The In Vitro Activity of Omadacycline and Comparators Against Anaerobic Bacteria

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P-1264

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ABSTRACT

Background: A diverse array of anaerobic bacteria exist as part of the normal human microflora. Most anaerobic infections occur upon disruption of this commensal relationship with the host, and involve a comparatively less diverse group of organisms. Omadacycline (OMC), a broad spectrum aminomethylcycline under development for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community acquired bacterial pneumonia (CABP), has shown efficacy clinically in ABSSSI including anaerobes and in animal models of intra-abdominal infections due to anaerobes. In this study, the in vitro activity of omadacycline and comparators against clinically relevant anaerobes is reported.

Methods: Overall, 186 non-duplicate clinical isolates consisting of *Bacteroides* spp. (*B. fragilis*, *B. thetaiotaomicron*, *B. vulgatus*, *B. ovatus*), *Clostridium* spp. (*C. difficile*, *C. perfringens*), *Peptostreptococcus* spp. (*P. micros*, *P. anaerobius*), *Prevotella* spp. (*P. bivia*, *P. melaninogenica*, *P. disiens*, *P. denticola*), and *Porphyromonas asaccharolytica* were evaluated. Susceptibility to omadacycline (OMC), tigecycline (TGC), meropenem (MEM), moxifloxacin (MXF), clindamycin (CLI), metronidazole (MTZ), and piperacillin-tazobactam (P/T) was determined by broth microdilution (*Bacteroides* spp.) and agar dilution (non-*Bacteroides*) testing in accordance with guidelines from the Clinical and Laboratory Standards Institute (CLSI M11-A8 and M100-S26).

Results: Minimum inhibitory concentration (MIC) values for OMC and comparators were within quality control limits throughout testing. As shown in the Table below, both OMC and TGC had similar activity by $MIC_{50/90}$ values (mg/L). With the exception of *C. perfringens*, isolates were highly susceptible (S) to TGC (based on current FDA interpretive criteria).

Organism (n)	OMC $MIC_{50/90}$	TGC $MIC_{50/90}$	TGC (%S / I / R)
B. fragilis (21)	0.5/4	0.5/2	95.2 / 4.8 / 0.0
B. thetaiotaomicron (21)	1/4	1/8	85.7 / 9.5 / 4.8
B. vulgatus (21)	0.12/1	0.25/1	100 / 0.0 / 0.0
B. ovatus (15)	0.5/8	0.5/8	86.6 / 6.7 / 6.7
Prevotella spp. (22)	0.5/2	1/4	95.5 / 0.0 / 4.5
P. asaccharolytica (21)	0.25/0.5	0.25/0.5	100 / 0.0 / 0.0
C. difficile (21)	0.25/0.5	0.25/0.25	100 / 0.0 / 0.0
C. perfringens (22)	4/16	8/>16	40.9 / 9.1 / 50.0
Peptostreptococcus spp. (22)	0.12/1	0.12/2	100 / 0.0 / 0.0

The evaluated isolates were highly susceptible to P/T (100% across species) and MEM (>95% across species). MTZ was also highly active with >90%S across species, including *B. fragilis* (81.0%S), *B. ovatus* (80.0%S), and *Peptostreptococcus* spp. (77.3%S). The %S of MXF and CLI did not exceed 90% for any evaluated species, and in the majority of instances was below 75%.

Conclusions: OMC had potent in vitro activity against both Gram-negative and -positive anaerobes commonly isolated from human infections. This activity was similar to that observed with TGC, a glycylcycline, which is indicated for the treatment of anaerobes in skin and intra-abdominal infections. The demonstrated *in vitro* activity taken together with the previously established *in vivo* efficacy in animal models of anaerobic infection highlight the potential of OMC for the treatment of human infections involving anaerobes.

BACKGROUND

- Anaerobic bacteria are ubiquitous in nature and are primary components of the human microflora associated with the mucous membranes[1,2].
- Anaerobic infections span a variety of syndromes typically due to disruption of the mucous membrane barrier at or near the site of infection, are frequently polymicrobial, and most commonly result in abscess formation[1,2].
- Tetracyclines, β-lactams w/ β-lactamase inhibitors, metronidazole, chloramphenicol, clindamycin, carbapenems, and select fluoroquinolones have been used in the treatment of anaerobic infections[1,2].
- Omadacycline (OMC) is an aminomethylcycline currently undergoing phase 3 clinical development by Paratek Pharmaceuticals as a once daily oral or IV treatment of community acquired skin and respiratory infections.
- OMC has shown clinical efficacy in skin infections involving anaerobes[3] and in animal models of intra-abdominal infections due to anaerobes[4].

PURPOSE

To evaluate the in vitro potency of omadacycline, tigecycline, and other comparators against clinically relevant anaerobes.

