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In Vitro Activity of Omadacycline (OMC) Against Biothreat Bacteria

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Abstract

Introduction: Omadacycline (OMC) is a novel aminomethylcycline of the tetracycline family, designed to overcome antibiotic resistance, and is currently in advanced clinical development for acute bacterial skin and skin structure infections (ABSSSI) and community acquired bacterial pneumonia (CABP). OMC's development is based on its demonstrated potent activity against key pathogens in these indications, including MRSA, MDRSP, and atypical pathogens, and its lack of cross resistance to older generation tetracyclines and other antibiotic classes. OMC is being developed as both an intravenous and oral formulation and would therefore be well suited for use in the treatment or post-exposure prophylaxis of infections of concern in both the biodefense and public health settings.

Methods: MICs were determined by the microbroth dilution method according to CLSI guidelines. Medium was supplemented as necessary. Test plates were incubated for 18-24 or 42-48 h, depending on the organism. Quality control for the testing was done using QC organisms and OMC QC MIC ranges established by CLSI. Thirty isolates of each pathogen, representing broad geographic diversity, were tested.

Results: OMC was active against *B. anthracis* (MIC_{90} = 0.06 µg/mL), *Y. pestis* (MIC_{90} = 1 µg/mL), *F. tularensis* (MIC_{90} = 2 µg/mL), and *B. mallei* (MIC_{90} = 0.25 µg/mL), but not against *B. pseudomallei* (MIC_{90} ≥ 64 µg/mL). OMC was less active than comparator ciprofloxacin against *Y. pestis* (MIC_{90} = 0.03 µg/mL) and *F. tularensis* (MIC_{90} = 0.015 µg/mL), but slightly more active against *B. anthracis* (MIC_{90} = 0.12 µg/mL). OMC was more active than comparator azithromycin against *B. mallei* (MIC_{90} = 1 µg/mL). OMC activity was comparable to historical data for both tetracycline and doxycycline.

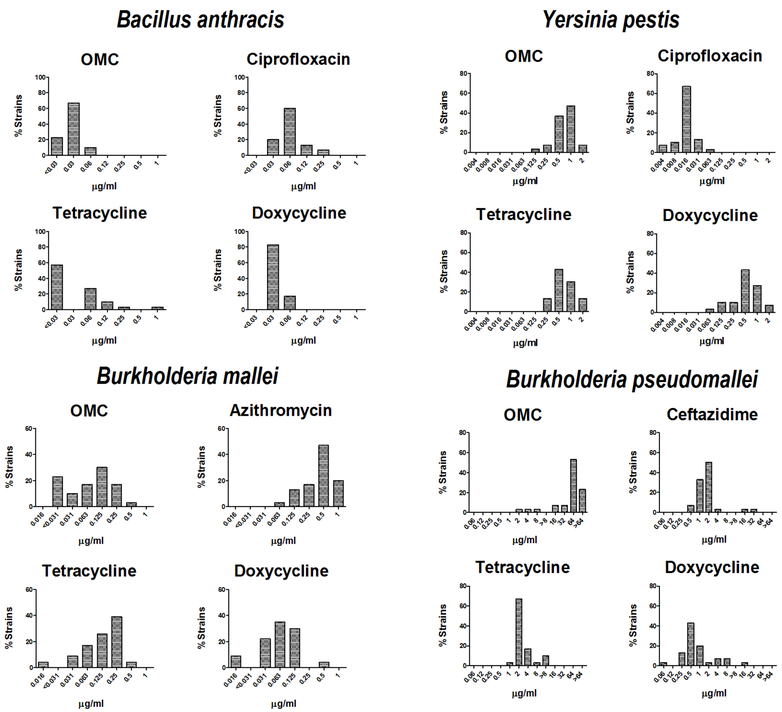
Conclusion: Based on the *in vitro* activity of OMC and its well-characterized IV and oral pharmacokinetics, safety and tolerability, further assessment of its utility in combating these biothreat organisms *in vivo* is underway.

Introduction

Omadacycline is the first antibiotic of the aminomethylcycline class of compounds, which are semi-synthetic derivatives related to the tetracyclines. As a class, the tetracyclines have been in use for over 60 years. They are well-tolerated, and have proven effective in the treatment of a variety of bacterial infections including infections caused by bacterial species considered to be high priority biologic threats (Plague, Anthrax, Tularemia). Omadacycline is designed to overcome antibiotic resistance, and is currently in advanced clinical development for acute bacterial skin and skin structure infections (ABSSSI) and community acquired bacterial pneumonia (CABP). Current treatment options against five Category A and B biothreat bacteria - *Bacillus anthracis* (BA), *Burkholderia mallei* (BM), *Burkholderia pseudomallei* (BP), *Francisella tularensis* (FT), and *Yersinia pestis* (YP) – are limited, and new therapeutic options are needed for prophylaxis and treatment of the diseases caused by these agents.

