Activity of Omadacycline When Tested Against Respiratory Pathogens *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus* Isolated During 2016 From Medical Centers in the USA

Poster A6856
Abstract 5989

RK Flamm[1]; JN Steenbergen[2]; MD Huband[1]; PR Rhomberg[1]; HS Sader[1]

[1]JMI Laboratories, North Liberty, Iowa, USA; [2]Paratek Pharmaceuticals, King of Prussia, Pennsylvania, USA

ABSTRACT

Rationale: Omadacycline (oral and intravenous once daily formulations) is a broad spectrum aminomethylcycline in late-stage clinical development for community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections. It has excellent activity against respiratory tract pathogens and tetracycline-resistant organisms. The activity of omadacycline and comparator agents was tested against select respiratory tract pathogens collected in the United States during 2016.

Methods: A total of 480 *Streptococcus pneumoniae*, 306 *Haemophilus influenzae*, 195 *Moraxella catarrhalis*, and 776 *Staphylococcus aureus* (hospitalized pneumonia only) isolates were selected from patients with community-acquired respiratory and hospitalized pneumonia infections. Isolates were collected during 2016 from patients at 30 medical centers distributed across the United States; only 1 isolate per infection episode. Susceptibility testing for omadacycline and commonly used antimicrobials was performed following Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods.

Results: For all *S. aureus* isolates, the MIC_{50} and MIC_{90} for omadacycline were 0.06 and 0.12 mg/L (100.0% ≤1 mg/L). A total of 43.9% of *S. aureus* were methicillin-resistant (MRSA) and the omadacycline MIC_{50} and MIC_{90} for MRSA were 0.06 and 0.25 mg/L (83.9% ≤0.25 mg/L). Resistance was elevated for *S. aureus* for levofloxacin (39.3%), erythromycin (53.5%), and clindamycin (18.4%). Susceptibilities to vancomycin, linezolid, and tigecycline were all 100.0%. Omadacycline was highly active against *S. pneumoniae*, exhibiting an MIC_{50} and MIC_{90} at 0.06 and 0.06 mg/L (100.0% ≤0.25 mg/L), respectively. All *S. pneumoniae* isolates were susceptible to vancomycin and linezolid, 99.0% were susceptible to tigecycline, and 98.8% susceptible to levofloxacin. Resistance to erythromycin (45.6%) and tetracycline (21.5%) was high. Penicillin resistance was at 12.7% (oral breakpoints; 36.9% nonsusceptible) and at 0.2% (parenteral non-meningitis breakpoint; 4.2% nonsusceptible). For ceftriaxone, 2.3% were nonsusceptible (non-meningitis breakpoints; 14.4%, meningitis breakpoints). There were 28.1% β-lactamase-positive isolates of *H. influenzae*. Omadacycline was active against *H. influenzae* and the activity was unaffected by β-lactamase status (MIC_{50} and MIC_{90}, 0.5 and 1 mg/L for β-lactamase-positive or -negative isolates). Omadacycline was also very active against *M. catarrhalis* exhibiting an MIC_{50} and MIC_{90} at 0.12 and 0.25 mg/L, respectively. All *M. catarrhalis* isolates were susceptible to various comparators including tetracycline, ciprofloxacin, levofloxacin, ceftriaxone, and ceftazidime. Susceptibility to azithromycin and clarithromycin was 99.5% and was 96.9% to trimethoprim-sulfamethoxazole.

Conclusions: Omadacycline demonstrated potent *in vitro* activity against respiratory pathogens that include those resistant to multiple antimicrobials, such as tetracycline and the fluoroquinolones. These data indicate that omadacycline merits further study in infections where multidrug-resistant respiratory pathogens may occur.

