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In Vitro and *In Vivo* Antibacterial Activities of Omadacycline, a Novel Aminomethylcycline

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Omadacycline is the first intravenous and oral 9-aminomethylcycline in clinical development for use against multiple infectious diseases including acute bacterial skin and skin structure infections (ABSSSI), community-acquired bacterial pneumonia (CABP), and urinary tract infections (UTI). The comparative *in vitro* activity of omadacycline was determined against a broad panel of Gram-positive clinical isolates, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), Lancefield groups A and B beta-hemolytic streptococci, penicillin-resistant *Streptococcus pneumoniae* (PRSP), and *Haemophilus influenzae* (*H. influenzae*). The omadacycline MIC_{90}s for MRSA, VRE, and beta-hemolytic streptococci were 1.0 μg/ml, 0.25 μg/ml, and 0.5 μg/ml, respectively, and the omadacycline MIC_{90}s for PRSP and *H. influenzae* were 0.25 μg/ml and 2.0 μg/ml, respectively. Omadacycline was active against organisms demonstrating the two major mechanisms of resistance, ribosomal protection and active tetracycline efflux. *In vivo* efficacy of omadacycline was demonstrated using an intraperitoneal infection model in mice. A single intravenous dose of omadacycline exhibited efficacy against *Streptococcus pneumoniae*, *Escherichia coli*, and *Staphylococcus aureus*, including *tet*(M) and *tet*(K) efflux-containing strains and MRSA strains. The 50% effective doses (ED_{50}s) for *Streptococcus pneumoniae* obtained ranged from 0.45 mg/kg to 3.39 mg/kg, the ED_{50}s for *Staphylococcus aureus* obtained ranged from 0.30 mg/kg to 1.74 mg/kg, and the ED_{50} for *Escherichia coli* was 2.02 mg/kg. These results demonstrate potent *in vivo* efficacy including activity against strains containing common resistance determinants. Omadacycline demonstrated *in vitro* activity against a broad range of Gram-positive and select Gram-negative pathogens, including resistance determinant-containing strains, and this activity translated to potent efficacy *in vivo*.

Widespread resistance to antibiotics, including resistance to the older tetracyclines (tetracycline, doxycycline, and minocycline), has limited their usefulness in recent years (1, 2). New tetracycline derivatives that inhibit resistant organisms have been approved or are in development, including the glycylcyclines and specifically tigecycline, and fluorocyclines, including eravacycline (TP-434), and both tigecycline and eravacycline have potent Gram-positive and Gram-negative *in vitro* activity (3–6). The discovery of the 9-aminomethyl class of tetracyclines has led to the identification of omadacycline (PTK 0796) that is poised to begin phase 3 clinical trials in acute bacterial skin and skin structure infections (ABSSSI), community-acquired (CA) bacterial pneumonia (CABP), and urinary tract infections (UTI) with both an intravenous (i.v.) and oral tablet formulation. Omadacycline, (4*S*,4a*S*,5a*R*,12a*S*)-4,7-bis(dimethylamino)-9{[(2,2-dimethylpropyl)amino]methyl}-3,10,12,12a-tetrahydroxy-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide, contains a four-ring carbocyclic skeleton and is a semisynthetic compound prepared by chemical modification of minocycline (Fig. 1) (7, 8).

Omadacycline is distinct from older tetracyclines because it demonstrates *in vitro* activity against a relatively broad spectrum of organisms, including Gram-positive, Gram-negative, anaerobic, and atypical pathogens, and demonstrates similar *in vitro* activity against pathogens that express not only tetracycline resistance but resistance to other antibiotics, including methicillin, vancomycin, erythromycin, and ciprofloxacin (9–20). This broad *in vitro* activity has been confirmed in various *in vivo* models of infection (21–24). Omadacycline is bioavailable in humans by both oral and intravenous routes and does not demonstrate significant gastrointestinal side effects (25–28). The targeted indications encompass acute bacterial infections where a broad-spectrum antibiotic with activity against the most prevalent community-acquired multidrug-resistant organisms is desired. This report is the initial description of the *in vitro* spectrum and *in vivo* efficacy of omadacycline. The *in vitro* activity of omadacycline translates into potent *in vivo* efficacy in a lethal infection model, suggesting that the pharmacodynamic requirements necessary for human clinical trial investigation can be achieved.

