P1322

Bactericidal activity of omadacycline, a novel aminomethylcycline

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REVISED ABSTRACT

Background: Omadacycline (OMC) is the first of a new class of tetracyclines, the aminomethylcyclines, and is being developed as a once-daily oral and IV treatment for acute bacterial skin and skin structure infection (ABSSSI) and community-acquired bacterial pneumonia (CABP). The objective of the present study was to evaluate the bactericidal activity of OMC compared with other antibacterial agents. **Materials/methods**: Minimal inhibitory concentrations (MICs) and minimal bactericidal concentrations (MBCs) were determined against 85 bacterial isolates following CLSI guidelines. A subset of isolates was further investigated with time-kill studies (TK), where bactericidal activity was defined as a 3-log reduction in viable count (99.9% kill) over 24 hours. **Results**: OMC showed low MICs against the test isolates, including antibiotic-resistant strains. MBC data indicated bactericidal activity against streptococci, *M. catarrhalis,* and *H. influenzae* but bacteriostatic activity against enterococci, *S. aureus,* and *E. coli.* TK studies generally confirmed the MBC data with omadacycline being rapidly bactericidal against *H. influenzae* and *S. pneumoniae*. Bactericidal activity was species and strain dependent, and time to achieve 99.9% killing for these isolates varied between 3.1 to 20.4 hours. **Conclusion**: Omadacycline demonstrated good activity against the pathogens tested with particularly strong bactericidal activity against *H. influenzae, M. catarrhalis,* and *S. pneumoniae*. The spectrum and rapidity of the bactericidal activity of omadacycline was comparable to tigecycline. The inhibitory and bactericidal activity of omadacycline was not affected by resistance to other antimicrobials.

INTRODUCTION

Paratek Pharmaceuticals is developing the aminomethylcycline antibiotic omadacycline (OMC), as a once-daily oral and IV therapy for serious community-acquired infections. Omadacycline is currently in Phase 3 clinical development for acute bacterial skin and skin structure infections (ABSSSI) and for moderate to severe community-acquired bacterial pneumonia (CABP). In this study we investigated the bactericidal activity of omadacycline *in vitro* against bacterial pathogens involved in CABP and ABSSSI, including resistant isolates.

METHODS

- Minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC), and time-kill kinetics (TKK) were performed in line with CLSI susceptibility testing standards methodology (1, 2, 3).
- MICs were determined against 85 isolates (see Table 1) by broth microdilution methodology (final volume 100 µL).
- For MBCs the number of colony forming unit (CFU) was determined in each well of the MIC microtiter plate containing antibiotic concentration greater or equal to the MIC.
- Prior to performing TKK, MICs were determined using macrobroth dilution methodology in line with CLSI standards (1, 2). The test volume was 10 ml with shaking (200 rpm) to emulate the conditions used in the time-kill experiments.
- TKK were performed in presence of antibiotic concentration equal to 4x and 16x MIC by determination of CFU of samples taken at time 0, 2, 4, 6 and 24 hours.
- Bactericidal activity was defined by at least 99.9% of killing, i.e ≥3 log reduction of the initial inoculum.

RESULTS

- Omadacycline showed very good inhibitory activity against the majority of pathogens tested. The most potent activity was against *M. catarrhalis*, *S. aureus*, *S. pneumoniae*, *S. pyogenes,* and enterococci with MIC_{90} range of 0.12 - 0.25 mg/L (Table 2).
- MBC data showed bactericidal activity of omadacycline against *M. catarrhalis*, *H. influenzae*, *S. pneumoniae*, and *S. pyogenes* (Table 3).
- Omadacycline displayed a rapid bactericidal activity against *H. influenzae* and *S. pneumoniae* in TKK experiments at concentrations equal to 4x MIC, although the rapidity of killing was isolate dependent (Tables 3-4, Figures 1- 4) and a slow bactericidal activity against *M. catarrhalis* at concentration equal to 16x MIC (Tables 3 -4, Figure 5 - 6).
- Omadacycline did not display bactericidal activity against *S. pyogenes* in time-kill experiments contradictory to MBC data (Table 2-3). This discrepancy could be due to the difference in methodology between MBC and TKK.
- Omadacycline was bacteriostatic against enterococci, *S. aureus,* and most *E.coli* isolates (Tables 3 - 4).