METHODS

- Anaerobic test isolates (N=186; **Tables 1-3**) consisted of randomly selected, non-duplicate, human clinical isolates with the exception of 9 *P. asaccharolytica* isolates which were of veterinary origin.
- ATCC quality control isolates *B. fragilis* ATCC 25285, *B. thetaiotaomicron* ATCC 29741, and *C. difficile* ATCC 700057 were included during testing.
- Antibiotics tested included OMC, tigecycline (TGC), meropenem (MEM), moxifloxacin (MXF), clindamycin (CLI), metronidazole (MTZ), and piperacillin-tazobactam (P/T).
- MICs were determined by broth microdilution (*Bacteroides* spp. only) and agar dilution in accordance with Clinical and Laboratory Standards Institute (CLSI) guideline M7-A8[5] and M100-S26[6] using freshly prepared supplemented brucella broth and agar.
- MIC values interpreted as susceptible (S), intermediate (I), or resistant (R) in accordance with CLSI M100-S26[6] with the exception of TGC where FDA interpretive criteria were applied[7].

RESULTS

Table 1. Activity of omadacycline and comparators against *Bacteroides* spp.

Organism (no. of isolates)	Drug	MIC range	MIC_{50}	MIC_{90}	%S	%I	%R
B. fragilis (21)	OMC	0.25 - 16	0.5	4	-	-	-
	TGC	0.5 - 8	0.5	2	95.2	4.8	0
	MEM	0.12 - 4	0.25	1	100	0	0
	MXF	0.12 - 16	1	8	71.4	14.3	14.3
	CLI	0.06 - >32	1	>32	71.4	0	28.6
	MTZ	0.25 - >32	1	>32	81	0	19
	P/T	0.12 - 8	1	4	100	0	0
B. thetaiotaomicron (21)	OMC	0.12 - 16	1	4	-	-	-
	TGC	0.25 - 16	1	8	85.7	9.5	4.8
	MEM	0.12 - 8	0.25	2	95.2	4.8	0
	MXF	1 - >16	2	>16	52.3	4.8	42.9
	CLI	0.25 - >32	4	>32	38.1	19	42.9
	MTZ	0.25 - >32	1	2	90.5	0	9.5
	P/T	1 - 16	8	16	100	0	0
B. vulgatus (21)	OMC	0.06 - 2	0.12	1	-	-	-
	TGC	0.12 - 2	0.25	1	100	0	0
	MEM	0.12 - 2	0.25	0.5	100	0	0
	MXF	0.25 - >16	1	16	61.9	4.8	33.3
	CLI	≤0.03 - >32	1	>32	57.1	0	42.9
	MTZ	0.12 - >32	1	2	95.2	0	4.8
	P/T	0.25 - >16	4	8	100	0	0
B. ovatus (15)	OMC	0.06 - >16	0.5	8	-	-	-
	TGC	0.03 - >16	0.5	8	86.6	6.7	6.7
	MEM	≤0.015 - 4	0.25	2	100	0	0
	MXF	1 - >16	2	>16	53.3	6.7	40
	CLI	≤0.03 - >32	8	>32	40	6.7	53.3
	MTZ	0.12 - >32	1	>32	80	0	20
	P/T	≤0.015 - 16	4	8	100	0	0

Table 2. Activity of omadacycline and comparators against Gram-negative bacilli (non-*Bacteroides* spp.)

Organism (no. of isolates)	Drug	MIC range	MIC_{50}	MIC_{90}	%S	%I	%R
Prevotella spp.[1] (22)	OMC	0.12 - 8	0.5	2	-	-	-
	TGC	0.06 - 16	1	4	95.5	0	4.5
	MEM	0.03 - 1	0.12	0.5	100	0	0
	MXF	0.5 - >16	1	>16	63.6	22.8	13.6
	CLI	0.06 - >32	2	>32	51	4.5	44.5
	MTZ	0.25 - >32	1	8	95.5	0	4.5
	P/T	≤0.06 - 32	≤0.06	4	100	0	0
P. asaccharolytica (21)	OMC	0.06 - 2	0.25	0.5	-	-	-
	TGC	0.03 - 1	0.25	0.5	100	0	0
	MEM	≤0.015 - 0.3	0.03	0.12	100	0	0
	MXF	0.12 - >16	0.25	16	85.7	0	14.3
	CLI	0.02 - >32	0.5	>32	80.9	4.8	14.3
	MTZ	0.06 - >32	0.5	2	90.5	0	9.5
	P/T	≤0.06 - 0.5	≤0.06	0.25	100	0	0

[1] *Prevotella* spp. include 9 *P. bivia*, 8 *P. melaninogenica*, 2 *P. disiens*, and 1 *P. denticola*

Table 3. Activity of omadacycline and comparators against Gram-positive spore-forming bacilli and cocci

