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Antimicrobial Activity of Omadacycline Tested against Clinical Bacterial Isolates Collected from Hospitals in China, including Hong Kong, and Taiwan: Results from the SENTRY Antimicrobial Surveillance Program (2013–2016)

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Abstract

Background: Omadacycline (formerly PTK 0796) is a semisynthetic derivative of minocycline and the first agent of the aminomethylcycline class. Omadacycline received fast-track status from the United States Food and Drug Administration and is in late-stage clinical development for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired pneumonia (CABP) as oral and intravenous once-daily formulations.

Methods: A total of 3,282 organisms (1/patient) were consecutively collected from patients hospitalised in China (10 centres [excluding Hong Kong]; n=2,243; 2013), Hong Kong (1 centre; n=452; 2013–2014), and Taiwan (1 centre; n=587; 2014–2016) and susceptibility tested by broth microdilution methods in a central laboratory (JMI Laboratories). The collection included aerobic gram-positive and gram-negative organisms from patients with pneumonia (n=974; 29.7%), bloodstream infections (n=826; 25.2%), skin and skin structure infections (n=772; 23.5%), community-acquired respiratory tract infections (n=555; 16.9%), and other infections (n=155; 4.7%).

Results: Omadacycline was very potent against *Staphylococcus aureus* (n=689; $MIC_{50/90}$, 0.12/0.25 mg/L), including methicillin-resistant isolates (MRSA; n=299; $MIC_{50/90}$, 0.12/0.5 mg/L), and had similar activity among geographic regions. Omadacycline was also very active against *Streptococcus pneumoniae* (highest MIC, 0.25 mg/L), β-haemolytic streptococci (BHS; highest MIC, 1 mg/L), viridans group streptococci (VGS; highest MIC, 0.25 mg/L), and *Enterococcus* spp. (highest MIC, 0.5 mg/L) from all geographic regions. Overall, 53.8% of *S. pneumoniae* were penicillin-resistant (PRSP; penicillin MIC, ≥2 mg/L) and 10.7% of enterococci (21.2% among *E. faecium*) were vancomycin-resistant (VRE). Omadacycline was active against *Haemophilus influenzae* ($MIC_{50/90}$, 0.5/1 mg/L) regardless of β-lactamase production and was active against *Moraxella catarrhalis* ($MIC_{50/90}$, ≤0.12/0.25 mg/L). When tested against *Enterobacteriaceae,* omadacycline was most active against *Escherichia coli* ($MIC_{50/90}$, 1/2 mg/L), *Klebsiella oxytoca* ($MIC_{50/90}$, 1/4 mg/L), and *Enterobacter cloacae* ($MIC_{50/90}$, 2/4 mg/L).

Conclusions: Omadacycline showed potent *in vitro* activity against gram-positive and gram-negative pathogens isolated from Greater China, and retained activity against problem pathogens, such as MRSA, VRE, and PRSP. The results of this investigation support further clinical development of omadacycline in the geographic regions surveyed.

Introduction

- Omadacycline (formerly PTK 0796) is a semisynthetic derivative of minocycline and the first agent of the aminomethylcycline class
- This compound has demonstrated *in vitro* activity against most gram-positive and gram-negative aerobic bacteria, some anaerobic bacteria, and the atypical bacteria that are commonly associated with acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP)
- Omadacycline received fast-track status by the United States Food and Drug Administration (FDA) and is in late-stage clinical development for the treatment of ABSSSI and CABP as oral and intravenous once-daily formulations
- In the present study, we evaluated the antimicrobial activities of omadacycline and comparator agents tested against 3,282 isolates of gram-positive cocci and gram-negative bacilli collected in China, including Hong Kong, and Taiwan between 2013–2016

Materials and Methods

Organism collection

- A total of 3,282 organisms were consecutively collected (1/patient) from patients hospitalised in China (10 medical centres [excluding Hong Kong]; n=2,243; 2013), Hong Kong (1 medical centre; n=452; 2013–2014), and Taiwan (1 medical centre; n=587; 2014–2016
- All organisms were isolated from patients hospitalised with pneumonia (n=974; 29.7%), bloodstream infections (n=826; 25.2%), skin and soft tissue infections (n=772; 23.5%), community-acquired respiratory tract infections (n=555; 16.9%), and other types of infections (n=155; 4.7%)
- 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 the VITEK 2 system or matrix-assisted laser desorption ionization-time of flight technology mass spectrometry, when necessary

