C-614

Activity of Omadacycline Tested against Enterobacteriaceae Causing Urinary Tract Infections from a Global Surveillance Program (2014)

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ICAAC 2015
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ABSTRACT

Background: Omadacycline (OMC) is a broad spectrum new aminomethylcycline which is currently under clinical development for acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia, as oral and intravenous once daily formulations. It is active against many Gram-negative pathogens from the urinary tract and overcomes tetracycline (TET) resistance. In this study, OMC and comparators were tested against Enterobacteriaceae (EB) from UTI selected from a 2014 global surveillance program and compared to results of testing isolates causing UTI (urinary or bloodstream) from 2010 surveillance.

Methods: A total of 150 EB identified as causing UTI from Europe (EU) and the same numbers from North America (NA, 2014) were selected. OMC and comparators (except 2014 OMC and TET which were tested in frozen-form panels) were tested in validated dry-form panels by broth microdilution in CA-MHB following CLSI methods. CLSI/EUCAST interpretive criteria and CLSI quality control guidelines were applied. ESBL-phenotype (ESBL) for *Escherichia coli* or *Klebsiella pneumoniae* was defined as a MIC at ≥2 µg/mL for ceftriaxone, ceftazidime or aztreonam.

Results: The OMC $MIC_{50/90}$ for EB collected during 2014 was 2 and ≥8 µg/mL, respectively. The $MIC_{50/90}$ for *E. coli* was 1 and 2 µg/mL similar to 2010 ($MIC_{50/90}$, 0.5 and 2 µg/mL). The activity of OMC against ESBL *E. coli* was similar in 2010 and 2014 ($MIC_{50/90}$, 1 and 4 µg/mL). The MICs for 91.7% of *Klebsiella* spp. isolates in 2014 (89.7%, 2010) were ≤4 µg/mL. In 2014 and 2010, a total of 95.8 and 100.0% of ESBL *E. coli* and 75.0 and 73.9% of ESBL *Klebsiella* spp. exhibited MIC values at ≤4 µg/mL. Tigecycline (TIG) susceptibility (CLSI or EUCAST) for EB was 94.0 (2014) and 99.4% (2010). TET susceptibility for EB (2014 and 2010) ranged from 60.1-66.1%, ceftazidime from 82.1-92.3%, gentamicin (GEN) from 85.7-90.9%, imipenem from 91.0-99.3% and levofloxacin (LEV) from 75.1-79.9%. TIG S for EB for 2014 and 2010 for NA and EU ranged from 94.0-99.5%, GEN from 82.8-93.6%, and LEV from 69.5-82.0%.

Conclusions: OMC was active against EB isolates from NA and EU causing UTI and activity was similar between 2010 and 2014. Further study with OMC in the treatment of UTI caused by EB is indicated.

INTRODUCTION

Urinary tract infections (UTI) are common infections that occur in the community and healthcare settings. The most common cause of bacterial UTI is *Escherichia coli*. In the healthcare setting, bacterial resistance to commonly prescribed antibacterials is an issue. Extended-spectrum β-lactamases and carbapenemases may occur, thus limiting β-lactam options. Further clones such as *E. coli* ST-131 may occur which are often also resistant to other antibacterial classes such as the fluoroquinolones. The resistance to oral agents in the community setting and the emergence of the ESBL-positive *E. coli* into the community indicate an urgent need for new alternatives to treat UTI.

Omadacycline (PTK 0796; [7-dimethylamino, 9-(2,2-dimethyl-propyl)-aminomethylcycline]) is a novel tetracycline antibacterial agent, which is currently under clinical development for use as both an oral and intravenous formulation against acute bacterial skin and skin structure infections, community-acquired pneumonia, and urinary tract infections. Omadacycline has broad spectrum activity against Gram-positive, Gram-negative, atypical and anaerobic bacteria, including those with multi-drug resistance (MDR).

In this study, the activity of omadacycline and comparator agents was evaluated against isolates causing UTI in 2014. These results were compared to those from a 2010 global surveillance program.

