

Abstract

Background: Omadacycline (OMC) is the first aminomethylcycline antibiotic under development for use as a once daily oral and IV treatment in skin and soft tissue and respiratory infections. Omadacycline is currently in Phase 3 clinical development for acute bacterial skin and skin structure infections. This study compares spectrum of activity studies of OMC performed in 2003, 2007 and 2015. **Materials and Methods:** All three studies used the Clinical and Laboratory Standards Institute (CLSI) frozen broth microdilution (BMD) methods described in the M7 and M45 documents current at the time of testing. MIC panels were prepared using fresh broth (<12 hrs old) and frozen at -70° C until use. Clinical isolates used for each of these studies were < 3 years old at the time of testing for >80% of the total isolates tested in each study. **Results:** MIC_{50-90s} and range of MICs are listed in Table 1.

Spectrum of Activity of Omadacycline from 2003 to 2015

ORGANISM GROUP	2003 SURVEY		2007 SURVEY		2015 SURVEY	
	MIC _{50/90}	MIC Range	MIC _{50/90}	MIC Range	MIC _{50/90}	MIC Range
All Enterococci	0.12/0.25	0.03-0.5	0.12/0.25	0.06-0.5	0.12/0.25	0.03-1
<i>E. faecalis</i>	0.12/0.25	0.06-0.5	0.25/0.25	0.06-0.5	0.12/0.12	0.03-0.5
<i>E. faecium</i>	0.12/0.12	0.03-0.25	0.12/0.12	0.06-0.5	0.12/0.12	0.03-1
All <i>Staphylococcus aureus</i>	0.25/0.25	0.06-4	0.25/0.25	0.12-0.5	0.25/0.25	0.06-2
<i>S. aureus</i> oxacillin susceptible	0.25/0.25	0.06-0.25	0.25/0.25	0.06-0.5	0.12/0.25	0.06-1
<i>S. aureus</i> oxacillin resistant	0.25/0.25	0.06-4	0.25/0.25	0.12-0.5	0.25/0.25	0.06-2
<i>Moraxella catarrhalis</i>	0.25/0.25	0.25	0.25/0.25	0.25-0.5	0.12/0.25	0.12-0.5
All <i>Escherichia coli</i>	1/2	0.5-4	2/4	0.12-8	1/4	0.25-8
<i>Klebsiella pneumoniae</i>	2/8	2-8	2/8	0.5-32	2/8	0.5->16
β-hemolytic streptococci	0.12/0.12	0.06-0.5	0.12/0.12	0.12-0.25	0.06/0.12	0.03-0.25
<i>Streptococcus pneumoniae</i>	0.06/0.12	0.015-0.25	0.12/0.12	0.06-0.25	0.06/0.06	0.015-0.12
<i>Haemophilus influenzae</i>	0.5/2	0.25-4	0.5/1	0.25-1	1/1	0.5-1

All MIC values listed are in µg/mL

Conclusions: The activity of OMC has remained stable from 2003 through 2015. OMC had good activity against *Enterococcus faecium*, *Enterococcus faecalis*, *Staphylococcus aureus*, β-hemolytic streptococci, *Streptococcus pneumoniae* and *Moraxella catarrhalis* with MIC_{50s} ranging from 0.06 to 0.25 µg/ml and MIC_{90s} from 0.06 to 0.25. *Haemophilus influenzae* had slightly higher MIC_{50s} which ranged from 0.5 to 1 µg/ml and MIC_{90s} from 1 to 2. OMC MIC_{50s} vs. *Escherichia coli* ranged from 1 to 2 µg/ml and MIC_{90s} from 2-4 µg/ml. *Klebsiella pneumoniae* MIC_{50s} were 2 µg/ml and MIC_{90s} were 8 µg/ml.

Background

Omadacycline is the first aminomethylcycline to enter clinical development. OMC is being developed globally as an intravenous and oral, once daily monotherapy therapy for ABSSSI and CABP. OMC was designed to overcome tetracycline resistance mechanisms and has been shown to have potent in vitro activity and in vivo efficacy against the key pathogens of ABSSSI and CABP, including isolates resistant to standards of care. The IV and oral formulations are bioequivalent and neither shown the dose-limiting nausea and vomiting exhibited by other tetracycline derivatives.

Acknowledgement

This study was sponsored by a grant from Paratek Pharmaceuticals

Materials and Methods

- Spectrum of activity studies for omadacycline were performed in 2003, 2007 and 2015 using the CLSI reference broth microdilution methods ^{1,2}.
- Clinical isolates tested were <3 years old at the time of testing for >80% of the total isolates for each study.
- Known stock isolates were also tested in order to include a variety of resistance mechanisms.
- All Mueller Hinton broth lots were <12 hrs old at the time the panels were prepared and frozen at -70 degrees C.
- Test organisms included *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *Streptococcus agalactiae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Escherichia coli* and *Klebsiella pneumoniae*.