Susceptibility testing

- Susceptibility testing was performed in frozen-form panels produced by JMI Laboratories following Clinical and Laboratory Standards Institute (CLSI) recommendations
- Quality control and results interpretation were performed in accordance with CLSI M100 and European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines
- *Escherichia coli, Klebsiella pneumoniae, K. oxytoca*, and *Proteus mirabilis* were considered screen-positive for extended-spectrum β-lactamase (ESBL) production based on the CLSI screening criteria for potential ESBL production, i.e., ceftazidime, ceftriaxone, or aztreonam MIC of ≥2 mg/L

Table 1 Antimicrobial activity of omadacycline tested against the main organisms and organism groups of isolates from all countries combined

Organism/organism group (no. of isolates)	No. of isolates at MIC (mg/L; cumulative %)												MIC_{50}	MIC_{90}
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32		
Staphylococcus aureus (689)	1 0.1	39 5.8	487 76.5	117 93.5	35 98.5	10 100.0							0.12	0.25
Methicillin-susceptible (390)	0 0.0	23 5.9	333 91.3	32 99.5	2 100.0								0.12	0.12
Methicillin-resistant (299)	1 0.3	16 5.7	154 57.2	85 85.6	33 96.7	10 100.0							0.12	0.5
Enterococcus spp. (103)	15 14.6	54 67.0	28 94.2	5 99.0	1 100.0								0.06	0.12
Vancomycin-nonsusceptible (>4 mg/L; 13)	2 15.4	9 84.6	2 100.0										0.06	0.12
Enterococcus faecalis (48)	5 10.4	19 50.0	18 87.5	5 97.9	1 100.0								0.06	0.25
Enterococcus faecium (52)	10 19.2	32 80.8	10 100.0										0.06	0.12
Streptococcus pneumoniae (392)	20 5.1	233 64.5	134 98.7	5 100.0									0.06	0.12
Penicillin-resistant oral (≥2 mg/L; 211)	6 2.8	125 62.1	77 98.6	3 100.0									0.06	0.12
Viridans group streptococci (94)	20 21.3	53 77.7	15 93.6	6 100.0									0.06	0.12
β-haemolytic streptococci (166)	0 0.0	36 21.7	76 67.5	38 90.4	14 98.8	2 100.0							0.12	0.25
Enterobacteriaceae (1,041)			0 0.0	8 0.8	137 13.9	357 48.2	277 74.8	146 88.9	47 93.4	44 97.6	21 99.6	4 100.0	2	8
Escherichia coli (425)			0 0.0	7 1.6	124 30.8	180 73.2	86 93.4	23 98.8	3 99.5	2 100.0			1	2
ESBL-phenotype (249)			0 0.0	5 2.0	70 30.1	104 71.9	50 92.0	15 98.0	3 99.2	2 100.0			1	2
Klebsiella pneumoniae (307)			0 0.0	1 0.3	11 3.9	114 41.0	91 70.7	54 88.3	20 94.8	12 98.7	3 99.7	1 100.0	2	8
ESBL-phenotype (134)				0 0.0	2 1.5	33 26.1	37 53.7	37 81.3	14 91.8	9 98.5	1 99.3	1 100.0	2	8
Klebsiella oxytoca (16)					0 0.0	10 62.5	2 75.0	3 93.8	1 100.0				1	4
Enterobacter cloacae species complex (110)					0 0.0	23 20.9	59 74.5	18 90.9	5 95.5	3 98.2	2 100.0		2	4
Ceftazidime-nonsusceptible (>4 mg/L; 52)					0 0.0	6 11.5	26 61.5	12 84.6	5 94.2	2 98.1	1 100.0		2	8
Serratia marcescens (46)						0 0.0	12 26.1	33 97.8	1 100.0				4	4
Acinetobacter baumannii (225)		0 0.0	2 0.9	24 11.6	6 14.2	1 14.7	9 18.7	90 58.7	81 94.7	7 97.8	4 99.6	1 100.0	4	8
Pseudomonas aeruginosa (300)							0 0.0	4 1.3	2 2.0	20 8.7	121 49.0	153 100.0	>32	>32
Haemophilus influenzae (181)			0 0.0	12 6.6	88 55.2	69 93.4	12 100.0						0.5	1
β-lactamase-positive (69)				0 0.0	35 50.7	29 92.8	5 100.0						0.5	1
Haemophilus parainfluenzae (7)				0 0.0	1 14.3	6 100.0							1	
Moraxella catarrhalis (75)			57 76.0	18 100.0									≤0.12	0.25