MATERIALS AND METHODS

Organism collection: A total of 151 Enterobacteriaceae which were identified as urinary tract isolates from patients in medical centers in Europe and 150 from North America (2014 Global Surveillance; n=301) were selected for susceptibility testing. These organisms were chosen to represent approximate percentages of Enterobacteriaceae species in the complete collection of UTI (2014). Organisms (number) included *Citrobacter amalonaticus* (1), *C. freundii* (11), *C. koseri* (8), *Enterobacter aerogenes* (7), *E. coli* (138), *E. cloacae* (16), *Klebsiella oxytoca* (8), *K. pneumoniae* (52), *Morganella morganii* (14), *Proteus mirabilis* (22), *P. vulgaris* (7), *Providencia rettgeri* (6), *P. stuartii* (5), *Serratia marcescens* (6). Enterobacteriaceae from UTI (including isolates from blood, designated by the medical center as having originated from UTI) from Europe and North America from a 2010 surveillance program were identified. The organism collection contained *C. freundii* (5), *C. koseri* (3), *E. aerogenes* (12), *E. asburiae* (1), Unspeciated *Enterobacter* (1), *E. coli* (543), *E. cloacae* (23), *K. oxytoca* (32), *K. pneumoniae* (123), *M. morganii* (8), *P. mirabilis* (50), Unspeciated *Providencia* (4), *P. vulgaris* (3), *P. rettgeri* (1), *P. stuartii* (1), Unspeciated *Salmonella* (1), *S. marcescens* (15). The susceptibility results for isolates from 2014 were compared to the results of 826 isolates from 2010.

Susceptibility testing: Comparator agents were tested in validated dry-form panels manufactured by Thermo Fisher Scientific Inc. (Cleveland, Ohio, USA) by broth microdilution in cation-adjusted Mueller-Hinton broth following Clinical and Laboratory Standards Institute (CLSI) methods. Omadacycline was tested in dry-form panels in 2010 and panels with fresh frozen medium made at JMI Laboratories (North Liberty, Iowa, USA) were used to test the 2014 isolates. Concurrent quality control (QC) testing was performed to assure proper test conditions and procedures (M07-A10, M100-S25). The QC strains tested were *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 (M100-S25). All QC results were within published ranges. Interpretive criteria used were those of CLSI (M07-A10, M100-S25) and EUCAST (2015).

Table 1. Cumulative frequency distribution of omadacycline MIC results for urinary tract isolates from Europe (EU) and North America (NA).

Organism/region	Year	No. of Isolates	MIC in µg/mL (cumulative %): ≤0.12	0.25	0.5	1	2	4	≥8	MIC_{50}	MIC_{90}
Enterobacteriaceae											
NA + EU	2014	301	--	2 (0.7)	66 (22.6)	78 (48.5)	67 (70.8)	28 (80.1)	60 (100.0)[a]	2	≥8
NA + EU	2010	826	--	49 (5.9)	279 (39.7)	199 (63.8)	170 (84.4)	47 (90.1)	82 (100.0)[b]	1	4
NA	2014	150	--	--	39 (26.0)	33 (48.0)	35 (71.3)	8 (76.7)	35 (100.0)	2	≥8
NA	2010	377	--	27 (7.2)	124 (40.1)	103 (67.4)	69 (85.7)	17 (90.2)	37 (100.0)	1	4
EU	2014	151	--	2 (1.3)	27 (19.2)	45 (49.0)	32 (70.2)	20 (83.4)	25 (100.0)	2	≥8
EU	2010	449	--	22 (4.9)	155 (39.4)	96 (60.8)	101 (83.3)	30 (90.0)	45 (100.0)	1	≥8
E. coli											
NA+EU	2014	138	--	2 (1.4)	58 (43.5)	49 (79.0)	20 (93.5)	8 (99.3)	1 (100.0)	1	2
NA+EU	2010	543	--	49 (9.0)	273 (59.3)	134 (84.0)	70 (96.9)	15 (99.6)	2 (100.0)	0.5	2
NA	2014	59	--	--	33 (55.9)	16 (83.1)	9 (98.3)	1 (100.0)	--	0.5	2
NA	2010	224	--	27 (12.1)	122 (66.5)	56 (91.5)	16 (98.7)	3 (100.0)	--	0.5	1
EU	2014	79	--	2 (2.5)	25 (34.2)	33 (75.9)	11 (89.9)	7 (98.7)	1 (100.0)	1	4
EU	2010	319	--	22 (6.9)	151 (54.2)	78 (78.7)	54 (95.6)	12 (99.4)	2 (100.0)	0.5	2
E. coli ESBL-positive											
NA+EU	2014	24	--	--	6 (25.0)	8 (58.3)	6 (83.3)	3 (95.8)	1 (100.0)	1	4
NA+EU	2010	48	--	--	15 (31.2)	10 (52.1)	18 (89.6)	5 (100.0)	--	1	4
NA	2014	8	--	--	2 (25.0)	4 (75.0)	1 (87.5)	1 (100.0)	--	1	--
NA	2010	19	--	--	3 (15.8)	6 (47.4)	8 (89.5)	2 (100.0)	--	2	4
EU	2014	16	--	--	4 (25.0)	4 (50.0)	5 (81.2)	2 (93.8)	1 (100.0)	1	4
EU	2010	29	--	--	12 (41.4)	4 (55.2)	10 (89.7)	3 (100.0)	--	1	4
Klebsiella spp.											
NA+EU	2014	60	--	--	1 (1.7)	22 (38.3)	23 (76.7)	9 (91.7)	5 (100.0)	2	4
NA+EU	2010	155	--	--	5 (3.2)	53 (37.4)	67 (80.6)	14 (89.7)	16 (100.0)	2	≥8
NA	2014	31	--	--	1 (3.2)	14 (48.4)	13 (90.3)	1 (93.5)	2 (100.0)	2	2
NA	2010	103	--	--	1 (1.0)	44 (43.7)	38 (80.6)	12 (92.2)	8 (100.0)	2	4
EU	2014	29	--	--	--	8 (27.6)	10 (62.1)	8 (89.7)	3 (100.0)	2	≥8
EU	2010	52	--	--	4 (7.7)	9 (25.0)	29 (80.8)	2 (84.6)	8 (100.0)	2	≥8
Klebsiella spp. ESBL-positive											
NA+EU	2014	16	--	--	--	2 (12.5)	5 (43.8)	5 (75.0)	4 (100.0)	4	≥8
NA+EU	2010	23	--	--	1 (4.3)	1 (8.7)	10 (52.2)	5 (73.9)	6 (100.0)	2	≥8
NA	2014	2	--	--	--	--	1 (50.0)	0 (50.0)	1 (100.0)	2	--
NA	2010	7	--	--	--	--	2 (28.6)	4 (85.7)	1 (100.0)	4	--
EU	2014	14	--	--	--	2 (14.3)	4 (42.9)	5 (78.6)	3 (100.0)	4	≥8
EU	2010	16	--	--	1 (6.2)	1 (12.5)	8 (62.5)	1 (68.8)	5 (100.0)	2	≥8

