainfluenzae*; and 313 *Moraxella catarrhalis* isolates (Tables 1 and 2).

3.2. Susceptibility of Gram-positive isolates to omadacycline

The MIC distributions for omadacycline and each organism or organism group from the 69 participating medical centres are shown in Table 1. Omadacycline was very potent when tested against *S. aureus* isolates (98.7% susceptible [ABSSSI breakpoints]) with $MIC_{50/90}$ values of 0.12/0.25 mg/L (Table 1). Of these, 96.5% of MRSA, 99.8% of methicillin-susceptible *S. aureus*, and 93.9% of tetracycline-resistant *S. aureus* were susceptible (ABSSSI breakpoints) to omadacycline (Table 1). Omadacycline inhibited 90.1% of all CoNS and 96.8% of tetracycline-resistant CoNS at $\leq$ 0.5 mg/L (Table 1). All (100.0%) *S. lugdunensis* isolates were susceptible to omadacycline (ABSSSI breakpoints) (Table 1).

Omadacycline was highly active against *E. faecalis* ($MIC_{50/90}$ 0.12/0.25 mg/L; 97.2% susceptible [ABSSSI breakpoints]) isolates, including tetracycline-resistant (96.2% susceptible) isolates (Table 1). In addition, 87.5% (7/8) of vancomycin nonsusceptible isolates were susceptible to omadacycline. Against *E. faecium* ($MIC_{50/90}$ 0.06/0.12 mg/L), 96.3% of isolates were inhibited by $\leq$ 0.25 mg/L of omadacycline (susceptible breakpoint for *E. faecalis*), including 93.8% of vancomycin-nonsusceptible and 93.7% of tetracycline-resistant *E. faecium* isolates (Table 1).

Penicillin resistance (MIC $\geq$ 2 mg/L; CLSI) among *S. pneumoniae* isolates was 11.6% overall and ranged from 11.2% in EUR to 11.9% in the USA (data not shown). Overall, 98.6% of *S. pneumoniae* isolates were susceptible to omadacycline (CABP breakpoints), including 98.2% of penicillin-resistant (MIC $\geq$ 2 mg/L), 98.1% of macrolide-resistant, and 97.2% of tetracycline-resistant isolates (Table 1). All (100.0%) *S. anginosus* group isolates were susceptible to omadacycline (ABSSSI breakpoints), including 14 tetracycline-resistant isolates (Table 1). Against *S. pyogenes*, 97.7% of isolates were susceptible to omadacycline (ABSSSI breakpoints), including 90.6% of macrolide-resistant and 88.7% of tetracycline-resistant isolates (Table 1). Similarly, 86.2% of *S. agalactiae* isolates were inhibited by $\leq$ 0.12 mg/L of omadacycline (susceptible breakpoint for *S. pyogenes*) and all isolates (100.0%) were inhibited at $\leq$ 0.25 mg/L (Table 1).

3.3. Susceptibility of Gram-negative isolates to omadacycline

Omadacycline demonstrated in vitro activity against 5993 Enterobacteriaceae isolates ($MIC_{50/90}$ 1/8 mg/L) inhibiting 86.9% of

Table 1
Antimicrobial activity of omadacycline tested against the main organisms and organism groups of Gram-positive cocci.