MATERIALS AND METHODS

Bacterial strains. Routine clinical isolates were obtained from the following sources: Children's Hospital, Boston, MA; Channing Laboratories, Boston, MA; Clinical Microbiology Institute, Wilsonville, OR; Glaxo Smith Kline, Collegeville, PA; Tufts Medical Center, Boston, MA; University of California at Los Angeles Medical Center, Los Angeles, CA; University of Wisconsin Hospitals and Clinics, Madison, WI. For testing, isolates were chosen randomly so that all sites would be represented. All isolates were stored frozen at −80°C in tryptic soy broth or Mueller-Hinton broth (Northeast Laboratories, Waterville, ME) plus 20% glycerol (Becton, Dickinson, Sparks MD). Horse or sheep blood supplementation was used for fastidious organisms. Isolates were subcultured twice onto appropriate solid medium (tryptic soy agar with 5% sheep blood or chocolate agar; Becton, Dickinson, Sparks MD) prior to MIC testing. Quality-control isolates were obtained from the American Type Culture Collection (ATCC, Manassas, VA).

For the *in vivo* experiments, the bacterial strains *Streptococcus pneumoniae* 700905 and *Staphylococcus aureus* 29213 and the clinical isolate *S.*

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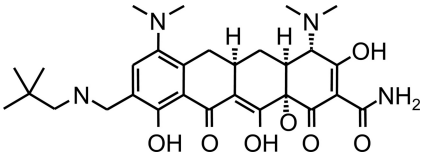

FIG 1 Chemical structure of omadacycline.

aureus USA300 were obtained from the American Type Culture Collection (ATCC 700905, ATCC 29213, and CA USA300 FPR3757/ATCCBAA 1556, respectively) (ATCC, Manassas, VA). Tetracycline-sensitive *S. pneumoniae* PBS1339 (GSK1629) was obtained from GlaxoSmithKline, Philadelphia, PA. *S. pneumoniae* 157E-2 was derived from passing *S. pneumoniae* 157E (originally called GSK157E and obtained from GlaxoSmithKline) twice through mice. *S. aureus* USA400 is a clinical isolate (CA USA400 REF 571) obtained from Paul Fey, University of Nebraska Medical Center, Omaha, NE. *S. aureus* MRSA5 (where MRSA is methicillin-resistant *S. aureus*) was obtained from the University of Maryland, College Park, MD. *Escherichia coli* PBS1478 (also referred to as SC8294) was originally obtained from Bristol Meyers Squibb, Fort Devens, MA.

Antibiotics and *in vitro* susceptibility testing. Omadacycline was synthesized at Paratek Pharmaceuticals, Inc. Antibiotic comparators used for the *in vitro* studies were obtained from Sigma-Aldrich, St. Louis, MO. For the *in vivo* studies, tigecycline was obtained from Bosche Scientific, New Brunswick, NJ. Doxycycline was obtained from Hovione, East Windsor, NJ. Linezolid and levofloxacin were purchased from Sequoia Research, Pangbourne, United Kingdom. Vancomycin HCl and ceftriaxone were purchased from Sigma, Atlanta, GA. Daptomycin was obtained from Cubist Pharmaceuticals, Inc., Lexington, MA. Microdilution broth MICs were performed according to CLSI (formerly NCCLS) guidelines (18).

PCR for detection and identification of tetracycline resistance genes. The presence of the efflux genes *tet*(K) and *tet*(L), as well as *tet*(A), *tet*(B), and genes of the ribosomal protection (RP) family [*tet*(M), *tet*(O), and *tet*(S)] was assessed by multiplex PCR (29).