a. 55/60 isolates were either *Proteus, Morganella*, or *Providencia* spp.
b. 56/82 isolates were either *Proteus, Morganella,* or *Providencia* spp.

RESULTS

Activity of omadacycline against Enterobacteriaceae (combined Europe and North America): 2010 compared to 2014

- The MIC_{50} and MIC_{90} for omadacycline for Enterobacteriaceae causing UTI from the 2010 surveillance program from Europe and North America combined was 1 and 4 µg/mL, respectively (**Table 1**). The MIC_{50} and MIC_{90} for omadacycline for Enterobacteriaceae causing UTI from the 2014 surveillance program from Europe and North America combined was 2 and ≥8 µg/mL, respectively (**Table 1**). The Enterobacteriaceae collection from 2010 contained more *Proteus/Providencia/Morganella* (17.9%) compared to the 2014 collection (8.1%). *Proteus/Providencia/Morganella* tend to have higher MIC values for omadacycline than *E. coli* and *Klebsiella* spp.
- The *E. coli* MIC_{90} was 2 µg/mL for Europe and North America combined isolates for both 2014 and 2010 isolates (**Table 1**). For ESBL-negative phenotype *E. coli,* the MIC_{90} for isolates from either year for Europe and North America combined was 2 µg/mL and it was 4 µg/mL for the ESBL-positive phenotype (**Table 1**).
- The MIC_{50} and MIC_{90} for omadacycline for *Klebsiella* spp. causing UTI from the 2010 surveillance program from Europe and North America combined was 2 and ≥8 µg/mL, respectively (**Table 1**). The MIC_{50} and MIC_{90} for omadacycline for the selected *Klebsiella* spp. causing UTI from the 2014 surveillance program from Europe and North America was 2 and 4 µg/mL, respectively (**Table 1**). For ESBL-negative phenotype *Klebsiella* spp., the MIC_{90} for isolates from Europe and North America combined either year was 4 µg/mL and ≥8 µg/mL for the ESBL-positive phenotype (**Table 1**).

Activity of omadacycline against Enterobacteriaceae: Europe compared to North America

- The omadacycline MIC_{90} for Enterobacteriaceae from North America (2010) was 4 µg/mL and it was ≥8 µg/mL for the European isolates (**Table 1**). For the 2014 isolates, the MIC_{90}s were ≥8 µg/mL (**Table 1**).

Table 2. Activity of omadacycline and comparator antimicrobial agents when tested against combined North American and European urinary tract isolates by year (2014 vs. 2010).