Organism (no. of isolates)	Drug	MIC range	MIC_{50}	MIC_{90}	%S	%I	%R
C. difficile (21)	OMC	0.25 - 8	0.25	0.5	-	-	-
	TGC	0.25 - 4	0.25	0.25	100	0	0
	MEM	0.5 - 4	2	2	100	0	0
	MXF	1 - >16	2	>16	61.9	0	38.1
	CLI	4 - >32	8	>32	0	38.1	61.9
	MTZ	0.25 - 8	0.5	1	100	0	0
	P/T	4 - 16	8	16	100	0	0
C. perfringens (22)	OMC	0.12 - 16	4	16	-	-	-
	TGC	0.25 - >16	8	>16	40.9	9.1	50
	MEM	≤0.015 - 8	0.015	1	95.5	4.5	0
	MXF	0.5 - >16	0.5	4	86.4	4.5	9.1
	CLI	0.06 - >32	2	>32	72.8	4.5	22.7
	MTZ	0.5 - >32	1	4	90.9	0	9.1
	P/T	≤0.06 - 32	0.5	16	100	0	0
Peptostreptococcus spp.[1] (22)	OMC	0.06 - 2	0.12	1	-	-	-
	TGC	0.06 - 4	0.12	2	100	0	0
	MEM	≤0.015 - 16	0.25	0.5	95.5	0	4.5
	MXF	0.25 - >16	0.5	8	77.2	0	22.8
	CLI	0.06 - >32	0.5	>32	63.7	4.5	31.8
	MTZ	0.12 - >32	0.5	>32	77.3	0	22.7
	P/T	≤0.06 - 32	0.25	2	100	0	0

[1] *Peptostreptococcus* spp. include 11 *P. micros* and 11 *P. anaerobius*

- MIC values for QC isolates were within established quality control ranges for all drugs.
- Omadacycline had potent activity by $MIC_{50/90}$ against Gram-negative anaerobes (**Table 1 and 2**).
- Against Gram-positive anaerobes (**Table 3**), omadacycline also had potent activity by $MIC_{50/90}$ against *C. difficile* and *Peptostreptococcus* spp. but was less active against *C. perfringens*.
- Omadacycline activity was similar to tigecycline both by $MIC_{50/90}$ with values identical or within 2-fold and overlapping MIC distribution (**Figures 1 and 2**).
- Among the evaluated comparators, all isolates were susceptible to piperacillin/tazobactam and nearly all isolate were susceptible to meropenem and tigecycline (excluding *C. perfringens* for tigecycline; 40.9%S) (**Tables 1-3**).
- MTZ was also highly active with >90%S across species excluding *B. fragilis* (81%S), *B. ovatus* (80%S), and *Peptostreptococcus* spp. (77.3%S) (**Tables 1-3**).
- Susceptibility to both CLI and MXF did not exceed 90% and in most instances was below 75% (**Tables 1-3**).

Figure 1. MIC distribution of omadacycline and tigecycline against Gram-negative bacilli: (A) *B. fragilis*, (B) *Bacteroides* spp. (non-*fragilis*), and (C) non-*Bacteroides* spp.

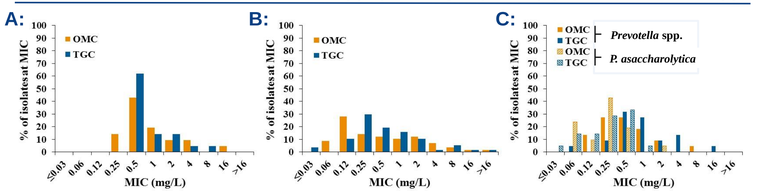
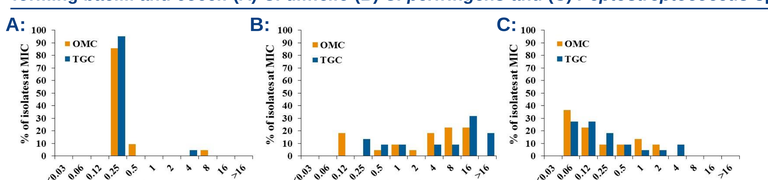


Figure 2. MIC distribution of omadacycline and tigecycline against Gram-positive spore-forming bacilli and cocci: (A) *C. difficile* (B) *C. perfringens* and (C) *Peptostreptococcus* spp.



CONCLUSIONS

- Omadacycline had potent activity *in vitro* against Gram-negative and -positive anaerobes commonly isolated from human infections.
- The potency of omadacycline against anaerobes was similar to that observed with tigecycline, an agent indicated for the treatment of anaerobes in skin and intra-abdominal infections[7], both by $MIC_{50/90}$ and MIC distribution.
- The *in vitro* activity of omadacycline against anaerobic pathogens along with the *in vivo* efficacy against anaerobes in animal models of anaerobic infection and in human skin infections highlight the potential of omadacycline for the treatment of human anaerobic infections.

Acknowledgements

The authors would like to acknowledge the Sponsor (Paratek Pharmaceuticals) for funding the study described herein.

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