Systemic i.p. challenge model. Six-week-old, specific-pathogen-free, male CD-1 mice, weighing 18 to 30 g (Charles River, Wilmington, MA), were used for all experiments. Animals were acclimated for 1 week following delivery. Mice were allowed food and water *ad libitum* and kept in a constant 12-h light/dark cycle. Bacterial cultures were grown by either streaking frozen colonies onto tryptic soy agar II plates with 5% sheep's blood (Northeast Laboratories, Waterville, ME) and incubating them overnight in a CO_2 enriched environment at 37°C (*S. pneumoniae*) or growing frozen isolates in a 37°C shaker at 180 rpm in Mueller-Hinton broth (Northeast Labs, Waterville, ME) (for *S. aureus* and *E. coli*). For *S. pneumoniae*, following the overnight incubation, the colonies were aseptically collected from two to three agar plates and resuspended in 3 ml of sterile phosphate-buffered saline (PBS) (Fisher Scientific, Boston, MA) for a final concentration of approximately 1×10^9 CFU/ml. For *S. aureus* and *E. coli* strains, an overnight broth was grown to a concentration of approximately 1×10^9 CFU/ml. Serial dilutions of all bacterial suspensions were performed in sterile PBS to obtain the infectious dose used for individual experiments. Infectious doses used in each experiment were confirmed by plating serial dilutions on tryptic soy agar II plates with 5% sheep's blood and incubating plates overnight (in a CO_2 enriched environment for *S. pneumoniae*) at 37°C, after which bacterial colonies were then enumerated. Septicemia was induced by infecting mice intraperitoneally (i.p.) with 500 μl containing $(6.85 \pm 1.58) \times 10^2$ CFU (mean ± standard deviation) of *S. pneumoniae* PBS1339, $(1.07 \pm 1.15) \times 10^6$ CFU of *S. pneumoniae* 700905, $(1.02 \pm 1.22) \times 10^5$ CFU of *S. pneumoniae* 157E-2, $(7.13 \pm 3.31) \times 10^7$ CFU of *S. aureus* USA300, $(6.40 \pm 1.53) \times 10^6$ CFU of *S. aureus* 29213, $(1.08 \pm 0.43) \times 10^3$/ml CFU of *S. aureus* USA400, $(1.06 \pm 0.56) \times 10^8$ CFU of *S. aureus* MRSA5, and $(6.60 \pm 2.34) \times 10^6$ CFU of *E. coli* PBS1478 in an autoclaved 4.5% bacteriological mucin (VWR Scientific, Pittsburg, PA) suspension. Mice were infected using a 3-ml lock-top sterile syringe with a sterile 25-gauge, 5/8-in. needle (Becton, Dickinson, Franklin Lakes, NJ). At 1 h postinfection (p.i.), mice were dosed intravenously (i.v.) with omadacycline or comparator compounds of interest, dissolved in sterile saline for injection at a volume of 10 ml/kg. All drug doses were formulated fresh immediately prior to administration and adjusted to account for percent activity. A minimum of four dose levels were tested per experiment with 5 mice/group. The typical doses tested ranged from 0.11 to 18 mg/kg of body weight, with exceptions for comparators that required significantly higher or lower doses to achieve 50% efficacy (dose range minimum-maximum, 0.08 to 54 mg/kg). Each study also included an untreated control group. Mice were housed in filter-topped cages in an isolated room and monitored for morbidity at least every 24 h for 7 days. Efficacy was determined by calculating the 50% effective dose (ED_{50}) for all drugs tested. The ED_{50} is defined as the dose required to achieve 50% survival at 7 days p.i. and was estimated when possible using the formula $y = 1/[1 + 10^{(\log(k)-\log(x)\times 4.2)}]$, where $k = 0.5$, by nonlinear regression analysis with Prism, version 3.0 software. All animal protocols were critically reviewed and approved by the Paratek Pharmaceuticals, Inc., Institutional Animal Care and Use Committee.

RESULTS

MICs of omadacycline, tetracycline, and doxycycline on characterized tetracycline-resistant Gram-positive and Gram-negative bacteria. Omadacycline demonstrated activity against the Gram-positive pathogens *S. aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *S. pneumoniae*, and beta-hemolytic streptococci carrying ribosomal protection [*tet*(M), *tet*(O), and *tet*(S)] and efflux [*tet*(K) and *tet*(L)] tetracycline resistance genes (Table 1). The concentration of omadacycline required to inhibit growth of several strains of *E. coli* carrying efflux genes [*tet*(A)] was also reduced compared to conventional tetracyclines.

Omadacycline demonstrates *in vitro* activity against a broad panel of clinically relevant Gram-positive and Gram-negative bacterial strains. The comparative *in vitro* activity of omadacycline was assessed against a broad panel of clinically significant Gram-positive and Gram-negative bacteria. Omadacycline was as active as comparators against susceptible *S. aureus* and was more active than most comparators against MRSA strains, most of which were resistant to more than one comparator antibiotic (Table 2). These results indicate that omadacycline specifically overcomes the problem of tetracycline, doxycycline, and minocycline resistance in *S. aureus*.

One of the more difficult to treat pathogens, and the pathogen that has been the most problematic in terms of resistance to antibiotics, is the genus *Enterococcus*, including both *Enterococcus faecalis* and *Enterococcus faecium*. Isolates of both species have acquired mechanisms of resistance to vancomycin, and such strains present a difficult therapeutic challenge. Omadacycline is active against both species and is equally active against vancomycin-susceptible and -resistant isolates (Table 2). Omadacycline is also equally active against tetracycline-resistant and -susceptible isolates of *E. faecalis* and *E. faecium*.

S. pneumoniae is an important respiratory pathogen in the hospital and community. Of particular concern in the community are isolates resistant to accepted oral antibiotics, particularly penicillins and cephalosporins, macrolides, and tetracyclines. Omadacycline exhibits activity against all *S. pneumoniae* isolates tested, regardless of resistance to these agents and even when isolates are resistant to multiple antibiotics (tetracycline plus penicillin plus azithromycin) (Table 2).