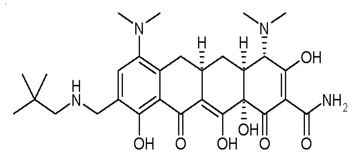
Results

Minimum Inhibitory Concentration Distributions (n = 30)



B. anthracis	Omadacycline	Ciprofloxacin	Tetracycline	Doxycycline
MIC Range (µg/mL)	<0.03 – 0.06	0.03 – 0.25	<0.03 – 1	0.03 – 0.06
MIC_{50}	0.03	0.06	<0.03	0.03
MIC_{90}	0.06	0.12	0.12	0.06
Y. pestis	**Omadacycline**	**Ciprofloxacin**	**Tetracycline**	**Doxycycline**
MIC Range (µg/mL)	0.12 – 2	0.004 – 0.06	0.25 – 2	0.06 – 2
MIC_{50}	1	0.015	0.5	0.5
MIC_{90}	1	0.03	2	1
F. tularensis	**Omadacycline**	**Ciprofloxacin**	**Tetracycline**	**Doxycycline**
MIC Range (µg/mL)	0.5 – 2	0.008 – 0.25	<0.03 – 1	0.03 – 4
MIC_{50}	1	0.008	0.12	0.25
MIC_{90}	2	0.015	0.5	0.5
B. mallei	**Omadacycline**	**Azithromycin**	**Tetracycline**	**Doxycycline**
MIC Range (µg/mL)	<0.03 – 0.5	0.06 - 1	0.015 – 0.5	0.015 – 0.5
MIC_{50}	0.12	0.5	0.12	0.06
MIC_{90}	0.25	1	0.25	0.12
B. pseudomallei	**Omadacycline**	**Ceftazidime**	**Tetracycline**	**Doxycycline**
MIC Range (µg/mL)	2 - >64	0.5 - 32	1 - >8	0.06 - 16
MIC_{50}	64	2	2	0.5
MIC_{90}	>64	4	>8	8

Omadacycline Structure



Methods

MICs were determined by the microdilution method in 96-well plates according to Clinical and Laboratory Standards Institute (CLSI). Antibiotics were serially diluted two-fold in 50 µL of cation-adjusted Mueller-Hinton broth (CAMHB). For all steps with FT, 2% Isovitalex (Becton Dickinson) was added to CAMHB. The antibiotic ranges were 8 - 0.004 µg/mL or 64 - 0.03 µg/mL based on a final well volume of 100 µL after inoculation.

Bacterial inoculums were prepared by suspending colonies into CAMHB from 18-24 h (BA, BM, BP) or 42-48 h (FT and YP) plates that were incubated at 35ºC. Sheep Blood agar (SBA) plates were used for BA and YP, chocolate agar for FT, and trypticase soy agar (TSA) for BM and BP. Suspended cultures were diluted with CAMHB to a bacterial cell density of 10^5 CFU/mL adjusted based on OD_{600}.

To each well of the 96-well plate, 50 µL of this dilution was added for a final inoculum of ~5 x 10^4 CFU/well. Plates were incubated at 35ºC. MICs were determined visually at 18-24 h (BA, BM, BP) or 42-48 h (FT and YP) and also by absorbance at 600 nm (SpectroMax M2, Molecular Devices).

30 strains representing the genetic and geographic diversity of each bacterial species were used in these studies. Quality control of antibiotic stocks was established by using *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, and *S. aureus* ATCC 29213.

Conclusions

In general, a 4 µg/mL *in vitro* MIC value supports the progression of an antibiotic into further (*in vivo)* studies, because this value is reasonably achievable in serum, without regard for tissue accumulation or individual drug performance.

Based on the results of our *in vitro* testing, OMC should be further tested *in vivo* against *B. anthracis, F. tularensis, Y. pestis,* and *B. mallei*. OMC had MIC values ≤ 4 µg/mL against 100% of the 120 different isolates of these 4 biothreat pathogens.

As a novel aminomethylcycline compound that has been engineered to defeat existing resistance mechanisms of efflux and ribosomal protection, OMC might offer the only viable treatment alternative where current therapies are not indicated due to host drug reactions or resistance. OMC showed broad spectrum *in vitro* activity against USAMRIID's collection of biothreat bacteria isolates. OMC efficacy is currently being evaluated in murine infection models for these bacterial agents.

Acknowledgments

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