Table 1: Isolates Tested

Species	Phenotype	Isolates tested for MIC and MBC	Isolates tested for TKK
E. coli	ESBL-negative	6	1
	ESBL-positive	7	1
M. catarrhalis	-	10	2
H. influenzae	-	11	2
S. aureus	MSSA	7	1
	CA-MRSA	7	1
S. pyogenes		12	2
S. pneumoniae	PEN-S	6	1
	PEN-R	5	1
E. faecalis	-	7	0
E. faecium	-	7	0
Total		85	12

PEN-S, penicillin susceptible; PEN-R, penicillin resistant; ESBL, extended spectrum beta-lactamase; MSSA, methicillin susceptible *S. aureus*; CA-MRSA, community-acquired methicillin resistant *S. aureus*

The quality control organisms *E. coli* ATCC 25922, *H. influenzae* ATCC 49247, *S. aureus* ATCC 29213, *S. pneumoniae* ATCC 49619, and *E. faecalis* ATCC 29212 were also tested.

Table 2. Summary of MIC data for omadacycline and comparators against 85 isolates.

	MIC_{50}/MIC_{90} (mg/L)					
Species (number of isolates)	OMC	TIG	DOX	TSX	AZI	LZD
S. pneumoniae (n=11)	0.03/0.12	0.06/0.25	0.12/4	2/8	0.12/>32	0.5/2
S. pyogenes (n=12)	0.06/0.12	0.06/0.12	0.12/0.25	0.12/0.25	0.06/0.06	1/1
M. catarrhalis (n=10)	0.12/0.25	0.12/0.12	0.12/0.25	0.12/0.25	0.03/0.03	NT
H. influenzae (n=11)	1/1	0.25/0.5	0.5/1	2/8	1/2	NT
E. coli (n=13)	2/4	0.25/0.5	8/64	64/>64	NT	NT
Enterococci (n=14)	0.12/0.25	0.12/0.12	8/16	32/64	>32/>32	1/2
S. aureus (n=14)	0.25/0.25	0.25/0.25	0.12/0.12	≤0.03/0.12	1/>32	2/2

OMC, omadacycline; DOX, doxycycline; TIG, tigecycline; TSX, trimethoprim-sulfamethoxazole; LZD, linezolid; AZI, azithromycin; NT, not tested.

Table 3. Summary of MBC data for omadacycline and comparators against 85 isolates.

	MBC_{50}/MBC_{90} (mg/L)					
Species (number of isolates)	OMC	TIG	DOX	TSX	AZI	LZD
S. pneumoniae (n=11)	0.06/0.25	0.12/0.5	0.25/16	2/16	2/>32	2/8
S. pyogenes (n=12)	0.25/2	0.12/1	2/8	0.12/1	0.25/1	4/16
M. catarrhalis (n=10)	2/8	1/4	1/16	0.5/2	0.03/0.06	4/16
H. influenzae (n=11)	4/16	2/16	32/64	8/32	8/32	NT
E. coli (n=13)	>16/>16	>16/>16	64/>64	>64/>64	NT	NT
Enterococci (n=14)	>16/>16	>16/>16	>64/>64	>64/>64	>32/>32	NT
S. aureus (n=14)	16/>16	2/>16	16/32	0.06/8	>32/>32	64/128

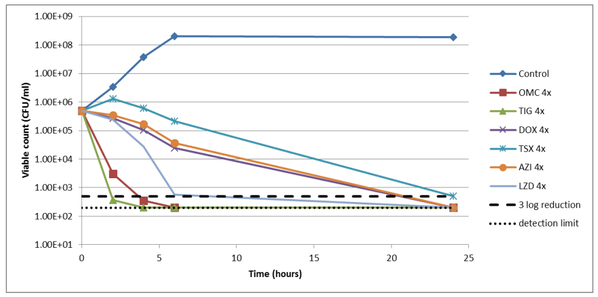
OMC, omadacycline; DOX, doxycycline; TIG, tigecycline; TSX, trimethoprim-sulfamethoxazole; LZD, linezolid; AZI, azithromycin; NT, not tested.