Omadacycline also exhibits *in vitro* activity against other strep-

TABLE 1 *In vitro* activity of omadacycline against tetracycline-resistant and -susceptible bacteria

Organism(s)	Tetracycline resistance gene(s)	No. of isolates	MIC range (μg/ml)[a]		
			Omadacycline	Tetracycline	Doxycycline
Staphylococcus aureus	*tet*(M)	19	0.125–1	32->64	2–16
	tet(K)	5	0.125–0.25	16–32	1–4
		35	≤0.06–0.5	≤0.06–0.25	≤0.06–0.125
Enterococcus faecalis	*tet*(M)	14	0.125–0.5	32–64	4–8
	tet(L)	1	0.25	64	16
	tet(M), *tet*(L)	3	0.5	>64	16
	tet(S)	1	0.25	32	2
		11	0.25–0.5	≤0.06–0.25	≤0.06–0.125
Enterococcus faecium	*tet*(M)	13	0.125–0.5	32–64	2–8
	tet(M), *tet*(L)	2	0.25	>64	8–16
	tet(K)	1	0.12	32	4
	tet(O)	1	0.12	32	4
		8	0.125–0.5	0.125–0.25	≤0.06
Streptococcus pneumoniae	*tet*(M)	22	≤0.06	4–64	2–4
		18	≤0.06–0.25	≤0.06–0.25	≤0.06–0.25
Beta-hemolytic streptococci[b]	*tet*(M)	17	≤0.06–0.5	4–64	2–16
	tet(O)	4	≤0.06–0.25	32–64	8
		26	≤0.06–0.5	≤0.06–0.125	≤0.06
Escherichia coli	*tet*(A)	4	2	64->64	16
		17	0.5–2	0.5–2	0.5–1

[a] Commercial-grade tigecycline was not available at the time of *in vitro* testing.
[b] *S. pyogenes* and *S. agalactiae*.

tococci. *Streptococcus pyogenes* (Lancefield group A, beta-hemolytic streptococcus) and *Streptococcus agalactiae* (Lancefield group B, beta-hemolytic streptococcus) are susceptible to omadacycline (Table 2).

Finally, omadacycline exhibits activity *in vitro* against some Gram-negative bacteria including *E. coli*, *Klebsiella pneumoniae*, and *Haemophilus influenzae* (Table 3).

Comparative efficacy studies in the *in vivo* systemic infection model. The efficacy of omadacycline was tested in a systemic infection model to determine if omadacycline has potential as a clinical therapy in humans. The i.p. challenge model is a standard *in vivo* model of systemic infection commonly used as a basic screening tool to evaluate the antibiotic potential of novel therapies (30).

Omadacycline has demonstrated favorable pharmacokinetics intravenously in multiple species and has demonstrated good intravenous and oral bioavailability in humans (27, 28, 31). Omadacycline is currently being developed as both an intravenous and oral broad-spectrum clinical therapy (25, 26, 32). However, the oral bioavailability of omadacycline in rodents is significantly lower, as demonstrated by pharmacokinetic evaluation and subsequent efficacy studies (data not shown). Because murine omadacycline bioavailability is particularly poor compared to the good oral bioavailability previously observed in other nonrodent species and humans, *in vivo* efficacy studies in mice were conducted by administering omadacycline intravenously.

A single i.v. dose of omadacycline demonstrated potent efficacy against tetracycline-sensitive and tetracycline-resistant strains of *S. pneumoniae* and *S. aureus*, as well as proving efficacious against the common Gram-negative pathogen *E. coli*, in the murine systemic i.p. challenge model (Table 4). Efficacy was evaluated by determining the ED_{50}s for omadacycline and each comparator antibiotic. Against the highly virulent, mucoid, tetracycline-sensitive *S. pneumoniae* PBS1339 strain, the ED_{50} of 3.34 mg/kg for omadacycline was similar to that of the glycycline, tigecycline (4.13 mg/kg). Omadacycline was over 4 to 5 times more efficacious than doxycycline, vancomycin, and levofloxacin and over 7 times more efficacious than linezolid (with ED_{50}s of 14.23 mg/kg, 15.7 mg/kg, 19.35 mg/kg, and 24.47 mg/kg, respectively). Ceftriaxone and daptomycin were slightly more potent than omadacycline (1.10 mg/kg and 1.43 mg/kg, respectively).

Against the tetracycline-resistant, azithromycin-resistant Tet M *S. pneumoniae* 700905 strain, the ED_{50} for omadacycline (0.45 mg/kg) was lower than that of all the other comparators tested. Omadacycline was over 30 times more active than linezolid (13.88 mg/kg) and slightly more efficacious than vancomycin (0.91 mg/kg) and tigecycline (1.72 mg/kg). Doxycycline failed to demonstrate any efficacy even at the highest dose tested (54 mg/kg); thus, an ED_{50} value could not be calculated.