Organism group (no. tested)/ antimicrobial agent	2014 CLSI[a] %S	2014 CLSI[a] %R	2014 EUCAST[a] %S	2014 EUCAST[a] %R	2014 (µg/mL) $MIC_{50/90}$	2014 (µg/mL) MIC range	2010 CLSI[a] %S	2010 CLSI[a] %R	2010 EUCAST[a] %S	2010 EUCAST[a] %R	2010 (µg/mL) $MIC_{50/90}$	2010 (µg/mL) MIC range
Enterobacteriaceae					(301)						(826)	
Omadacycline	-	-	-	-	2/≥8	0.25 — ≥8	-	-	-	-	1/4	0.25 — >32
Tigecycline	98.3	0.0[b]	94.0	1.7	0.12/1	≤0.015 — 4	99.4	0.0[b]	95.9	0.6	0.12/0.5	≤0.03 — 4
Doxycycline	61.5	32.2	-	-	2/≥16	0.25 — ≥16	69.1	23.4	-	-	1/≥16	≤0.06 — ≥16
Tetracycline	60.1	37.5	-	-	2/≥32	0.5 — ≥32	66.1	32.6	-	-	2/≥32	≤0.25 — ≥16
AMX-CLV[c]	63.5	36.5[d]	63.5	36.5	8/≥16	≤1 — ≥16	75.5	24.5[d]	75.5	24.5	4/≥16	≤1 — ≥16
Aztreonam	84.4	14.0	82.1	15.6	≤0.12/16	≤0.12 — ≥32	90.9	7.3	89.5	9.1	≤0.12/4	≤0.12 — ≥32
Ceftazidime	87.4	10.6	82.1	12.6	0.25/16	0.03 — >32	92.3	6.1	89.5	7.7	0.12/2	0.03 — >32
Ceftriaxone	79.7	18.6	79.7	18.6	≤0.06/≥16	≤0.06 — ≥16	88.4	11.0	88.4	11.0	≤0.06/4	≤0.06 — ≥16
Gentamicin	88.0	11.6	85.7	12.0	≤1/≥16	≤1 — ≥16	90.9	8.4	90.4	9.1	≤1/2	≤1 — ≥16
Imipenem	91.0	2.7	97.3	0.0	≤0.12/1	≤0.12 — 4	97.3	0.7	99.3	0.2	≤0.12/0.5	≤0.12 — ≥16
Levofloxacin	78.4	17.9	75.1	21.6	≤0.12/≥8	≤0.12 — ≥8	79.9	18.2	79.0	20.1	≤0.5/≥8	≤0.5 — ≥8
TMP-SMX[e]	67.8	32.2	67.8	31.6	≤0.5/≥8	≤0.5 — ≥8	73.1	26.9	73.1	26.8	≤0.5/≥8	≤0.5 — ≥8
E. coli					(138)						(543)	
Omadacycline	-	-	-	-	1/2	0.25 — ≥8	-	-	-	-	0.5/2	0.25 — 8
Tigecycline	100.0	0.0[b]	100.0	0.0	0.06/0.12	≤0.015 — 1	100.0	0.0[b]	100.0	0.0	0.12/0.25	≤0.03 — 1
Doxycycline	68.1	24.6	-	-	2/≥16	0.25 — ≥16	73.1	18.4	-	-	1/≥16	≤0.06 — ≥16
Tetracycline	65.9	33.3	-	-	2/≥32	0.5 — ≥32	69.8	29.8	-	-	2/≥16	≤0.25 — ≥16
AMX-CLV[c]	81.9	18.1[d]	81.9	18.1	4/≥16	≤1 — ≥16	80.5	19.5[d]	80.5	19.5	8/≥16	≤1 — ≥16
Aztreonam	86.2	12.3	84.1	13.8	≤0.12/16	≤0.12 — ≥32	93.0	5.5	91.5	7.0	≤0.12/0.5	≤0.12 — ≥32
Ceftazidime	91.3	5.8	87.0	8.7	0.25/4	0.03 — >32	93.7	5.0	91.7	6.3	0.12/0.5	0.03 — >32
Ceftriaxone	84.1	14.5	84.1	14.5	≤0.06/≥16	≤0.06 — ≥16	91.3	8.7	91.3	8.7	≤0.06/0.25	≤0.06 — ≥16
Gentamicin	87.7	11.6	85.5	12.3	≤1/≥16	≤1 — ≥16	92.4	6.8	92.3	7.6	≤1/2	≤1 — ≥16
Imipenem	100.0	0.0	100.0	0.0	≤0.12/≤0.12	≤0.12 — 0.5	100.0	0.0	100.0	0.0	≤0.12/≤0.12	≤0.12 — 1
Levofloxacin	73.9	26.1	73.9	26.1	≤0.12/≥8	≤0.12 — ≥8	76.8	22.0	76.8	23.2	≤0.5/≥8	≤0.5 — ≥8
TMP-SMX[e]	66.7	33.3	66.7	33.3	≤0.5/≥8	≤0.5 — ≥8	69.9	30.1	69.9	30.1	≤0.5/≥8	≤0.5 — ≥8
Klebsiella spp.					(60)[F]						(155)[G]	
Omadacycline	-	-	-	-	2/4	0.5 — ≥8	-	-	-	-	2/8	0.5 — 32
Tigecycline	100.0	0.0[b]	96.7	0.0	0.25/0.5	≤0.015 — 2	99.4	0.0[b]	96.8	0.6	0.25/0.5	0.06 — 4
Doxycycline	70.0	23.3	-	-	2/≥16	0.5 — ≥16	78.1	16.8	-	-	1/≥16	0.25 — ≥16
Tetracycline	75.0	23.3	-	-	1/≥32	0.5 — ≥32	78.1	18.7	-	-	/≥16	0.5 — ≥16
AMX-CLV[c]	75.0	25.0[d]	75.0	25.0	2/≥16	≤1 — ≥16	83.2	16.8[d]	83.2	16.8	2/≥16	≤1 — ≥16
Aztreonam	75.0	23.3	75.0	25.0	≤0.12/≥32	≤0.12 — ≥32	87.1	11.6	85.2	12.9	≤0.12/16	≤0.12 — ≥32
Ceftazidime	80.0	16.7	76.7	20.0	0.12/>32	0.06 — >32	89.0	8.4	87.1	11.0	0.12/8	0.03 — >32
Ceftriaxone	73.3	26.7	73.3	26.7	≤0.06/≥16	≤0.06 — ≥16	86.5	13.5	86.5	13.5	≤0.06/≥16	≤0.06 — ≥16
Gentamicin	80.0	20.0	80.0	20.0	≤1/≥16	≤1 — ≥16	90.3	9.7	89.7	9.7	≤1/4	≤1 — ≥16
Imipenem	96.7	3.3	96.7	0.0	≤0.12/0.25	≤0.12 — 4	98.7	1.3	98.7	1.3	≤0.12/0.25	≤0.12 — ≥16
Levofloxacin	85.0	11.7	80.0	15.0	≤0.12/≥8	≤0.12 — ≥8	87.7	9.7	86.5	12.3	≤0.5/4	≤0.5 — ≥8
TMP-SMX[e]	63.3	36.7	63.3	36.7	≤0.5/≥8	≤0.5 — ≥8	82.6	17.4	82.6	16.8	≤0.5/≥8	≤0.5 — ≥8