Organism/organism group (number of isolates)	Number and cumulative % of isolates at MIC (mg/L) of:								MIC_{50}	MIC_{90}	%S	%R
	≤ 0.03	0.06	0.12	0.25	0.5	1	2	4				
Staphylococcus aureus (2684)	3	194	2125	289	39	31	2	1	0.12	0.25	98.7[a]	0.1
	0.1	7.3	86.5	97.3	98.7	99.9	> 99.9	100.0				
Methicillin-susceptible (1792)	2	112	1475	188	12	3			0.12	0.25	99.8[a]	0.0
	0.1	6.4	88.7	99.2	99.8	100.0					99.2[b]	0.2
Methicillin-resistant (892)	1	82	650	101	27	28	2	1	0.12	0.25	96.5[a]	0.3
	0.1	9.3	82.2	93.5	96.5	99.7	99.9	100.0				
Tetracycline-resistant (148)	0	10	96	27	6	8	1		0.12	0.5	93.9[a]	0.7
	0.0	6.8	71.6	89.9	93.9	99.3	100.0					
Coagulase-negative staphylococci (373)	9	94	105	40	86	36	1		0.12	0.5		
	2.9	28.2	56.3	67.0	90.1	99.7	100.0					
Methicillin-susceptible (152)	7	55	51	8	16	13			0.12	0.5		
	5.9	42.1	75.7	80.9	91.4	100.0						
Methicillin-resistant (221)	2	39	54	32	70	23	1		0.25	1		
	0.9	18.6	43.0	57.5	89.1	99.5	100.0					
Tetracycline-resistant (31)	0	3	8	3	16	1			0.5	0.5		
	0.0	9.7	35.5	45.2	96.8	100.0						
Staphylococcus lugdunensis (48)	6	33	9						0.06	0.12	100.0[a]	0.0
	12.5	81.2	100.0									
Enterococcus spp. (665)	37	254	259	94	17	1	2		0.12	0.25		
	5.7	43.9	82.9	97.0	99.5	99.7	100.0					
Vancomycin-susceptible (≤ 4 mg/L) (570)	32	212	223	88	12	0	2		0.12	0.25		
	5.8	43.0	82.1	97.5	99.6	99.6	100.0					
Vancomycin-nonsusceptible (> 4 mg/L) (95)	5	42	36	6	5	1			0.12	0.25		
	5.3	49.5	87.4	93.7	98.9	100.0						
Enterococcus faecalis (427)	23	139	172	81	10	0	2		0.12	0.25	97.2[a]	0.5
	5.4	37.9	78.2	97.2	99.5	99.5	100.0					
Vancomycin-susceptible (≤ 4 mg/L) (419)	23	135	171	79	9	0	2		0.12	0.25	97.4[a]	0.5
	5.5	37.7	78.5	97.4	99.5	99.5	100.0					
Vancomycin-nonsusceptible (> 4 mg/L) (8)	0	4	1	2	1				0.06		87.5[a]	0.0
	0.0	50.0	62.5	87.5	100.0							
Tetracycline-resistant (315)	15	86	121	81	10	0	2		0.12	0.25	96.2[a]	0.6
	4.8	32.1	70.5	96.2	99.4	99.4	100.0					
Enterococcus faecium (218)	12	110	75	12	7	1			0.06	0.12		
	6.0	56.4	90.8	96.3	99.5	100.0						
Vancomycin-susceptible (≤ 4 mg/L) (138)	8	72	46	8	3				0.06	0.12		
	6.5	58.7	92.0	97.8	100.0							
Vancomycin-nonsusceptible (> 4 mg/L) (80)	4	38	29	4	4	1			0.06	0.25		
	5.0	52.5	88.8	93.8	98.8	100.0						
Tetracycline-resistant (> 4 mg/L) (127)	4	48	57	10	7	1			0.12	0.25		
	3.1	40.9	85.8	93.7	99.2	100.0						
Other enterococcus (20)	2	5	12	1					0.12	0.12		
	10.0	35.0	95.0	100.0								
Streptococcus pneumoniae (968)	119	633	195	14					0.06	0.12	98.6[b]	0.0
	13.0	78.4	98.6	100.0								
Penicillin-susceptible oral (≤ 0.06 mg/L) (656)	98	437	105	10					0.06	0.12	98.5[b]	0.0
	15.9	82.5	98.5	100.0								
Penicillin-intermediate oral (> 0.06 mg/L and ≤ 1 mg/L) (200)	17	126	54	2					0.06	0.12	99.0[b]	0.0
	9.0	72.0	99.0	100.0								
Penicillin-resistant oral (≥ 2 mg/L; CLSI) (112)	4	70	36	2					0.06	0.12	98.2[b]	0.0
	3.6	66.1	98.2	100.0								
Penicillin-resistant non-meningitis (> 2 mg/L; EUCAST) (42)	3	27	12						0.06	0.12	100.0[b]	0.0
	7.1	71.4	100.0									
Macrolide-resistant (erythromycin and azithromycin) (320)	23	202	88	6					0.06	0.12	98.1[b]	0.0