Results and Conclusions

- The activity of OMC has remained stable from 2003 through 2015
- OMC had good activity against *Enterococcus faecium*, *Enterococcus faecalis*, *Staphylococcus aureus*, β-hemolytic streptococci, *Streptococcus pneumoniae* and *Moraxella catarrhalis* with MIC_{50s} ranging from 0.06 to 0.25 µg/ml
- Haemophilus influenzae* had slightly higher MIC_{50s} which ranged from 0.5 to 1 µg/ml and MIC_{90s} from 1 to 2.
- OMC MIC_{50s} vs. *Escherichia coli* ranged from 1 to 2 µg/ml and MIC_{90s} from 2-4 µg/ml.
- Klebsiella pneumoniae* MIC_{50s} were 2 µg/ml and MIC_{90s} were 8 µg/ml.

References

- Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard-Sixth, Seventh, and Tenth Editions, M07-A6, M07-A7 and M07-A10. January 2003, 2006 and 2015, Clinical Laboratory Standards Institute, Wayne PA.
- Performance Standards for Antimicrobial Susceptibility Testing; Thirteenth, Seventeenth and Twenty Fifth Informational Supplements, M100-S13, M100-S17 and M100-S25 January 2003, 2007 and 2015, Clinical Laboratory Standards Institute, Wayne, PA.

Table 1. Omadacycline MIC Distributions 2003 to 2015

Species	2003 Study			2007 study		2015 Study		
	MIC (mg/ml)	MIC Frequency	Cumulative % Inhibited	MIC Frequency	Cumulative % Inhibited	MIC Frequency	Cumulative % Inhibited	
All Enterococci	0.016							
	0.03	1	0.4%			1	1%	
	0.06	40	15.8%	22	7%	26	26%	
	0.12	178	84.6%	201	72%	50	73%	
	0.25	39	99.6%	71	95%	19	91%	
	0.5	1	100.0%	16	100%	9	100%	
	1					1	100.0%	
	2							
Totals	259	100.0%	310	100%	253	100.0%		
Species	MIC (mg/ml)	MIC Frequency	Cumulative % Inhibited	MIC Frequency	Cumulative % Inhibited	MIC Frequency	Cumulative % Inhibited	
All <i>S. aureus</i>	0.03							
	0.06	2	1.2%	1	1%	4	2.8%	
	0.12	39	25.0%	40	24%	61	45.8%	
	0.25	114	94.5%	114	92%	70	95.1%	
	0.5	3	96.3%	12	99%	1	95.8%	
	1	4	98.8%	1	100%	3	97.9%	
	2		98.8%			2	99.3%	
	4	2	100.0%			1	100.0%	
	>4							
	Totals	164	100.0%	168	100%	142	100.0%	
Species	MIC	MIC	Cumulative	MIC	Cumulative	MIC	Cumulative	
<i>Moraxella catarrhalis</i>	0.12							
	0.25	10	100.0%	97	92%	44	86.3%	
	0.5			7	99%	6	98.0%	
	1			1	100%	1	100.0%	
	Totals	10	100.0%	105	100%	51	100.0%	
	Species	MIC (mg/ml)	MIC Frequency	Cumulative % Inhibited	MIC Frequency	Cumulative % Inhibited	MIC Frequency	Cumulative % Inhibited
	<i>E. coli</i>	0.12			2	1.0%		
0.25						1	0.9%	
0.5		9	42.9%	12	6.9%	33	31.5%	
1		4	61.9%	79	45.8%	35	63.9%	
2		6	90.5%	74	82.3%	21	83.3%	
4		2	100.0%	34	99.0%	17	99.1%	
>4				2	100.0%	1	100.0%	
Totals		21	100.0%	203	100.0%	108	100.0%	
Species	MIC (mg/ml)	MIC Frequency	Cumulative % Inhibited	MIC Frequency	Cumulative % Inhibited	MIC Frequency	Cumulative % Inhibited	
<i>K. pneumoniae</i>	0.25							
	0.5			3	1.5%	2	1.6%	
	1			35	18.6%	13	11.6%	
	2	12	60.0%	100	67.6%	63	60.5%	
	4	3	75.0%	35	84.8%	28	82.2%	
	>4	5	100.0%	23	96.1%	14	93.0%	
	>8			6	99.0%	4	96.1%	
	>16			2	100.0%	5	100.0%	
	Totals	20	100.0%	204	100.0%	129	100.0%	
	Species	MIC (mg/ml)	MIC Frequency	Cumulative % Inhibited	MIC Frequency	Cumulative % Inhibited	MIC Frequency	Cumulative % Inhibited
Beta-Hemolytic Streptococci	0.03			1	0.3%	9	8.8%	
	0.06	23	44.2%	5	1.9%	47	54.9%	
	0.12	24	90.3%	293	95.2%	42	96.1%	
	0.25	4	98.1%	11	98.7%	4	100.0%	
	0.5	1	100.0%	4	100%			
	1							
Totals	52	100.0%	314	100%	102	100.0%		
Species	MIC (mg/ml)	MIC Frequency	Cumulative % Inhibited	MIC Frequency	Cumulative % Inhibited	MIC Frequency	Cumulative % Inhibited	
<i>S. pneumoniae</i>	0.016	1	0.9%			1	1.1%	
	0.03	8	8.4%			19	21.5%	
	0.06	79	82.2%	5	4.8%	70	96.8%	
	0.12	18	99.1%	98	99.0%	3	100.0%	
	0.25	1	100.0%	1	100%			
	0.5							
	Totals	107	100.0%	104	100%	93	100.0%	
Species	MIC (mg/ml)	MIC Frequency	Cumulative % Inhibited	MIC Frequency	Cumulative % Inhibited	MIC Frequency	Cumulative % Inhibited	
<i>H. influenzae</i>	0.12							
	0.25	3	4.5%	1	1.0%	2	1.8%	
	0.5	38	62.1%	58	56.2%	38	36.4%	
	1	20	92.4%	36	90.5%	46	78.2%	
	2	4	98.5%	10	100.0%	22	98.2%	
	4	1	100.0%			2	100.0%	
	>4							
	Totals	66	100.0%	105	100.0%	110	100.0%	