a. Criteria as published by CLSI [2015] and EUCAST [2015].
b. Breakpoints from FDA Package Insert revised 12/2014.
c. AMX-CLV = Amoxicillin-clavulanate.
d. Includes both intermediate and resistant isolates.
e. TMP-SMX = Trimethoprim-sulfamethoxazole.
f. Organisms include: *Klebsiella oxytoca* (8), *K. pneumoniae* (52).
g. Organisms include: *Klebsiella oxytoca* (32), *K. pneumoniae* (123).

- For all *E. coli*, the MIC_{90}s for the 2010 isolates ranged from 1-2 µg/mL and for the 2014 isolates from 2-4 µg/mL (**Table 1**). MIC_{90}s for ESBL-negative phenotype *E. coli* ranged from 1-2 µg/mL for both years in both regions (**Table 1**). ESBL-positive phenotype *E. coli* exhibited MIC_{90} values of 4 µg/mL for both years in Europe and 2010 in North America (too few to calculate a MIC_{90} in 2014 [range, 0.5-4 µg/mL for eight isolates]; **Table 1**).
- For *Klebsiella* spp. in North America, MIC_{90} values ranged from 2-4 µg/mL in 2010 and 2014 and in Europe were ≥8 µg/mL (**Table 1**). ESBL-negative phenotype *Klebsiella* spp. exhibited MIC_{90} values of 2-4 µg/mL for both years and regions (**Table 1**). ESBL-positive phenotype *Klebsiella* spp. exhibited MIC_{90} values of ≥8 µg/mL in Europe (2010 and 2014; **Table 3**). In North America, the MIC values ranged from 2 - ≥8 µg/mL (too few to calculate a MIC_{90} value; **Table 1**).