	7.5	70.6	98.1	100.0							
Tetracycline-resistant (≥ 4 mg/L; CLSI) (213)	18	116	72	6				0.06	0.12	97.2[b]	0.0
	8.9	63.4	97.2	100.0							
Tetracycline-resistant (> 2 mg/L; EUCAST) (213)	18	116	72	6				0.06	0.12	97.2[b]	0.0
	8.9	63.4	97.2	100.0							
Viridans group streptococci (132)	27	64	29	9	0	0	1	0.06	0.12		
	22.0	70.5	92.4	99.2	99.2	99.2	100.0				
Penicillin-susceptible (≤ 0.12 mg/L; CLSI) (101)	23	52	18	5	0	0	1	0.06	0.12		
	24.8	76.2	94.1	99.0	99.0	99.0	100.0				
Penicillin-susceptible (≤ 0.25 mg/L; EUCAST) (114)	25	58	22	6	0	0	1	0.06	0.12		
	23.7	74.6	93.9	99.1	99.1	99.1	100.0				
Penicillin-resistant (≥ 4 mg/L; CLSI) (4)	0	1	2	1				0.12			
	0.0	25.0	75.0	100.0							
Penicillin-resistant (> 2 mg/L; EUCAST) (4)	0	1	2	1				0.12			
	0.0	25.0	75.0	100.0							
Tetracycline-resistant (38)	1	17	12	7	0	0	1	0.12	0.25		
	2.6	47.4	78.9	97.4	97.4	97.4	100.0				
Streptococcus anginosus group (50)	18	27	3					0.06	0.06	100.0[a]	0.0
	40.0	94.0	100.0								
Tetracycline-resistant (14)	1	11	2					0.06	0.12	100.0[a]	0.0
	7.1	85.7	100.0								
β-haemolytic streptococci (651)	0	274	305	59	12	1		0.12	0.25		
	0.0	42.1	88.9	98.0	99.8	100.0					
Tetracycline-resistant (295)	0	34	198	51	11	1		0.12	0.25		
	0.0	11.5	78.6	95.9	99.7	100.0					
Streptococcus pyogenes (299)	0	206	86	6	1			0.06	0.12	97.7[a]	0.3
	0.0	68.9	97.7	99.7	100.0						
Macrolide-resistant (erythromycin MIC ≥ 1 mg/L; CLSI) (32)	0	10	19	3				0.12	0.12	90.6[a]	0.0
	0.0	31.2	90.6	100.0							
Macrolide-resistant (erythromycin MIC > 0.5 mg/L; EUCAST) (32)	0	10	19	3				0.12	0.12	90.6[a]	0.0
	0.0	31.2	90.6	100.0							
Tetracycline-resistant (53)	0	12	35	5	1			0.12	0.25	88.7[a]	1.9
	0.0	22.6	88.7	98.1	100.0						
Streptococcus agalactiae (261)	0	62	163	36				0.12	0.25		
	0.0	23.8	86.2	100.0							
Macrolide-resistant (erythromycin MIC ≥ 1 mg/L; CLSI) (124)	0	25	78	21				0.12	0.25		
	0.0	20.2	83.1	100.0							
Macrolide-resistant (erythromycin MIC > 0.5 mg/L; EUCAST) (124)	0	25	78	21				0.12	0.25		
	0.0	20.2	83.1	100.0							
Tetracycline-resistant (211)	0	21	154	36				0.12	0.25		
	0.0	10.0	82.9	100.0							
Other (91)	0	6	56	17	11	1		0.12	0.5		
	0.0	6.6	68.1	86.8	98.9	100.0					

CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, United States Food and Drug Administration; ABSSSIs, acute bacterial skin and skin structure infections; CABP, community-acquired bacterial pneumonia; %S, % susceptible; %R, % resistant.