Table 4. Summary of time-kill data for omadacycline and comparators against 12 isolates.

	Time to kill 99.9% (3 log) 4xMIC/16xMIC (h)					
Isolate (resistance phenotype)	OMC	TIG	DOX	TSX	AZI	LZD
S. pneumoniae 925168 (PEN-S)	3.7/3.1	1.9/1.8	20.5/5.4	24/21.2	21/3.8	8.3/3.7
S. pneumoniae 927009 (PEN-R)	21.5/20.3	18.4/12	22/21.6	20.1/21.9	21/19.4	22/21
S. pyogenes 921737	--/--[a]	--/--[a]	--/--[a]	--/--[a]	--/--[a]	--/--[a]
S. pyogenes 938918	--/--[a]	--/--[a]	--/--[a]	--/--[a]	--/--[a]	--/--[a]
M. catarrhalis 943604	--/--[a]	--/--[a]	--/--[a]	--/--[a]	--[a] /5.7	NT/NT
M. catarrhalis 953887	--[a] /20.4	--[a] /20.1	--[a] /22.6	--/--[a]	20.7/19.2	NT/NT
H. influenzae 977279	13.9/11.7	12.2/9.5	21.6/14.9	20.4/--[a]	7.8/3.4	NT/NT
H. influenzae 1030791	3.7/3.3	2.6/1.4	3.4/3.3	12/13	1.4/1.4	NT/NT
E. coli 1133865 (ESBL-)	5.9/3.1	--/--[a]	1.6/1.6	NT/NT	NT/NT	NT/NT
E. coli 1070142 (ESBL+)	--/--[a]	--/--[a]	--/--[a]	20.9/20.8	--/--[a]	NT/NT
S. aureus 928751 (MSSA)	--/--[a]	--/--[a]	--/--[a]	18/17.5	--/--[a]	--/--[a]
S. aureus 1018391(CA-MRSA)	--/--[a]	--/--[a]	--/--[a]	15.1/13	--/--[a]	--/--[a]

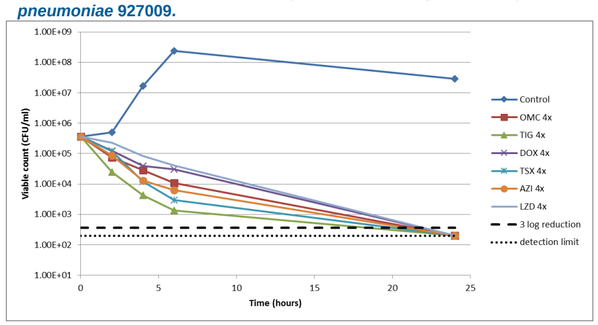
OMC, omadacycline; DOX, doxycycline; TIG, tigecycline; TSX, trimethoprim-sulfamethoxazole; LZD, linezolid; AZI, azithromycin; NT, not tested; [a]--Not Achieved; PEN-S, penicillin susceptible; PEN-R, penicillin resistant; ESBL, extended spectrum beta-lactamase; MSSA, Methicillin susceptible *S. aureus*; CA-MRSA, community-acquired methicillin resistant *S. aureus*.

Figure 1. Time-kill of omadacycline and comparators against *S. pneumoniae* 925168.



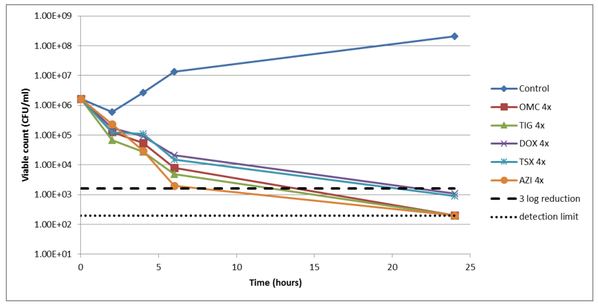
OMC, omadacycline; DOX, doxycycline; TIG, tigecycline; TSX, trimethoprim-sulfamethoxazole; LZD, linezolid; AZI, azithromycin.