Table 2. Omadacycline vs. Comparators MIC Data 2015

Species	N	Drug	Minimum	Maximum	MIC50	MIC90
All <i>Enterococcus</i> species	253	Omadacycline MIC	0.03	1	0.12	0.25
	253	Tigecycline MIC	0.03	1	0.06	0.12
	253	Levofloxacin MIC	0.25	8	8	8
	253	Doxycycline MIC	0.06	32	8	16
	253	Amoxicillin/Clavulanate MIC	0.12	32	0.5	32
	253	Linezolid MIC	1	8	2	2
253	Vancomycin MIC	0.5	16	2	16	
Species	N	Drug	Minimum	Maximum	MIC50	MIC90
All <i>S. aureus</i>	142	Omadacycline MIC	0.06	2	0.25	0.25
	142	Tigecycline MIC	0.06	0.5	0.12	0.12
	142	Levofloxacin MIC	0.06	8	8	8
	142	Doxycycline MIC	0.06	8	0.12	1
	142	Ceftriaxone MIC	2.00	16	8	16
	142	Cefuroxime MIC	0.12	2	0.5	1
	142	Azithromycin MIC	0.5	8	8	8
	142	Linezolid MIC	1	4	2	2
142	Vancomycin MIC	0.5	16	0.5	1	
142	Clindamycin MIC	0.25	8	0.25	8	
Species	N	Drug	Minimum	Maximum	MIC50	MIC90
<i>M. catarrhalis</i>	51	Omadacycline MIC	0.12	0.5	0.12	0.25
	51	Tigecycline MIC	0.03	0.12	0.06	0.06
	51	Levofloxacin MIC	0.008	0.06	0.03	0.06
	51	Doxycycline MIC	0.12	0.5	0.12	0.12
	51	Ceftriaxone MIC	0.03	2	0.5	1
	51	Amoxicillin/Clavulanate MIC	0.12	0.5	0.25	0.25
	51	Azithromycin MIC	0.06	4	0.06	0.06
51	Clindamycin MIC	1	8	2	4	
Species	N	Drug	Minimum	Maximum	MIC50	MIC90
All <i>E. coli</i>	108	Omadacycline MIC	0.25	8	1	4
	108	Tigecycline MIC	0.06	0.5	0.12	0.25
	108	Levofloxacin MIC	0.03	8	4	8
	108	Doxycycline MIC	0.5	32	2	32
	108	Ceftriaxone MIC	0.03	16	16	16
	108	Cefuroxime MIC	0.03	8	8	8
	108	Cefepime MIC	0.03	8	8	8
	108	Amoxicillin/Clavulanate MIC	2	32	8	16
Species	N	Drug	Minimum	Maximum	MIC50	MIC90
All <i>K. pneumoniae</i>	129	Omadacycline MIC	0.5	32	2	8
	129	Tigecycline MIC	0.12	8	0.5	1
	129	Levofloxacin MIC	0.03	8	0.12	8
	129	Doxycycline MIC	0.5	32	2	32
	129	Ceftriaxone MIC	0.03	16	0.5	16
	129	Cefuroxime MIC	0.03	8	2	8
	129	Amoxicillin/Clavulanate MIC	0.5	32	4	32
Species	N	Drug	Minimum	Maximum	MIC50	MIC90
All β-Hemolytic Streptococci	102	Omadacycline MIC	0.03	0.25	0.06	0.12
	102	Tigecycline MIC	0.015	0.12	0.06	0.06
	102	Levofloxacin MIC	0.25	1	0.5	1
	102	Doxycycline MIC	0.03	16	0.25	16
	102	Ceftriaxone MIC	0.015	0.25	0.03	0.06
	102	Cefuroxime MIC	0.008	8	0.03	0.25
	102	Azithromycin MIC	0.03	8	0.25	8
102	Clindamycin MIC	0.25	8	0.25	8	
102	Penicillin MIC	0.03	0.06	0.03	0.06	
Species	N	Drug	Minimum	Maximum	MIC50	MIC90
<i>S. agalactiae</i> (51) <i>S. pyogenes</i> (51)	93	Omadacycline MIC	0.015	0.12	0.06	0.06
	93	Tigecycline MIC	0.015	0.06	0.03	0.06
	93	Levofloxacin MIC	0.5	8		