[a] Applying FDA identified breakpoints for ABSSSIs.

[b] Applying FDA identified breakpoints for CABP.

Table 2
Antimicrobial activity of omadacycline tested against the main organisms and organism groups of Gram-negative bacilli.

Organism/organism group (number of isolates)	Number and cumulative % of isolates at MIC (mg/L) of:											MIC_{50}	MIC_{90}	%S	%R
	≤ 0.06	0.12	0.25	0.5	1	2	4	8	16	32	> 32				
Enterobacteriaceae (5993)[a]	0	3	97	1480	1865	1202	558	305	277	153	53	1	8		
	0.0	0.1	1.7	26.4	57.5	77.5	86.9	91.9	96.6	99.1	100.0				
ESBL-SP phenotype (1002)		0	11	176	297	220	147	81	32	25	13	2	8		
		0.0	1.1	18.7	48.3	70.3	84.9	93.0	96.2	98.7	100.0				
Tetracycline-resistant (2136)		0	8	212	360	450	402	241	262	150	51	4	16		
		0.0	0.4	10.3	27.2	48.2	67.0	78.3	90.6	97.6	100.0				
Escherichia coli (2581)	0	1	81	1,325	763	303	86	10	11	1		0.5	2		
	0.0	< 0.1	3.2	54.5	84.1	95.8	99.1	99.5	> 99.9	100.0					
Non-ESBL-phenotype (2059)	0	1	70	1,166	576	191	45	5	5			0.5	2		
	0.0	< 0.1	3.4	60.1	88.1	97.3	99.5	99.8	100.0						
ESBL-SP phenotype (522)		0	11	159	187	112	41	5	6	1		1	4		
		0.0	2.1	32.6	68.4	89.8	97.7	98.7	99.8	100.0					
Tetracycline-resistant (904)		0	8	209	323	259	83	10	11	1		1	4		
		0.0	0.9	24.0	59.7	88.4	97.6	98.7	99.9	100.0					
Klebsiella pneumoniae (1269)		0	4	52	531	370	154	101	39	13	5	2	8	87.5[b,c]	4.5
		0.0	0.3	4.4	46.3	75.4	87.5	95.5	98.6	99.6	100.0				
Non-ESBL-phenotype (855)		0	4	37	437	267	56	35	17	2		1	4	93.7[b,c]	2.2
		0.0	0.5	4.8	55.9	87.1	93.7	97.8	99.8	100.0					
ESBL-SP phenotype (414)			0	15	94	103	98	66	22	11	5	2	8	74.9[b,c]	9.2
			0.0	3.6	26.3	51.2	74.9	90.8	96.1	98.8	100.0				
Tetracycline-resistant (353)			0	2	26	92	89	88	38	13	5	4	16	59.2[b,c]	15.9
			0.0	0.6	7.9	34.0	59.2	84.1	94.9	98.6	100.0				
Klebsiella oxytoca (278)			0	21	220	22	11	4				1	2		
			0.0	7.6	86.7	94.6	98.6	100.0							
Tetracycline-resistant (16)				0	2	5	6	3				4	8		
				0.0	12.5	43.8	81.2	100.0							
Other *Klebsiella* spp. (5)				0	1	2	1	1				2			
				0.0	20.0	60.0	80.0	100.0							
Enterobacter cloacae species complex (488)		0	2	3	116	294	30	22	17	4		2	4	91.2[b]	4.3
		0.0	0.4	1.0	24.8	85.0	91.2	95.7	99.2	100.0					
Ceftazidime-susceptible (≤ 4 mg/L) (356)		0	2	2	93	223	14	10	9	3		2	4	93.8[b]	3.4
		0.0	0.6	1.1	27.2	89.9	93.8	96.6	99.2	100.0					
Ceftazidime-nonsusceptible (> 4 mg/L) (132)			0	1	23	71	16	12	8	1		2	8	84.1[b]	6.8
			0.0	0.8	18.2	72.0	84.1	93.2	99.2	100.0					
Tetracycline-resistant (66)				0	2	22	7	15	16	4		8	16	47.0[b]	30.3
				0.0	3.0	36.4	47.0	69.7	93.9	100.0					
Other *Enterobacter* spp. (179)			0	4	84	69	6	6	10			2	4		
			0.0	2.2	49.2	87.7	91.1	94.4	100.0						
Tetracycline-resistant (20)				0	1	2	3	4	10			8	16		
				0.0	5.0	15.0	30.0	50.0	100.0						
Citrobacter spp. (253)			0	60	116	53	10	9	5			1	2		
			0.0	23.7	69.6	90.5	94.5	98.0	100.0						
Tetracycline-resistant (21)			0	1	1	9	3	5	2			2	8		
			0.0	4.8	9.5	52.4	66.7	90.5	100.0						
Citrobacter freundii species complex (145)			0	11	77	38	6	9	4			1	4		

