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SUSCEPTIBILITY

Comparative *In Vitro* Activity of Omadacycline against Dog and Cat Bite Wound Isolates

Ellie J. C. Goldstein,[a,b] Diane M. Citron,[a] Kerin L. Tyrrell,[a] Eliza Leoncio,[a] C. Vreni Merriam[a]

[a]R. M. Alden Research Lab, Culver City, California, USA

[b]David Geffen School of Medicine at UCLA, Los Angeles, California, USA

ABSTRACT Omadacycline was tested against 125 isolates recovered from infected cat and dog bites in humans. Its activity was similar to that of other compounds in the tetracycline class, and it was active against strains exhibiting tetracycline resistance. Against anaerobic isolates, resistance to tetracyclines was more prominent and omadacycline was the most active of the group. All isolates had omadacycline MICs of <1 μg/ml, with the exception of *Eikenella corrodens*, which showed reduced susceptibility to the entire tetracycline group.

KEYWORDS *Bacteroides pyogenes*, *Eikenella corrodens*, *Pasteurella*, *Prevotella heparinolytica*, bite wounds, cellulitis, omadacycline, tetracyclines

It is estimated that between 2015 and 2016, approximately 65% (79.7 million) of U.S. households owned a total of 163.5 million dogs and cats (1). Therefore, it is not surprising that more than 5 million Americans each year sustain an animal bite, most often by a dog or cat, leading to approximately 10,000 hospitalizations and 1% (300,000) of all emergency department visits annually (2). These bite wounds are usually polymicrobial, harboring a broad combination of aerobic and anaerobic microorganisms (3, 4). Clinicians select agents to cover this range of organisms, and amoxicillin-clavulanate has been an empirical agent of choice; however, approximately 20% of patients report a penicillin allergy and require alternative therapies.

Omadacycline is a new aminomethylcycline antibiotic under development for acute bacterial skin and skin structure infections (5, 6). To overcome both efflux and ribosomal protection tetracycline resistances, omadacycline was designed with modifications of the C7 and C9 positions of the core structure (5). It has *in vitro* activity against aerobic Gram-positive cocci, including methicillin-resistant *Staphylococcus aureus*, members of the family *Enterobacteriaceae*, and some anaerobes (5). To evaluate omadacycline's potential in the treatment of bite wound infections, we performed a comparative *in vitro* study of its activity against 116 aerobic and 126 anaerobic bite pathogens.

Results. Tables 1 and 2 show the MICs (range, MIC_{50}, and MIC_{90}) for the isolates tested. All aerobic isolates had omadacycline MICs that were $\leq$0.5 μg/ml, with the exception of *Eikenella corrodens*, which had an MIC_{90} of 16 μg/ml and showed reduced susceptibility to the entire tetracycline group studied. All of the anaerobes tested had omadacycline MICs of $\leq$1 μg/ml. Tetracycline and minocycline had good activity against all of the aerobes and some of the anaerobes, but both showed limited activity against *Prevotella heparinolytica* and other *Prevotella* species tested. The MICs for the quality control (QC) strains were within acceptable ranges.

Omadacycline shows excellent *in vitro* activity against the full spectrum of organisms recovered from dog and cat bites in humans and should prove useful for the treatment of bite wound infections.

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Address correspondence to Ellie J. C. Goldstein, ejcgmd@aol.com.

TABLE 1 Comparative MICs of omadacycline and comparator agents tested against aerobic dog and cat bite isolates[a]

Organism (no. of isolates) and drug	MIC range	MIC_{50}	MIC_{90}
Bergeyella zoohelcum (11)			
Omadacycline	≤0.015–0.25	0.06	0.125
Tigecycline	≤0.015–0.125	0.06	0.06
Tetracycline	0.125–0.5	0.25	0.25
Minocycline	0.03–0.06	0.03	0.06
Amoxicillin-clavulanate	≤0.015–0.125	0.03	0.06
Neisseria weaveri (11)			
Omadacycline	0.125–0.5	0.25	0.25
Tigecycline	0.03–0.06	0.06	0.06
Tetracycline	0.06–0.25	0.125	0.25
Minocycline	0.03–0.125	0.06	0.125
Amoxicillin-clavulanate	0.03–0.5	0.25	0.25
Neisseria zoodegmatis (11)			
Omadacycline	0.125–0.5	0.25	0.5
Tigecycline	0.03–0.125	0.06	0.06
Tetracycline	0.06–0.25	0.125	0.125
Minocycline	0.03–0.125	0.06	0.06
Amoxicillin-clavulanate	0.03–0.5	0.25	0.25
Pasteurella canis (10)			
Omadacycline	0.125–0.25	0.25	0.25
Tigecycline	0.03–0.06	0.06	0.06
Tetracycline	0.125–0.25	0.125	0.25
Minocycline	0.06–0.125	0.06	0.125
Amoxicillin-clavulanate	0.06–0.25	0.125	0.125
Pasteurella multocida subsp. *multocida* (11)			
Omadacycline	0.125–0.25	0.25	0.25
Tigecycline	0.03–0.03	0.03	0.03
Tetracycline	0.06–8	0.125	0.25
Minocycline	0.06–0.125	0.06	0.125
Amoxicillin-clavulanate	0.06–0.25	0.25	0.25
Pasteurella multocida subsp. *septica* (10)			
Omadacycline	0.125–0.25	0.25	0.25
Tigecycline	0.03–0.06	0.06	0.06
Tetracycline	0.125–0.25	0.125	0.25
Minocycline	0.03–0.125	0.06	0.06
Amoxicillin-clavulanate	0.125–0.25	0.25	0.25
Staphylococcus pseudintermedius (9)			
Omadacycline	0.125–0.125	0.125	
Tigecycline	0.06–.06	0.06	
Tetracycline	0.125–32	0.125	
Minocycline	0.03–4	0.03	
Amoxicillin-clavulanate	0.06–2	0.06	

[a]Values are in micrograms per milliliter.