Results

- Omadacycline was very potent against *Staphylococcus aureus* ($MIC_{50/90}$, 0.12/0.25 mg/L), including methicillin-resistant isolates (MRSA; $MIC_{50/90}$, 0.12/0.5 mg/L; Table 1), and had similar activity among geographic regions (Tables 1 and 2)
- Omadacycline was also highly active against the following bacteria from all geographic regions (Tables 1 and 2)
  - *Streptococcus pneumoniae* ($MIC_{50/90}$, 0.06/0.12 mg/L)
  - β-haemolytic streptococci ($MIC_{50/90}$, 0.12/0.25 mg/L)
  - Viridans group streptococci ($MIC_{50/90}$, 0.06/0.12 mg/L)
  - *Enterococcus* spp. ($MIC_{50/90}$, 0.06/0.12 mg/L)
- The omadacycline epidemiological cutoff values (ECV; also known as ECOFF) for selected organism groups are shown in Table 3
- Omadacycline ECV 95.0%, ECV 97.5%, and ECV 99.0% for *S. aureus* were all at 0.25 mg/L and 93.5% of isolates were inhibited at these ECVs (Table 3)
- Omadacycline was highly active against penicillin-resistant *S. pneumoniae* (53.8% of isolates; where penicillin MIC, ≥2 mg/L) and against vancomycin-resistant enterococci (10.7% overall [21.2% among *E. faecium*])
- Omadacycline was active against *Haemophilus influenzae* ($MIC_{50/90}$, 0.5/1 mg/L) and *Moraxella catarrhalis* ($MIC_{50/90}$, ≤0.12/0.25 mg/L) regardless of β-lactamase production or geographic region (Tables 1 and 2)
- When tested against *Enterobacteriaceae,* omadacycline demonstrated low MIC values against *E. coli* ($MIC_{50/90}$, 1/2 mg/L), *K. oxytoca* ($MIC_{50/90}$, 1/4 mg/L), and *E. cloacae* ($MIC_{50/90}$, 2/4 mg/L); moderate activity against *K. pneumoniae* ($MIC_{50/90}$, 2/8 mg/L), *Citrobacter* spp. ($MIC_{50/90}$, 1/8 mg/L), and *Serratia marcescens* ($MIC_{50/90}$, 4/4 mg/L); and very limited activity against *P. mirabilis* ($MIC_{50/90}$, 16/32 mg/L) and indole-positive *Proteus* spp. ($MIC_{50/90}$, 8/16 mg/L), with some geographic variation (Table 2)
- Omadacycline inhibited 58.7% of 225 *Acinetobacter baumannii* isolates at ≤4 mg/L ($MIC_{50/90}$, 4/8 mg/L) and exhibited very limited *in vitro* activity against *P. aeruginosa* ($MIC_{50/90}$, >32/>32 mg/L; Tables 1 and 2); these organisms exhibited low susceptibility to most antimicrobial agents tested (data not shown)