Susceptibility to comparator agents (combined regions): 2010 vs. 2014

- Tigecycline was the most active agent (94.0-99.4% susceptible) tested against Enterobacteriaceae for both years (**Table 2**). Levofloxacin resistance ranged from 17.9-21.6% and trimethoprim-sulfamethoxazole from 26.8-32.2% for both years (**Table 2**). Susceptibility tended to be lower and MIC_{90} values higher for 2014 isolates for most agents compared to 2010 (**Table 2**). The agent which exhibited the highest susceptibility, tigecycline, exhibited a higher MIC_{90} value in 2014 compared to 2010 (MIC_{90}, 0.5 µg/mL, 95.9-99.4% susceptible, 2010; MIC_{90}, 1 µg/mL, 94.0-98.3% susceptible, 2014; **Table 2**).
- For *E. coli*, tigecycline and imipenem exhibited 100.0% susceptibility for both years (**Table 2**). As was noted for Enterobacteriaceae in general, susceptibility for most agents was decreased in 2014 (MIC_{90}s were increased) compared to 2010 (**Table 2**). This pattern of decreased susceptibility for most agents was true for ESBL- negative and -positive phenotype *E. coli* (data not shown).
- For *Klebsiella* spp., the most active agents were tigecycline (96.7-100.0% susceptible, 2010 and 2014) and imipenem (96.7-98.7% susceptible, 2010 and 2014; **Table 2**). Susceptibility was generally decreased in 2014 and MIC_{90s} were generally increased (**Table 2**). Susceptibility was high for most agents (>90.0%) against the ESBL-negative phenotype *Klebsiella* spp. for both years except for tetracycline (82.6-88.6% susceptible), doxycycline (82.6-84.1%) and trimethoprim-sulfamethoxazole (81.8-93.2%; data not shown). Against ESBL-positive phenotype *Klebsiella* spp., tigecycline (87.5-100.0% susceptible) and imipenem (87.5-91.3% susceptible) were the most active agents (data not shown). Susceptibility for other agents was generally poor and susceptibility was decreased in 2014 (data not shown).

Susceptibility: Europe compared to North America

- Tigecycline (94.0-99.3%) and imipenem (91.4-98.9%) were the most active agents tested against the European Enterobacteriaceae isolates (2010 and 2014; **Table 3**). Susceptibility tended to be slightly lower for 2014 isolates than for 2010 isolates.
- *E. coli* was generally more susceptible than *Klebsiella* spp. (**Table 3**).
- Tigecycline (94.0-99.5%) and imipenem (90.7-99.7%) were the most active agents against all Enterobacteriaceae from North America (2014 and 2010; **Table 3**). Susceptibility tended to be slightly lower for 2014 than for 2010. *E. coli* was generally more susceptible than *Klebsiella* spp. (**Table 3**).

Table 3. Activity of omadacycline and comparator antimicrobial agents when tested against North American and European urinary tract isolates by year (2014 vs. 2010).