Methods. Organisms were tested by standard methods as described by the Clinical and Laboratory Standards Institute (7, 8, 9). Many isolates were recently recovered from infected dog and cat bite wounds in humans, although some of the unusual species were older and stored as pure cultures in 20% skim milk at −70°C. They were taken from the freezer and subcultured onto blood agar plates at least twice for purity and good growth. Fastidious aerobic organisms were tested by broth microdilution. Anaerobic and microaerophilic fastidious organisms (*Eikenella*) were tested by agar dilution.

Broth microdilution for aerobic organisms. For aerobic organisms, Mueller-Hinton broth supplemented with 5% lysed horse blood was used for testing. The antimicrobial agents were reconstituted in accordance with the manufacturer's instructions or guidelines published in CLSI document M100. Stock solutions were prepared and stored at −70°C, and serial 2-fold dilutions were prepared on the day of plate preparation. The

TABLE 2 Comparative MICs of omadacycline and comparator agents tested against anaerobic dog and cart bite isolates[a]

Organism (no. of isolates) and drug	MIC range	MIC_{50}	MIC_{90}
Bacteroides pyogenes (10)			
Omadacycline	0.06–0.25	0.25	0.25
Tigecycline	0.125–0.5	0.25	0.5
Tetracycline	0.25–16	0.25	16
Minocycline	≤0.03–2	≤0.03	2
Amoxicillin-clavulanate	0.06–1	0.06	1
Eikenella corrodens (10)			
Omadacycline	4–16	8	16
Tigecycline	2–8	4	8
Tetracycline	2–4	4	4
Minocycline	0.5–4	1	2
Amoxicillin-clavulanate	1–2	2	2
Fusobacterium sp. (10)[b]			
Omadacycline	0.25–1	0.25	0.25
Tigecycline	≤0.03–0.125	0.06	0.125
Tetracycline	0.06–0.5	0.125	0.5
Minocycline	≤0.03–0.125	≤0.03	0.125
Amoxicillin-clavulanate	0.125–4	0.125	2
Porphyromonas sp. (12)[c]			
Omadacycline	0.06–0.5	0.06	0.06
Tigecycline	≤0.03–0.25	≤0.03	≤0.03
Tetracycline	0.06–0.125	0.06	0.125
Minocycline	≤0.03–≤0.03	≤0.03	≤0.03
Amoxicillin-clavulanate	≤0.03–0.5	≤0.03	0.125
Prevotella heparinolytica (10)			
Omadacycline	0.125–0.125	0.125	0.125
Tigecycline	0.06–0.125	0.06	0.125
Tetracycline	0.06–8	0.125	8
Minocycline	≤0.03–4	≤0.03	4
Amoxicillin-clavulanate	0.125–0.5	0.25	0.5
Prevotella sp. (10)[d]			
Omadacycline	0.125–1	0.25	0.25
Tigecycline	≤0.03–1	0.25	0.25
Tetracycline	0.06–16	0.25	16
Minocycline	≤0.03–8	≤0.03	4
Amoxicillin-clavulanate	0.06–1	0.125	1

[a]Values are in micrograms per milliliter.
[b]*Fusobacterium canifelinum* ($n = 5$) and *F. nucleatum* ($n = 5$).
[c]*P. cangingivalis* ($n = 2$), *P. canoris* ($n = 2$), *P. cansulci* ($n = 2$), *P. circumdentaria* ($n = 1$), *P. gingivalis* ($n = 2$), *P. gulae* ($n = 2$), and *P. macaccae* ($n = 1$).
[d]*P. bivia* ($n = 2$), *P. denticola* ($n = 1$), *P. intermedia/nigrescens* ($n = 1$), *P. loescheii* ($n = 1$), *P. melaninogenica* ($n = 1$), *P. enoeca* ($n = 1$), *Prevotella* species ($n = 1$), and *P. zoogleoformans* ($n = 2$).

Quick-Spense apparatus was used to dispense 100-μl volumes of the dilutions into 96-well microtiter trays, which were immediately placed into the −70°C freezer for storage. On the day of the test, they were removed from the freezer and thawed at room temperature. Aerobic strains were suspended in saline to equal a 0.5 McFarland standard, further diluted 1:30 in saline, and added to the trays with a 96-prong inoculation device that delivered ~10 μl to each well for a final concentration of approximately 5×10^4 CFU/well. The plates were incubated in an ambient atmosphere at 35°C for 20 h.

Agar dilution for anaerobes. Serial 2-fold dilutions of the antimicrobials were prepared and added to molten brucella agar deeps for preparation of the plates. Drug-free plates were included as growth controls.

Organisms. On the day of testing, organisms were suspended in brucella broth to equal the turbidity of a 0.5 McFarland standard and applied to the plates with a Steers replication device that delivers ~2 to 5 μl per spot for a final concentration of

approximately 10^5 CFU/spot. The plates were incubated in the anaerobic chamber at 36°C for 44 h and examined for growth. The MIC was defined as the lowest concentration of antimicrobial agent that completely inhibited growth or resulted in a major reduction of growth compared to the drug-free control. The QC organisms included *S. aureus* ATCC 29213, *Escherichia coli* ATCC 25922, and *Bacteroides fragilis* ATCC 25285.

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