INTRODUCTION

- Community-acquired bacterial pneumonia (CABP) continues to be a frequent infectious disease causing morbidity and mortality even though effective antibiotics and vaccines are available
- The most common pathogen in CABP is *Streptococcus pneumoniae*, and the increasing occurrence of penicillin-resistant, multidrug-resistant, and ceftriaxone–nonsusceptible *S. pneumoniae* represents a challenge for existing antibacterial agents
- Omadacycline is the first of the novel class of aminomethylcyclines, and its mechanism of action is binding to the 30S ribosomal subunit in gram-positive and gram-negative bacteria, thereby inhibiting protein synthesis
- Omadacycline has excellent activity against gram-positive and gram–negative pathogens, including tetracycline-resistant organisms
- Omadacycline has been shown to be non-inferior to linezolid in a phase 3 study of acute bacterial skin and skin structure infections (ABSSSI) treatment and is in phase 3 development for treatment of ABSSSI and CABP
- In the present study, we evaluated the *in vitro* activity of omadacycline and comparator agents tested by Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution methods against *S. pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus* isolates collected during 2016 from patients at 30 medical centers distributed across the United States

MATERIALS AND METHODS

- A total of 480 *S. pneumoniae*, 306 *H. influenzae*, 195 *M. catarrhalis*, and 776 *S. aureus* (hospitalized pneumonia only) isolates were selected from patients with community-acquired respiratory and hospitalized pneumonia infections. Isolates were collected from approximately 30 medical centers across the US during 2016
- Broth microdilution tests conducted according to the Clinical and Laboratory Standards Institute (CLSI) documents were performed to determine antimicrobial susceptibility of omadacycline and numerous comparator antimicrobials
- The broth medium used for testing isolates was cation-adjusted Mueller Hinton broth for *S. aureus* and *M. catarrhalis*
- *S. pneumoniae* isolates were tested in cation-adjusted Mueller Hinton broth supplemented with 2.5-5% lysed horse blood
- *H. influenzae* isolates were tested in *Haemophilus* test medium
- *S. aureus* ATCC 29213, *S. pneumoniae* ATCC 49619, and *H. influenzae* ATCC 49247 and 49766 were concurrently tested for quality control (QC)
- Interpretation of susceptibility was based on the CLSI guidelines
- 1,757 respiratory isolates (480 *S. pneumoniae*, 306 *H. influenzae*, 195 *M. catarrhalis*, and 776 *S. aureus*) were selected for evaluation from 30 medical centers in the United States during 2016

RESULTS

Table 1. Summary of omadacycline *in vitro* activity against pathogens isolated from respiratory infections from US medical centers (2016)

		No. of isolates (cumulative %) inhibited at MIC (mg/L) of									MIC (mg/L)	
Organism	Drug	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	≥4	50%	90%
S. pneumoniae (480)	Omadacycline	10 (2.1)	94 (21.7)	338 (92.1)	36 (99.6)	2 (100.0)					0.06	0.06
	Tetracycline					282 (58.8)[a]	91 (77.7)	3 (78.3)	1 (78.5)	103 (100.0)	≤0.25	≥4
	Erythromycin	13 (2.7)	182 (40.6)	56 (52.3)	2 (52.7)	5 (53.8)	3 (54.4)	10 (56.5)	16 (59.8)	193 (100.0)	0.06	≥4
S. aureus (776)	Omadacycline	1 (0.1)	35 (4.6)	431 (60.2)	235 (90.5)	39 (95.5)	21 (98.2)	14 (100.0)			0.06	0.12
	Tetracycline						705 (90.9)[b]	18 (93.2)	14 (95.0)	39 (100.0)	≤0.5	≤0.5
	Erythromycin	0 (0)	0 (0)	6 (0.8)	194 (25.8)	97 (38.3)	1 (38.4)	4 (38.9)	31 (42.9)	443 (100.0)	≥4	≥4
H. influenzae (306)	Omadacycline	0 (0)	0 (0)	0 (0)	0 (0)	8 (2.6)	153 (52.6)	125 (93.5)	19 (99.7)	1 (100.0)	0.5	1
M. catarrhalis (195)	Omadacycline	0 (0)	0 (0)	13 (6.7)	145 (81.0)	37 (100.0)					0.12	0.25

[a] Lowest dilution tested was 0.25 mg/L.
[b] Lowest dilution tested was 0.5 mg/L.