The ED_{50} of 1.10 mg/kg for omadacycline was lower than that of all the other antibiotics tested against the tetracycline-sensitive *S. pneumoniae* 157E-2 strain. The efficacy of omadacycline was similar to that of doxycycline (1.55 mg/kg) and tigecycline (1.72 mg/kg), but omadacycline was over 11 times more active than vancomycin (12.32 mg/kg). Linezolid failed to protect the mice at the highest dose tested (27 mg/kg); thus, an ED_{50} value could not be calculated.

In the tetracycline-sensitive *S. aureus* 29213 i.p. challenge model, omadacycline was more than 3 to 5 times more potent than vancomycin and linezolid (1.74 mg/kg versus 6.09 mg/kg and

TABLE 2 *In vitro* activity against Gram-positive organisms

Organism name or group	No. of isolates	Antibiotic[a]	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
S. aureus	55	Omadacycline	≤0.06–1	0.125	0.5
		Tetracycline	≤0.06–64	0.125	64
		Minocycline	≤0.06–16	0.125	8
		Cefotaxime	1–>64	32	>64
		Vancomycin	0.25–2	0.5	1
		Levofloxacin	≤0.06–>64	4	32
		Linezolid	0.5–2	2	2
		Azithromycin	0.25–>64	>64	>64
		Clindamycin	≤0.06–>64	0.125	>64
		Doxycycline	≤0.06–8	≤0.06	8
Methicillin-resistant *S. aureus*	39	Omadacycline	0.125–1	0.25	0.5
		Tetracycline	≤0.06–64	0.25	64
		Minocycline	≤0.06–16	0.25	8
		Cefotaxime	4–>64	>64	>64
		Vancomycin	0.25–2	0.5	1
		Levofloxacin	0.5–>64	8	32
		Linezolid	0.5–2	2	2
		Azithromycin	0.5–>64	>64	>64
		Clindamycin	≤0.06–>64	>64	>64
		Doxycycline	≤0.06–8	0.125	8
Methicillin-sensitive *S. aureus*	16	Omadacycline	≤0.06–0.25	0.125	0.125
		Tetracycline	≤0.06–16	≤0.06	0.125
		Minocycline	≤0.06–0.125	≤0.06	0.125
		Cefotaxime	1–2	2	2
		Vancomycin	0.25–0.5	0.5	0.5
		Levofloxacin	≤0.06–4	0.125	0.125
		Linezolid	1–2	1	2
		Azithromycin	0.25–32	0.5	0.5
		Clindamycin	≤0.06–0.125	≤0.06	0.125
		Doxycycline	≤0.06–1	≤0.06	≤0.06
Multidrug- and methicillin-resistant *S. aureus*	10	Omadacycline	0.25–0.5	0.5	0.5
		Tetracycline	32–>64	>64	>64
		Minocycline	2–16	8	8
		Cefotaxime	32–64	>64	>64
		Vancomycin	0.5–1	1	1
		Levofloxacin	8–32	8	32
		Linezolid	0.5–2	1	2
		Azithromycin	>64	>64	>64
		Clindamycin	>64	>64	>64
		Doxycycline	2–8	8	8
E. faecalis	31	Omadacycline	0.125–0.5	0.25	0.5
		Tetracycline	0.125–>64	32	64
		Minocycline	0.125–16	8	16
		Vancomycin	0.5–8	1	2
		Levofloxacin	0.5–64	1	32
		Linezolid	1–4	1	2
		Azithromycin	1–>64	8	>64
		Clindamycin	2–>64	32	>64
		Doxycycline	≤0.06–16	4	16
Multidrug-resistant *E. faecalis*	3	Omadacycline	0.25–0.5	0.25	0.5
		Tetracycline	32–64	32	64
		Minocycline	8–16	8	16
		Vancomycin	0.5–8	0.5	8
		Levofloxacin	16–64	32	64
		Linezolid	1	1	1

(Continued on following page)

TABLE 2 (Continued)