			0.0	7.6	60.7	86.9	91.0	97.2	100.0					
Tetracycline-resistant (18)				0	1	7	3	5	2			4	16	
				0.0	5.6	44.4	61.1	88.9	100.0					
Serratia marcescens (273)				0	2	59	185	20	3	2	2	4	4	
				0.0	0.7	22.3	90.1	97.4	98.5	99.3	100.0			
Tetracycline-resistant (258)				0	2	49	181	19	3	2	2	4	8	
				0.0	0.8	19.8	89.9	97.3	98.4	99.2	100.0			
Other *Serratia* spp. (15)			0	1	10	2	2					1	4	
			0.0	6.7	73.3	86.7	100.0							
Acinetobacter baumannii (227)	0	8	36	19	10	38	63	44	7	2		4	8	
	0.0	3.5	19.4	27.8	32.2	48.9	76.7	96.0	99.1	100.0				
Tetracycline-resistant (132)		0	2	4	6	10	57	44	7	2		4	8	
		0.0	1.5	4.5	9.1	16.7	59.8	93.2	98.5	100.0				
Other *Acinetobacter* spp. (23)	1	4	13	4	1							0.25	0.5	
	4.3	21.7	78.3	95.7	100.0									
Stenotrophomonas			0	1	7	36	55	20	9	1		4	8	
maltophilia (129)			0.0	0.8	6.2	34.1	76.7	92.2	99.2	100.0				
Haemophilus influenzae (556)		1	13	298	213	30	1					0.5	1	99.8[c]	0.0
		0.2	2.5	56.1	94.4	99.8	100.0								
β-lactamase-positive (166)		0	2	91	64	9						0.5	1	100.0[c]	0.0
		0.0	1.2	56.0	94.6	100.0									
β-lactamase-negative (390)		1	11	207	149	21	1					0.5	1	99.7[c]	0.0
		0.3	3.1	56.2	94.4	99.7	100.0								
Tetracycline-resistant (132)			0	7	1	1						0.5		100.0[c]	0.0
			0.0	77.8	88.9	100.0									
Haemophilus parainfluenzae (6)			0	1	3	1	1					1		83.3[c]	0.0
			0.0	16.7	66.7	83.3	100.0								
β-lactamase-negative (6)			0	1	3	1	1					1		83.3[c]	0.0
			0.0	16.7	66.7	83.3	100.0								
Moraxella catarrhalis (313)		236	77									≤0.12	0.25		
		75.4	100.0												
Other *Moraxella* spp. (3)		1	1	1								0.25			
		33.3	66.7	100.0											

ESBL-SP, extended-spectrum β-lactamase screen-positive; FDA, United States Food and Drug Administration; ABSSSIs, acute bacterial skin and skin structure infections; CABP, community-acquired bacterial.