Figure 2. Time-kill of omadacycline and comparators against *S. pneumoniae* 927009.



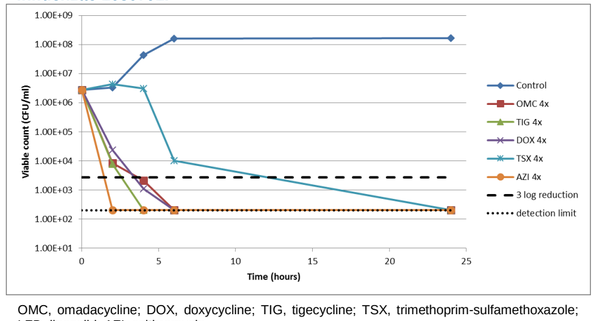
OMC, omadacycline; DOX, doxycycline; TIG, tigecycline; TSX, trimethoprim-sulfamethoxazole; LZD, linezolid; AZI, azithromycin.

Figure 3. Time-kill of omadacycline and comparators against *H. influenzae* 977279.



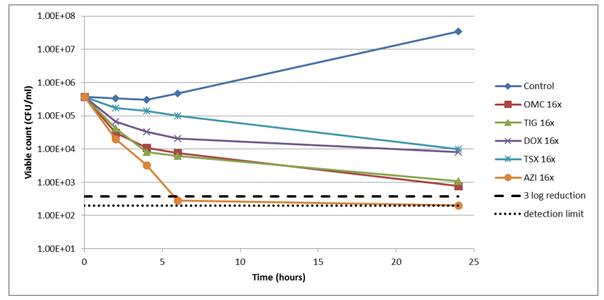
OMC, omadacycline; DOX, doxycycline; TIG, tigecycline; TSX, trimethoprim-sulfamethoxazole; LZD, linezolid; AZI, azithromycin.

Figure 4. Time-kill of omadacycline and comparators against *H. influenzae* 1030791.



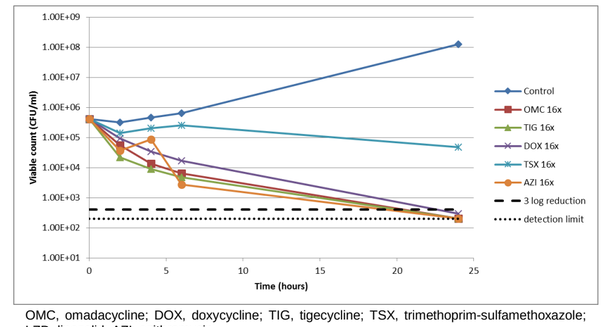
OMC, omadacycline; DOX, doxycycline; TIG, tigecycline; TSX, trimethoprim-sulfamethoxazole; LZD, linezolid; AZI, azithromycin.

Figure 5. Time-kill of omadacycline and comparators against *M. catarrhalis* 943604.



OMC, omadacycline; DOX, doxycycline; TIG, tigecycline; TSX, trimethoprim-sulfamethoxazole; LZD, linezolid; AZI, azithromycin.

Figure 6. Time-kill of omadacycline and comparators against *M. catarrhalis* 953887.



OMC, omadacycline; DOX, doxycycline; TIG, tigecycline; TSX, trimethoprim-sulfamethoxazole; LZD, linezolid; AZI, azithromycin.

CONCLUSION

- Omadacycline was bactericidal against *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* and bacteriostatic against enterococci, *S. aureus*, and most *E. coli* isolates.
- The extent and rapidity of the bactericidal activity of omadacycline was comparable to tigecycline and doxycycline.
- The inhibitory and bactericidal activity of omadacycline was not affected by other phenotypes of resistance included in this study.

References and Acknowledgment

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