Organism name or group	No. of isolates	Antibiotic[a]	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
		Azithromycin	>64	>64	>64
		Clindamycin	>64	>64	>64
		Doxycycline	4	4	4
E. faecium	24	Omadacycline	0.125–0.5	0.25	0.5
		Tetracycline	0.125–>64	32	64
		Minocycline	0.125–32	8	16
		Vancomycin	0.5–>64	>64	>64
		Levofloxacin	1–>64	64	>64
		Linezolid	0.5–4	2	2
		Azithromycin	4–>64	>64	>64
		Clindamycin	≤0.06–>64	>64	>64
		Doxycycline	≤0.06–16	2	8
Vancomycin-resistant *E. faecium*	19	Omadacycline	0.125–0.5	0.25	0.5
		Tetracycline	0.125–>64	32	64
		Minocycline	0.25–32	8	16
		Vancomycin	64–>64	>64	>64
		Levofloxacin	1–>64	64	>64
		Linezolid	0.5–4	2	2
		Azithromycin	>64	>64	>64
		Clindamycin	>64	>64	>64
		Doxycycline	≤0.06–8	2	4
Multidrug- and vancomycin-resistant *E. faecium*	12	Omadacycline	0.125–0.5	0.25	0.5
		Tetracycline	32–>64	32	>64
		Minocycline	4–16	8	16
		Vancomycin	>64	>64	>64
		Levofloxacin	8–>64	32	>64
		Linezolid	0.5–2	1	2
		Azithromycin	>64	>64	>64
		Clindamycin	>64	>64	>64
		Doxycycline	2–8	2	4
S. pneumoniae	41	Omadacycline	≤0.06–0.25	≤0.06	0.125
		Tetracycline	≤0.06–64	16	32
		Minocycline	≤0.06–8	2	8
		Cefotaxime	≤0.06–8	1	2
		Vancomycin	≤0.06–0.5	0.25	0.25
		Levofloxacin	0.25–1	0.5	1
		Penicillin	≤0.06–8	2	4
		Linezolid	0.25–2	1	1
		Azithromycin	≤0.06–>64	2	>64
		Clindamycin	≤0.06–>64	≤0.06	>64
		Doxycycline	≤0.06–4	2	4
Penicillin-resistant *S. pneumoniae*	23	Omadacycline	≤0.06	≤0.06	≤0.06
		Tetracycline	≤0.06–64	32	32
		Minocycline	0.125–8	8	8
		Cefotaxime	0.5–8	1	8
		Vancomycin	0.125–0.25	0.25	0.25
		Levofloxacin	0.5–1	0.5	1
		Penicillin	2–8	4	8
		Linezolid	0.5–2	1	1
		Azithromycin	≤0.06–>64	4	>64
		Clindamycin	≤0.06–>64	≤0.06	>64
		Doxycycline	≤0.06–4	4	4
Multidrug- and penicillin-resistant *S. pneumoniae*	18	Omadacycline	≤0.06	≤0.06	≤0.06
		Tetracycline	16–64	32	32
		Minocycline	4–8	8	8
		Cefotaxime	0.5–8	1	8

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TABLE 2 (Continued)

Organism name or group	No. of isolates	Antibiotic[a]	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
		Vancomycin	0.125–0.25	0.125	0.25
		Levofloxacin	0.5–1	0.5	1
		Penicillin	2–8	4	8
		Linezolid	0.5–1	1	1
		Azithromycin	2–>64	>64	>64
		Clindamycin	≤0.06–>64	>64	>64
		Doxycycline	2–4	4	4
S. pyogenes	30	Omadacycline	≤0.06–0.5	0.125	0.25
		Tetracycline	≤0.06–64	≤0.06	64
		Minocycline	0.125–8	0.25	8
		Cefotaxime	≤0.06	≤0.06	≤0.06
		Vancomycin	0.25	0.25	0.25
		Levofloxacin	0.25–1	0.25	1
		Linezolid	0.5–1	1	1
		Azithromycin	≤0.06–>64	≤0.06	8
		Clindamycin	≤0.06–>64	≤0.06	≤0.06
		Doxycycline	≤0.06–8	≤0.06	8
S. agalactiae	18	Omadacycline	≤0.06–0.25	0.125	0.125
		Tetracycline	≤0.06–64	32	64
		Minocycline	0.125–32	16	16
		Cefotaxime	≤0.06	≤0.06	≤0.06
		Vancomycin	0.125–0.5	0.25	0.5
		Levofloxacin	0.125–0.5	0.5	0.5
		Linezolid	1–1	1	1
		Azithromycin	≤0.06–8	≤0.06	0.125
		Clindamycin	≤0.06	≤0.06	≤0.06
		Doxycycline	≤0.06–16	8	8

[a] Commercial-grade tigecycline was not available at the time of *in vitro* testing.

TABLE 3 *In vitro* activity against Gram-negative organisms

Organism	No. of isolates	Antibiotic[a]	MIC range (μg/ml)	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
E. coli	23	Omadacycline	0.5–2	1	2
		Tetracycline	0.5–>64	2	>64
		Cefotaxime	≤0.06–0.5	≤0.06	0.125
		Levofloxacin	≤0.06–16	≤0.06	4
		Minocycline	0.5–16	1	8
		Ampicillin	2–>64	>64	>64
		Gentamicin	0.25–64	1	8
		Ciprofloxacin	≤0.06–32	≤0.06	8
		Doxycycline	0.5–64	1	64
K. pneumoniae	14	Omadacycline	1–8	2	4
		Tetracycline	0.5–>64	2	>64
		Cefotaxime	≤0.06–>64	≤0.06	32
		Levofloxacin	≤0.06–64	≤0.06	32
		Minocycline	2–>64	2	64
		Gentamicin	0.5–32	0.5	32
		Ciprofloxacin	≤0.06–>64	≤0.06	>64
		Doxycycline	1–64	2	32
H. influenzae	53	Omadacycline	0.5–8	1	2
		Tetracycline	0.125–64	2	32
		Cefotaxime	≤0.06–1	≤0.06	≤0.06
		Levofloxacin	≤0.06	≤0.06	≤0.06
		Ampicillin	≤0.06–>64	64	>64
		Azithromycin	0.25–4	1	2
		Doxycycline	0.125–8	0.5	4