[a] Omadacycline was not active against *Proteus mirabilis*, indole-positive Proteus spp., or *Pseudomonas aeruginosa* isolates with $MIC_{50/90}$ values of 16/> 32, 8/16, and 32/> 32 mg/L, respectively.

[b] Applying FDA identified breakpoints for ABSSSIs.

[c] Applying FDA identified breakpoints for CABP.

isolates at ≤ 4 mg/L (ABSSSI susceptible breakpoint for *E. cloacae* SC and *K. pneumoniae*) with the exceptions of *P. mirabilis* ($MIC_{50/90}$ 16/> 32 mg/L) and indole-positive *Proteus* spp. ($MIC_{50/90}$ 8/16 mg/L) (data not shown). Omadacycline was most active against *E. coli* ($MIC_{50/90}$ 0.5/2 mg/L; 99.1% inhibited at ≤ 4 mg/L), tetracycline-resistant *E. coli* ($MIC_{50/90}$ 1/4 mg/L; 97.6% inhibited at ≤ 4 mg/L), *Klebsiella oxytoca* ($MIC_{50/90}$ 1/2 mg/L; 98.6% inhibited at ≤ 4 mg/L), and *Citrobacter* spp. ($MIC_{50/90}$ 1/2 mg/L; 94.5% inhibited at ≤ 4 mg/L) (Table 2).

Susceptibilities of *E. cloacae* SC (ABSSSI breakpoints) and *K. pneumoniae* (ABSSSI and CABP breakpoints) isolates to omadacycline were 91.2% and 87.5% susceptible, respectively (Table 2). Reduced activity was observed for omadacycline against tetracycline-resistant *E. cloacae* SC and *K. pneumoniae* isolates ($MIC_{50/90}$ values 8/16 mg/L and 4/16 mg/L, respectively): 47.0% of tetracycline-resistant *E. cloacae* SC and 59.2% of tetracycline-resistant *K. pneumoniae* isolates were susceptible to omadacycline (Table 2). Similarly, against ceftazidime-nonsusceptible (MIC > 4 mg/L; AmpC-derepressed phenotype isolates) *E. cloacae* SC isolates, omadacycline was less active (84.1% S) compared to ceftazidime-susceptible isolates (93.8% susceptible) (Table 2).

Omadacycline demonstrated in vitro activity against other species of Enterobacteriaceae, including other *Enterobacter* spp., *Citrobacter freundii* (*C. freundii*) SC, and *S. marcescens* isolates inhibiting 91.1%, 91.0%, and 90.1% of isolates at ≤ 4 mg/L (Table 2). Among tetracycline-resistant isolates of other *Enterobacter* spp., *C. freundii* SC, and *S. marcescens*, omadacycline activity was reduced, inhibiting 30.0% of other *Enterobacter* spp. and 61.1% of *C. freundii* SC at ≤ 4 mg/L, whereas omadacycline retained activity against tetracycline-resistant strains of *S. marcescens* ($MIC_{50/90}$ 4/8 mg/L; 89.9% inhibited at ≤ 4 mg/L).

Omadacycline ($MIC_{50/90}$ 4/8 mg/L) inhibited 76.7% of *A. baumannii* and *S. maltophilia* isolates at ≤ 4 mg/L, as well as 59.8% of tetracycline-resistant *A. baumannii* isolates (Table 2). Omadacycline was not active against *P. aeruginosa* ($MIC_{50/90}$ 32/>32 mg/L; data not shown).

Omadacycline was active against β-lactamase-negative ($MIC_{50/90}$ 0.5/1 mg/L; 99.7% susceptible [CABP breakpoints]) and β-lactamase-positive ($MIC_{50/90}$ 0.5/1 mg/L; 100.0% susceptible [CABP breakpoints]) *H. influenzae* isolates (Table 2). Omadacycline inhibited 100.0% of *Moraxella catarrhalis* isolates at ≤ 0.25 mg/L (Table 2).