RESULTS

Table 2. Comparison of *in vitro* activity of omadacycline and other selected antimicrobial agents tested against *S. pneumoniae* and *S. aureus* isolates from respiratory tract infections in the US (2016)

	MIC (mg/L)		CLSI	
Antimicrobial agent (no. tested)	MIC_{50}	MIC_{90}	%S	%R
Streptococcus pneumoniae (480)				
Omadacycline	0.06	0.06		
Tigecycline	0.03	0.06	99.0	- [b]
Tetracycline	≤0.25	>8	78.3	21.5
Ceftaroline	≤0.008	0.12	100.0	-
Ceftriaxone	0.03	1	97.7	0.6[c]
Penicillin	0.015	2	63.1 95.8	12.7[d] 0.2[e]
Amoxicillin-clavulanic acid	≤0.03	2	94.6	1.9
Erythromycin	0.06	>32	53.8	45.6
Clindamycin	≤0.25	>2	85.6	14.2
Levofloxacin	1	1	98.8	1.0
Linezolid	1	2	100.0	-
Trimethoprim-sulfamethoxazole	0.25	>4	73.8	15.1
Vancomycin	0.25	0.25	100.0	-
Penicillin-nonsusceptible (MIC, ≥4 mg/L; 20)				
Omadacycline	0.06	0.06		
Tigecycline	0.06	0.06	95.0	- [b]
Tetracycline	>8	>8	0.0	100.0
Ceftaroline	0.12	0.25	100.0	-
Ceftriaxone	1	>2	50.0	15.0[c]
Penicillin	4	4	0.0 0.0	100.0[d] 5.0[e]
Amoxicillin-clavulanic acid	4	>4	15.0	45.0
Erythromycin	>32	>32	0.0	100.0
Clindamycin	>2	>2	15.0	85.0
Levofloxacin	1	1	100.0	0.0
Linezolid	0.5	1	100.0	-
Trimethoprim-sulfamethoxazole	>4	>4	0.0	95.0
Vancomycin	0.25	0.25	100.0	-
Ceftriaxone-nonsusceptible (MIC, ≥2 mg/L; 11)				
Omadacycline	0.06	0.06		
Tigecycline	0.03	0.06	90.9	- [b]
Tetracycline	>8	>8	9.1	90.9
Ceftaroline	0.25	0.5	100.0	-
Ceftriaxone	2	>2	0.0	27.3[c]
Penicillin	4	4	0.0 9.1	100.0[d] 9.1[e]
Amoxicillin-clavulanic acid	>4	>4	9.1	54.5
Erythromycin	>32	>32	0.0	100.0
Clindamycin	>2	>2	18.2	81.8
Levofloxacin	1	1	100.0	0.0
Linezolid	0.5	1	100.0	-
Vancomycin	0.25	0.25	100.0	-
Trimethoprim-sulfamethoxazole	>4	>4	0.0	100.0
Staphylococcus aureus (776)				
Omadacycline	0.06	0.12		
Tigecycline	0.06	0.12	100.0	- [b]
Tetracycline	≤0.5	≤0.5	95.9	3.4
Oxacillin	0.5	>2	56.1	43.9
Ceftaroline	0.25	1	98.2	0.0
Erythromycin	>8	>8	38.4	53.5
Clindamycin	≤0.25	>2	80.9	18.4
Levofloxacin	0.25	>4	59.3	39.3
Linezolid	1	1	100.0	0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	97.9	2.1
Vancomycin	0.5	1	100.0	0.0
MRSA (341)				
Omadacycline	0.06	0.25		
Tigecycline	0.06	0.12	100.0	- [b]
Tetracycline	≤0.5	1	95.3	3.8
Ceftaroline	0.5	1	95.9	0.0
Erythromycin	>8	>8	9.1	83.6
Clindamycin	≤0.25	>2	64.8	34.3
Levofloxacin	>4	>4	19.4	78.6
Linezolid	1	1	100.0	0.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	95.6	4.4
Vancomycin	0.5	1	100.0	0.0

[a] Criteria as published by the CLSI (2017).
[b] US FDA breakpoints were applied [Tygacil Product Insert, 2010].
[c] Using non-meningitis breakpoints.
[d] Using oral breakpoints.
[e] Using parenteral non-meningitis breakpoints.