[a] Commercial-grade tigecycline was not available at the time of *in vitro* testing.

9.91 mg/kg, respectively) but was slightly less effective than doxycycline and tigecycline (0.91 mg/kg and 0.73 mg/kg, respectively).

Against the clinical MRSA Tet K, Tet 38 *S. aureus* USA300 strain, omadacycline had an ED_{50} of 0.90 mg/kg and was over 9 times more active than linezolid (8.18 mg/kg). Omadacycline was over 4 times more potent than doxycycline (4.13 mg/kg) but slightly less potent than tigecycline (0.58 mg/kg). Vancomycin failed at all the doses tested including 18 mg/kg; thus, an ED_{50} could not be accurately calculated.

A single i.v. dose of omadacycline resulted in an ED_{50} of 0.45 mg/kg against the tetracycline-sensitive clinical *S. aureus* USA400 strain. Omadacycline was more efficacious than any of the other comparators tested. Omadacycline was twice as active as doxycycline and tigecycline (1.12 mg/kg and 1.09 mg/kg, respectively) and 7 and 18 times more effective, respectively, than vancomycin and linezolid (3.29 mg/kg and 8.12 mg/kg, respectively).

Omadacycline also had a lower ED_{50} than any of the other comparators tested against the MRSA Tet M *S. aureus* MRSA5 strain. With an ED_{50} of 0.30 mg/kg, omadacycline was over 5 times more efficacious than tigecycline (1.74 mg/kg) and over 80 times more active than linezolid (24.53 mg/kg). Neither vancomycin nor doxycycline demonstrated efficacy at the highest doses tested (18 mg/kg and 54 mg/kg, respectively).

With an ED_{50} of 2.02 mg/kg, omadacycline also demonstrated *in vivo* efficacy against the Gram-negative bacteria, tetracycline-sensitive *E. coli* PBS1478. Although omadacycline was not as potent as ciprofloxacin (0.07 mg/kg), a single i.v. dose of omadacy-

TABLE 4 *In vivo* efficacy of omadacycline versus clinically used antibiotic comparators in a murine i.p. challenge model

Strain (mean CFU/mouse) and compound	MIC (μg/ml)	ED_{50} (mg/kg [95% CI])[a]
S. pneumoniae PBS1339 (6.85×10^2)		
Omadacycline	0.125	3.34 ± 1.56
Ceftriaxone	0.015	1.1 (1.08–1.12)
Daptomycin	0.125	1.43 (1.24–1.62)
Doxycycline	≤0.06	14.23 (11.72–16.74)
Levofloxacin	0.25	19.35 (9.15–29.56)
Linezolid	1	24.47 (13.70–35.23)
Tigecycline	0.125	4.13 (2.46–5.79)
Vancomycin	0.5	15.70 (9.26–22.14)
S. pneumoniae 700905 (1.07×10^6)		
Omadacycline	≤0.06	0.45 (0.32–0.58)
Vancomycin	0.25	0.91 (0.73–1.09)
Doxycycline	4	>54
Tigecycline	0.125	1.72 (0.6–2.82)
Linezolid	0.5	13.88 (3.20–24.56)
S. pneumoniae 157E-2 (1.02×10^5)		
Omadacycline	≤0.06	1.10 (1.08–1.12)
Vancomycin	1	12.32 (6.83–17.81)
Doxycycline	≤0.06	1.55 (0.85–2.25)
Tigecycline	≤0.06	1.72 (0.06–3.37)
Linezolid	0.5	>27
S. aureus 29213 (6.40×10^6)		
Omadacycline	0.25	1.74 (0.91–2.58)
Vancomycin	1	6.09 (3.62–8.56)
Doxycycline	0.125	0.91 (0.89–0.92)
Tigecycline	0.125	0.73 (0.69–0.76)
Linezolid	2	9.91 (7.94–11.87)
S. aureus USA300 (7.13×10^7)		
Omadacycline	0.25	0.90 (0.33–1.46)
Vancomycin	0.5	>18
Doxycycline	1	4.13 (3.88–4.38)
Tigecycline	0.125	0.58 (0.40–0.75)
Linezolid	1	8.18 (8.05–8.31)
S. aureus USA400 (1.08×10^8)		
Omadacycline	0.5	0.45 (0.43–0.48)
Vancomycin	0.5	3.29 (0.42–6.16)
Doxycycline	≤0.06	1.12 (0.88–1.35)
Tigecycline	≤0.06	1.09 (0.49–1.69)
Linezolid	2	8.12 (3.07–13.17)
S. aureus MRSA5 (1.06×10^8)		
Omadacycline	0.25	0.30 (0.295–0.305)
Vancomycin	1	>18
Doxycycline	8	>54
Tigecycline	≤0.06	1.74 (0.91–2.57)
Linezolid	1	24.53 (16.13–32.94)
E. coli PBS1478 (6.60×10^6)		
Omadacycline	1	2.02 (1.09–2.96)
Ciprofloxacin	≤0.06	0.07 (0.05–0.09)
Doxycycline	1	17.46 (13.51–21.42)
Tigecycline	≤0.06	1.75 (1.12–2.38)