4. Conclusions

One approach to combat antimicrobial resistance is to develop antibacterials with novel mechanisms of action and greater potency against resistant strains of bacteria [9–11]. Chemical modifications to minocycline provide omadacycline with several advantages over the older tetracyclines, such as doxycycline and minocycline, including: a low propensity for selection of resistance, enhanced binding to the 30S ribosomal subunit, ability to overcome common tetracycline resistance mechanisms, lack of effect of other resistance mechanisms, availability as an intravenous or oral formulation, a prolonged half-life, and once-daily administration [5]. Omadacycline recently received FDA approval for treating ABSSSIs and CABP. A Phase 3 study of oral and intravenous administration of omadacycline for the treatment of acute cystitis in women is presently under investigation NCT03425396) [5].

Data from the present survey documents the in vitro activity of omadacycline against bacterial isolates from the 2017 USA and EUR SENTRY survey. Omadacycline was active (≥ 90.0% susceptibility) against GP isolates including MRSA, *S. lugdunensis*, *E. faecalis* (including tetracycline-resistant isolates), *S. anginosus* group, *S. pyogenes* (including macrolide-resistant and tetracycline-resistant isolates), and *S. pneumoniae* (including penicillin-resistant, macrolide-resistant, and tetracycline-resistant isolates) with susceptibilities ranging from 96.2–100.0% (Table 1). Most vancomycin-nonsusceptible *E. faecalis* isolates (7/8; 87.5%) were susceptible to omadacycline. Omadacycline inhibited 86.9% of Enterobacteriaceae and 99.1% of *E. coli* isolates at ≤ 4 mg/L. Tetracycline-resistant *E. cloacae* SC *and K. pneumoniae* isolates were less susceptible to omadacycline (47.0% and 59.2% susceptible, respectively) compared with all *E. cloacae* SC *and K. pneumoniae* isolates (91.2% and 87.5% susceptible, respectively). Omadacycline showed moderate in vitro activity against *A. baumannii* and *S. maltophilia*, inhibiting 76.7% of isolates at ≤ 4 mg/L (Table 2).

These data build upon information reported by previous SENTRY surveys [12] and indicate that omadacycline is active against many tetracycline-resistant and tetracycline-susceptible GPC and some GNB (using recently approved FDA breakpoint interpretive criteria) and merits further study in the treatment of ABSSSIs, CABP, and UTIs where mixed GPC and GNB infections are common.

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Competing interests

JMI Laboratories was contracted to perform services in 2017 for Achaogen, Allecra Therapeutics, Allergan, Amplyx Pharmaceuticals, Antabio, API, Astellas Pharma, AstraZeneca, Athelas, Basilea Pharmaceutica, Bayer AG, BD, Becton, Dickinson and Co., Boston Pharmaceuticals, CEM-102 Pharma, Cempra, Cidara Therapeutics, Inc., CorMedix, CSA Biotech, Cutanea Life Sciences, Inc., Entasis Therapeutics, Inc., Geom Therapeutics, Inc., GSK, Iterum Pharma, Medpace, Melinta Therapeutics, Inc., Merck & Co., Inc., MicuRx Pharmaceuticals, Inc., N8 Medical, Inc., Nabriva Therapeutics, Inc., NAEJA-RGM, Novartis, Paratek Pharmaceuticals, Inc., Pfizer, Polyphor, Ra Pharma, Rempex, Riptide Bioscience Inc., Roche, Scynexis, Shionogi, Sinsa Labs Inc., Skyline Antiinfectives, Sonoran Biosciences, Spero Therapeutics, Symbiotica, Synlogic, Synthes Biomaterials, TenNor Therapeutics, Tetraphase, The Medicines Company, Theravance Biopharma, VenatoRx Pharmaceuticals, Inc., Wockhardt, Yukon Pharma, Zai Laboratory, Zavante Therapeutics, Inc. There are no speakers' bureaus or stock options to declare.

Ethical approval

Not required.

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