Organism group (no. tested)/ antimicrobial agent	North America 2014 CLSI[a] %S	NA 2014 EUCAST[a] %S	NA 2014 $MIC_{50/90}$	NA 2014 MIC Range	NA 2010 CLSI[a] %S	NA 2010 EUCAST[a] %S	NA 2010 $MIC_{50/90}$	NA 2010 MIC Range	Europe 2014 CLSI[a] %S	EU 2014 EUCAST[a] %S	EU 2014 $MIC_{50/90}$	EU 2014 MIC Range	EU 2010 CLSI[a] %S	EU 2010 EUCAST[a] %S	EU 2010 $MIC_{50/90}$	EU 2010 MIC Range
Entetrobacteriaceae			(150)				(377)				(151)				(449)	
Omadacycline	-	-	2/≥8	0.5 — ≥8	-	-	1/4	0.25 — >32	-	-	2/≥8	0.25 — ≥8	-	-	1/8	0.25 — >32
Tigecycline	98.7[b]	94.0	0.12/1	≤0.015 — 4	99.5[b]	96.0	0.12/0.5	0.06 — 4	98.0[b]	94.0	0.12/1	≤0.015 — 4	99.3[b]	95.8	0.12/0.5	≤0.03 — 4
Doxycycline	64.7	-	2/≥16	0.5 — ≥16	74.3	-	1/≥16	0.25 — ≥16	58.3	-	2/≥16	0.25 — ≥16	64.8	-	2/≥16	≤0.06 — ≥16
Tetracycline	62.7	-	2/≥32	0.5 — ≥32	72.7	-	1/≥16	0.5 — ≥16	57.6	-	2/≥32	0.5 — ≥32	60.6	-	2/≥16	≤0.25 — ≥16
AMX-CLV[c]	67.3	67.3	4/≥16	≤1 — ≥16	80.1	80.1	4/≥16	≤1 — ≥16	59.6	59.6	8/≥16	≤1 — ≥16	71.7	71.7	8/≥16	≤1 — ≥16
Aztreonam	90.0	88.0	≤0.12/4	≤0.12 — ≥32	93.9	92.8	≤0.12/0.25	≤0.12 — ≥32	78.8	76.2	≤0.12/≥32	≤0.12 — ≥32	88.4	86.6	≤0.12/8	≤0.12 — ≥32
Ceftazidime	91.3	88.0	0.12/2	0.03 — >32	94.7	93.1	0.12/0.5	0.03 — >32	83.4	76.2	0.25/16	0.03 — >32	90.2	86.4	0.12/4	0.03 — >32
Ceftriaxone	87.3	87.3	≤0.06/4	≤0.06 — ≥16	92.6	92.6	≤0.06/0.25	≤0.06 — ≥16	72.2	72.2	≤0.06/≥16	≤0.06 — ≥16	84.9	84.9	≤0.06/≥16	≤0.06 — ≥16
Gentamicin	91.3	88.7	≤1/4	≤1 — ≥16	93.6	93.6	≤1/≤1	≤1 — ≥16	84.8	82.8	≤1/≥16	≤1 — ≥16	88.6	87.8	≤1/≥16	≤1 — ≥16
Imipenem	90.7	98.7	≤0.12/1	≤0.12 — 4	98.7	99.7	≤0.12/0.5	≤0.12 — 4	91.4	96.0	≤0.12/1	≤0.12 — 4	96.2	98.9	≤0.12/0.5	≤0.12 — ≥16
Levofloxacin	82.0	80.7	≤0.12/≥8	≤0.12 — ≥8	81.6	81.4	≤0.5/≥8	≤0.5 — ≥8	74.8	69.5	≤0.12/≥8	≤0.12 — ≥8	78.3	77.0	≤0.5/≥8	≤0.5 — ≥8
TMP-SMX[d]	74.0	74.0	≤0.5/≥8	≤0.5 — ≥8	75.9	75.9	≤0.5/≥8	≤0.5 — ≥8	61.6	61.6	≤0.5/≥8	≤0.5 — ≥8	70.8	70.8	≤0.5/≥8	≤0.5 — ≥8
E. coli			(59)				(224)				(79)				(319)	
Omadacycline	-	-	0.5/2	0.5 — 4	-	-	0.5/1	0.25 — 4	-	-	1/4	0.25 — ≥8	-	-	0.5/2	0.25 — 8
Tigecycline	100.0[b]	100.0	0.06/0.12	0.06 — 0.25	100.0[b]	100.0	0.12/0.25	0.06 — 0.5	100.0[b]	100.0	0.06/0.12	≤0.015 — 1	100.0[b]	100.0	0.12/0.25	≤0.03 — 1
Doxycycline	76.3	-	1/≥16	0.5 — ≥16	77.7	-	1/≥16	0.25 — ≥16	62.0	-	2/≥16	0.25 — ≥16	69.9	-	1/≥16	≤0.06 — ≥16
Tetracycline	74.6	-	2/≥32	0.5 — ≥32	75.9	-	1/≥16	0.5 — ≥16	59.5	-	2/≥32	0.5 — ≥32	65.5	-	2/≥16	≤0.25 — ≥16
AMX-CLV[c]	86.4	86.4	4/≥16	≤1 — ≥16	81.2	81.2	8/≥16	≤1 — ≥16	78.5	78.5	8/≥16	≤1 — ≥16	79.9	79.9	4/≥16	≤1 — ≥16
Aztreonam	88.1	86.4	≤0.12/16	≤0.12 — ≥32	92.9	92.0	≤0.12/0.5	≤0.12 — ≥32	84.8	82.3	≤0.12/16	≤0.12 — ≥32	93.1	91.2	≤0.12/0.5	≤0.12 — ≥32
Ceftazidime	91.5	89.8	0.25/4	0.06 — 32	93.3	92.4	0.12/0.5	0.03 — 32	91.1	84.8	0.25/4	0.03 — 32	94.0	91.2	0.12/0.5	0.03 — >32
Ceftriaxone	88.1	88.1	≤0.06/≥16	≤0.06 — ≥16	91.5	91.5	≤0.06/0.25	≤0.06 — ≥16	81.0	81.0	≤0.06/≥16/≥16	≤0.06 — ≥16	91.2	91.2	≤0.06/0.25	≤0.06 — ≥16
Gentamicin	88.1	86.4	≤1/≥16	≤1 — ≥16	92.4	92.4	≤1/2	≤1 — ≥16	87.3	84.8	≤1	≤1 — ≥16	92.5	92.2	≤1/2	≤1 — ≥16
Imipenem	100.0	100.0	≤0.12/≤0.12	≤0.12 — 0.5	100.0	100.0	≤0.12/≤0.12	≤0.12 — 0.5	100.0	100.0	≤0.12/≤0.12	≤0.12 — 0.25	100.0	100.0	≤0.12/≤0.12	≤0.12 — 1
Levofloxacin	79.7	79.7	≤0.12/≥8	≤0.12 — ≥8	76.3	76.3	≤0.5/≥8	≤0.5 — ≥8	69.6	69.6	≤0.12/≥8	≤0.12 — ≥8	77.0	77.0	≤0.5/≥8	≤0.5 — ≥8
TMP-SMX[d]	69.5	69.5	≤0.5/≥8	≤0.5 — ≥8	68.8	68.8	≤0.5/≥8	≤0.5 — ≥8	64.6	64.6	≤0.5/≥8	≤0.5 — ≥8	70.8	70.8	≤0.5/≥8	≤0.5 — ≥8
Klebsiella spp.			(31)[E]				(103)[F]				(29)[G]				(52)[H]	
Omadacycline	-	-	2/2	0.5 — ≥8	-	-	2/4	0.5 — 32	-	-	2/≥8	1 — ≥8	-	-	2/8	8
Tigecycline	100.0[b]	96.8	0.25/0.25	≤0.015 — 2	100.0[b]	97.1	0.25/0.5	0.06 — 2	100.0[b]	96.6	0.25/1	0.12 — 2	98.1[b]	96.2	0.25/0.5	0.5
Doxycycline	87.1	-	2/≥16	0.5 — ≥16	80.6	-	1/≥16	0.25 — ≥16	51.7	-	2/≥16	0.5 — ≥16	73.1	-	2/≥16	≥16
Tetracycline	87.1	-	1/16	0.5 — ≥32	80.6	-	1/≥16	0.5 — ≥16	62.1	-	2/≥32	0.5 — ≥32	73.1	-	2/≥16	≥16
AMX-CLV[c]	96.8	96.8	2/4	≤1 — ≥16	92.2	92.2	2/8	≤1 — ≥16	51.7	51.7	8/≥16	≤1 — ≥16	65.4	65.4	2/≥16	≥16
Aztreonam	93.5	93.5	≤0.12/0.25	≤0.12 — ≥32	95.1	93.2	≤0.12/0.25	≤0.12 — ≥32	55.2	55.2	0.25/≥32	≤0.12 — ≥32	71.2	69.2	≤0.12/≥32	≥32
Ceftazidime	93.5	93.5	0.12/0.25	0.06 — >32	97.1	94.2	0.12/0.5	0.03 — >32	65.5	58.6	0.25/>32	0.06 — >32	73.1	73.1	0.12/32	32
Ceftriaxone	93.5	93.5	≤0.06/0.12	≤0.06 — ≥16	94.2	94.2	≤0.06/0.25	≤0.06 — ≥16	51.7	51.7	0.25/≥16	≤0.06 — ≥16	71.2	71.2	≤0.06/≥16	≥16
Gentamicin	93.5	93.5	≤1/≤1	≤1 — ≥16	96.1	96.1	≤1/≤1	≤1 — ≥16	65.5	65.5	≤1/≥16	≤1 — ≥16	78.8	76.9	≤1/≥16	≥16
Imipenem	96.8	96.8	≤0.12/0.25	≤0.12 — 4	100.0	100.0	≤0.12/0.25	≤0.12 — 1	96.6	96.6	≤0.12/0.5	≤0.12 — 4	96.2	96.2	≤0.12/0.5	0.5
Levofloxacin	93.5	93.5	≤0.12/≤0.12	≤0.12 — ≥8	94.2	94.2	≤0.5/≤0.5	≤0.5 — ≥8	75.9	65.5	0.5/≥8	≤0.12 — ≥8	75.0	71.2	≤0.5/≥8	≥8
TMP-SMX[d]	80.6	80.6	≤0.5/≥8	≤0.5 — ≥8	87.4	87.4	≤0.5/≥8	≤0.5 — ≥8	44.8	44.8	≥8/≥8	≤0.5 — ≥8	73.1	73.1	≤0.5/≥8	≥8