Table 2 Omadacycline activity stratified by geographic region

Organism	Omadacycline MIC_{50}/MIC_{90} (mg/L)		
	China	Hong Kong	Taiwan
S. aureus	0.12/0.25	0.12/0.25	0.12/0.25
MSSA	0.12/0.12	0.12/0.12	0.12/0.12
MRSA	0.25/0.5	0.12/0.25	0.12/0.25
S. pneumoniae	0.06/0.12	0.06/0.12	0.06/0.12
Penicillin-S (MIC, ≤0.06 mg/L)	0.06/0.12	0.06/0.12	0.06/— [a]
Penicillin-I (MIC, 0.12-1 mg/L)	0.06/0.12	0.06/— [a]	0.06/0.12
Penicillin-R (MIC, ≥2 mg/L)	0.06/0.12	0.06/0.12	0.12/0.12
β-haemolytic streptococci	0.12/0.25	0.12/0.5	0.12/0.5
Viridans group streptococci	0.06/0.12	0.06/0.25	0.06/0.12
Enterococcus faecalis	0.06/0.25	0.12/— [a]	0.12/— [a]
Enterococcus faecium	0.06/0.12	0.06/— [a]	0.06/0.12
Vancomycin-NS (MIC, ≥8 mg/L)	0.06/— [a]	0.06/— [a]	0.06/— [a]
H. influenzae	0.5/1	1/1	0.5/1
M. catarrhalis	≤0.12/0.25	≤0.12/0.25	≤0.12/0.25
Enterobacteriaceae	1/4	2/16	2/8
E. coli	1/2	1/2	1/2
ESBL-phenotype	1/2	1/2	1/4
K. pneumoniae	2/4	2/8	2/8
ESBL-phenotype	2/8	2/— [a]	2/16
E. cloacae	2/8	2/— [a]	2/4
Citrobacter spp.	2/8	1/— [a]	1/— [a]
P. mirabilis	16/32	16/32	16/— [a]
Indole-positive *Proteus* spp.	4/16	8/— [a]	[b]
S. marcescens	4/4	4/4	4/— [a]
A. baumannii	4/8	4/32	4/8
P. aeruginosa	>32/>32	32/>32	>32/>32

Abbreviations: S, susceptible; I, intermediate; R, resistant; NS, nonsusceptible.
[a]—, fewer than 10 isolates tested.
[b]No isolate tested.

Table 3 Epidemiology cutoff values (ECV or ECOFF) for organism groups against omadacycline

Organism/organism group	ECV/ECOFF values in mg/L (cumulative % inhibited)		
	ECV 95.0% (wild type %)	ECV 97.5% (wild type %)	ECV 99.0% (wild type %)
Staphylococcus aureus (689)	0.25 (93.5%)	0.25 (93.5%)	0.25 (93.5%)
Enterococcus faecalis (48)	0.25 (97.9%)	0.25 (97.9%)	0.25 (97.9%)
Enterococcus faecium (52)	0.25 (100.0%)	0.25 (100.0%)	0.25 (100.0%)
Streptococcus pneumoniae (392)	0.25 (100.0%)	0.25 (100.0%)	0.25 (100.0%)
Viridans group streptococci (94)	0.25 (100.0%)	0.25 (100.0%)	0.25 (100.0%)
β-haemolytic streptococci (166)	0.25 (90.4%)	0.5 (98.8%)	0.5 (98.8%)
Enterobacteriaceae (1,041)	4 (88.9%)	8 (93.4%)	8 (93.4%)
Enterobacter cloacae (110)	4 (90.9%)	4 (90.9%)	8 (95.5%)
Escherichia coli (425)	2 (93.4%)	4 (98.8%)	4 (98.8%)
Klebsiella pneumoniae (307)	4 (88.3%)	8 (94.8%)	8 (94.8%)
Acinetobacter baumannii (225)	0.5 (14.2%)	0.5 (14.2%)	0.5 (14.2%)
Haemophilus influenzae (181)	4 (100.0%)	4 (100.0%)	4 (100.0%)

Conclusions

- Omadacycline showed potent *in vitro* activity against gram-positive and gram-negative pathogens isolated from Greater China and retained activity against problem pathogens, such as MRSA, VRE, and penicillin-resistant *S. pneumoniae*
- There were no discernible differences in susceptibility profiles between China, Hong Kong, and Taiwan isolates
- MIC ranges and MIC_{90} values were very similar to those found in other surveillance studies conducted recently for these pathogens in areas outside China (United States, European countries)
- The results of this investigation support further clinical development of omadacycline in the geographic regions surveyed

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