RESULTS

S. pneumoniae

- Omadacycline was highly active against *S. pneumoniae* isolates ($MIC_{50/90}$, 0.06/0.06 mg/L; **Table 1**)
- All isolates were susceptible to ceftaroline
- Ceftriaxone susceptibility was 97.7% (50.0% against penicillin-nonsusceptible isolates)
- Omadacycline $MIC_{50/90}$ for isolates with a penicillin MIC ≥4 mg/L were 0.06/0.06 mg/L, respectively
- The highest omadacycline MIC value was 0.25 mg/L
- Omadacycline $MIC_{50/90}$ for isolates that were nonsusceptible to ceftriaxone (MIC≥2 mg/L) were also 0.06/0.06 mg/L, respectively (**Table 2**)
- There were high rates of resistance among *S. pneumoniae* for erythromycin (45.6%) and tetracycline (21.5%)

S. aureus

- Omadacycline was highly active against *S. aureus*, exhibiting an $MIC_{50/90}$ at 0.06/0.12 mg/L (**Table 1**)
- For MRSA, the $MIC_{50/90}$ for omadacycline was 0.06/0.25 mg/L (**Table 2**)
- Ceftaroline susceptibly for all *S. aureus* was 98.2% and 95.9% for MRSA (**Table 2**)

Table 3 Comparison of *in vitro* activity of omadacycline and selected antimicrobial agents tested against *Haemophilus influenzae* and *Moraxella catarrhalis* isolates from respiratory tract infections in the US (2016)

Antimicrobial agent (no. tested)	MIC_{50}	MIC_{90}	CLSI[a] %S	CLSI[a] %R
H. influenzae (306)				
Omadacycline	0.5	1		
Tigecycline	0.12	0.25	97.1	- [b]
Tetracycline	0.5	0.5	99.7	0.3
Ceftaroline	0.008	0.03	99.7	-
Ceftriaxone	0.004	0.015	100.0	-
Amoxicillin-clavulanic acid	0.5	2	99.3	0.7
Azithromycin	0.5	1	99.0	-
Levofloxacin	0.015	0.03	100.0	-
Trimethoprim-sulfamethoxazole	0.12	>4	69.3	28.8
Moraxella catarrhalis (195)				
Omadacycline	0.12	0.25		
Tigecycline	0.06	0.06		
Tetracycline	0.25	0.5	100.0	0.0
Ceftaroline	0.06	0.25		
Ceftriaxone	0.25	0.5	100.0	-
Amoxicillin-clavulanic acid	0.12	0.25	100.0	0.0
Azithromycin	0.015	0.015	99.5	-
Levofloxacin	0.03	0.06	100.0	-
Trimethoprim-sulfamethoxazole	0.12	0.25	96.9	0.0

[a] Criteria as published by CLSI [2017].
[b] US FDA breakpoints applied [Tygacil Product Insert, 2010].

H. influenzae

- Omadacycline had potent activity against *H. influenzae* (28.1% β-lactamase-positive) with an MIC_{90} value at 1 mg/L for *H. influenzae*
- The $MIC_{50/90}$ for both β-lactamase-positive and β-lactamase-negative isolates were the same ($MIC_{50/90}$; 0.5/1 mg/L; data not shown)
- There was little tetracycline resistance (0.3%) (**Table 3**)
- The agent demonstrating the highest level of resistance among *H. influenzae* was trimethoprim-sulfamethoxazole (28.8%)

M. catarrhalis

- All agents were very active against *M. catarrhalis* (**Table 3**); the omadacycline $MIC_{50/90}$ values were 0.12/0.25 mg/L

CONCLUSIONS

- Omadacycline demonstrated potent activity against *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and *S. aureus* and its activity was unaffected by penicillin or tetracycline susceptibility patterns
- Omadacycline, which is undergoing clinical development for acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia, exhibited activity against key bacterial respiratory pathogens and merits continued study in this clinical indication

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DISCLOSURES

RK Flamm, MD Huband, PR Rhomberg, and HS Sader are an employees of JMI Laboratories. Paratek Pharmaceuticals provided funding support to JMI Laboratories for the study and preparation of this abstract/poster.

JN Steenbergen is an employee of Paratek Pharmaceuticals.

ACKNOWLEDGMENTS

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

Presented at: 113th Annual Conference of the American Thoracic Society; May 19-24, 2017; Washington, DC.