a. Criteria as published by CLSI [2015] and EUCAST [2015].
b. Tigecycline breakpoint from FDA Package Insert (revised 12/2014) used as no CLSI breakpoint is available.
c. AMX-CLV = Amoxicillin-clavulanate.
d. TMP-SMX = Trimethoprim-sulfamethoxazole.
e. Organisms include: *Klebsiella oxytoca* (4), *K. pneumoniae* (27).
f. Organisms include: *Klebsiella oxytoca* (25), *K. pneumoniae* (78).
g. Organisms include: *Klebsiella oxytoca* (4), *K. pneumoniae* (25).
h. Organisms include: *Klebsiella oxytoca* (7), *K. pneumoniae* (45).

CONCLUSIONS

- Omadacycline was active against a wide-range of Enterobacteriaceae isolates causing UTI from North America and Europe between 2010 and 2014.
- Omadacycline was active (MIC_{90} ≤4 µg/mL) against *E. coli* regardless of ESBL status. A similar level of activity was observed with *Klebsiella* species isolated in North America (MIC_{90}, ≤4 µg/mL) however there was less activity observed in *Klebsiella* isolates from Europe in 2014 (MIC_{90}, ≥8 µg/mL). Omadacycline was least active against *Proteus/Providencia/Morganella* species.
- Further clinical study with omadacycline in the treatment of UTI caused by Enterobacteriaceae is indicated.

ACKNOWLEDGEMENT

This study and abstract presentation were funded by a research grant from Paratek Pharmaceuticals, Inc.

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