[a] Values are means of seven independent *in vivo* experiments ± standard deviations. CI, confidence interval.

cline demonstrated similar efficacy as tigecycline (1.75 mg/kg) and was over 8 times more effective than doxycycline (17.46 mg/kg).

DISCUSSION

Omadacycline demonstrates *in vitro* activity against staphylococci, including methicillin-resistant *S. aureus* strains also resistant to conventional tetracyclines (tetracycline, doxycycline or minocycline), macrolides (azithromycin), or lincosamides (clindamycin). The *in vitro* activity of omadacycline was also superior to doxycycline, minocycline, clindamycin, linezolid, or vancomycin against enterococcus, including vancomycin-resistant *E. faecalis* or *E. faecium*, and *S. pneumoniae* strains including penicillin- and multiresistant strains. Commercial-grade tigecycline was not available when these *in vitro* studies were conducted. Like other new tetracyclines, omadacycline MICs were minimally affected by the presence of tetracycline ribosomal protection or major efflux determinants in Gram-positive or Gram-negative bacteria (6, 33, 34). Omadacycline exhibited *in vitro* activity against specific Gram-negative bacteria including *E. coli*, *H. influenzae*, and *K. pneumoniae*. Other new tetracyclines, including the previously approved tigecycline and eravacycline (TP-434), which is currently in development, have demonstrated excellent Gram-positive *in vitro* activity and clinical efficacy (tigecycline) and more potent *in vitro* Gram-negative activity (eravacycline and tigecycline) (6, 35). The excellent broad-spectrum activity of these new tetracyclines accounts in part for the pursuance of development and approval pathways for several serious Gram-positive (for ABSSSI and CABP, tigecycline and omadacycline) and Gram-negative disease indications (complicated intra-abdominal infection [cIAI], tigecycline; for cIAI and complicated UTI [cUTI], eravacycline (6, 35).

The *in vitro* activity of omadacycline was demonstrated in an *in vivo* systemic infection model. A single intravenous dose of omadacycline exhibited efficacy against a variety of clinically relevant strains of *S. aureus* and *S. pneumoniae*, as well as *E. coli*, in a lethal i.p. challenge model, indicating that omadacycline was comparable or more efficacious than other currently available antibiotics.

Omadacycline is metabolically stable and has demonstrated low protein binding across all concentrations and species tested (36). In a phase 1 oral absorption, distribution, metabolism, and excretion (ADME) study, no metabolites of omadacycline were isolated, and balanced elimination via the gut and urinary systems and a high concentration of omadacycline were detected in urine (27). These data support further consideration of clinical trial testing in patients with urinary tract infections. In a phase 2 study of patients with complicated skin and soft tissue infections, oral and i.v. omadacycline was well tolerated, with efficacy demonstrating comparability with the comparator linezolid. These data support further clinical trial investigation in skin and soft tissue infections (37).

Antimicrobial resistance continues to grow while the remaining effective antibiotic arsenal continues to diminish. Staphylococci including methicillin-resistant *S. aureus*, enterococcus including vancomycin-resistant *E. faecalis* and *E. faecium*, and pneumococcus including penicillin and multidrug-resistant *S. pneumoniae* remain problems in the community and the hospital, with limited treatment options (38–43). Omadacycline is capable of overcoming multiple mechanisms of tetracycline resistance as well as of maintaining efficacy against the tetracycline-susceptible strains, as demonstrated both *in vitro* and *in vivo*. Omadacycline

may be an important and desirable treatment alternative for patients with community-acquired infections where the epidemiology suggests a problematic prevalence of resistant pathogens. Our data support the clinical evaluation of intravenous and oral treatment with omadacycline for multiple infectious disease indications.

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