Omadacycline Efficacy in a Post-Exposure Prophylaxis Mouse Model of Inhalational Anthrax Caused by Ciprofloxacin-Resistant *Bacillus anthracis*

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Background

- *Bacillus anthracis*, the causative agent of anthrax, is a Category A biothreat pathogen. The *B. anthracis* Ames strain BAC^{r}4-2 is resistant to ciprofloxacin due to a *gyrA* mutation
- The untreated mortality from acute inhaled anthrax can approach 100% if not treated early and aggressively
- FDA-approved antibiotic indications for post-exposure prophylaxis (PEP) or treatment of anthrax are limited; preferred first line therapies include ciprofloxacin and other fluoroquinolones
- Alternate therapies evaluated in a fluoroquinolone-resistant background would prove useful in the event of an accidental or intentional release of resistant organisms

Methods

- Female BALB/c mice were challenged with aerosolized BAC^{r}4-2 spores and survival was monitored for 28 days post-challenge
- Treatment was initiated 24 hr after aerosol challenge and administered for 14 days
- Treatment groups included (n=10): omadacycline (intraperitoneal [IP] administration; 0.75, 2.5, 3.75, 5, 7.5, and 15 mg/kg every 12 hr [q12h]), ciprofloxacin (IP; 30 mg/kg q12h), doxycycline (IP; 2 and 40 mg/kg q12h) and vehicle control
- Mortality was assessed and recorded 3–4 times daily during antibiotic administration (14 days) and at least twice daily thereafter up to 28 days post-challenge
- All surviving animals from each group were euthanized via CO_2 exposure, blood was immediately drawn and plated for culture, and mice were necropsied for lung and spleen tissues

Results

28-day survival

- The survival curves for all the omadacycline and doxycycline cohorts differed significantly ($p<0.0001$) from that of the vehicle cohort
- The ciprofloxacin group was significantly different from the vehicle cohort ($p=0.0017$) indicating the infection was slowed with treatment, despite resistance

28-day blood and tissue bacterial load

- Bacterial load was below the limit of detection for spleens
- Lung tissue loads were all below the 10^5 CFU/g tissue previously observed to be the limit of reinfection

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Animal data supports further development of omadacycline as a potential treatment option against *B. anthracis*

Objectives

Determine the minimum effective dose of omadacycline for PEP against inhalation anthrax caused by ciprofloxacin-resistant *B. anthracis*, as measured by survival

Compare efficacy of omadacycline treatment, ciprofloxacin treatment and doxycycline treatment to negative (untreated) controls

Conclusions

The lowest omadacycline dose tested, 0.75 mg/kg q12h, provided efficacy equivalent to doxycycline at 2.5 mg/kg q12h, a current treatment option for anthrax

All omadacycline treatment arms were at, or below 15 mg/kg q12h, which was previously shown to be the dose in BALB/c mice that best represented the human area under the curve (AUC)

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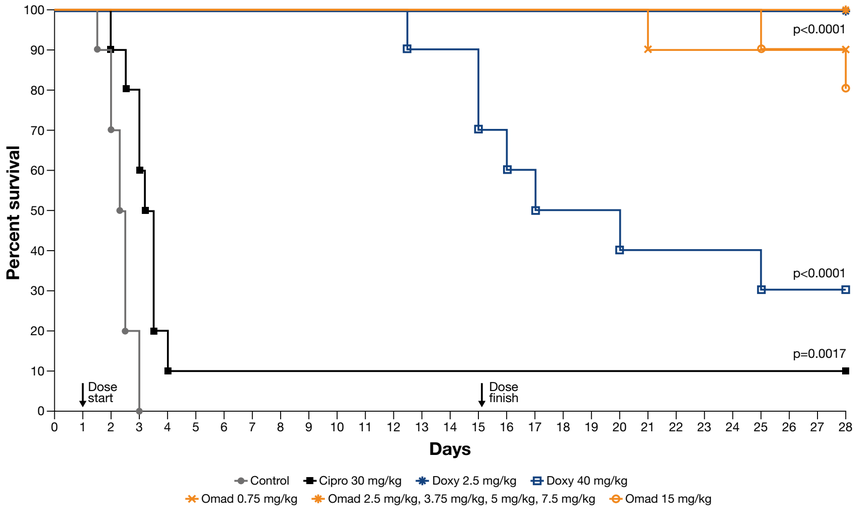
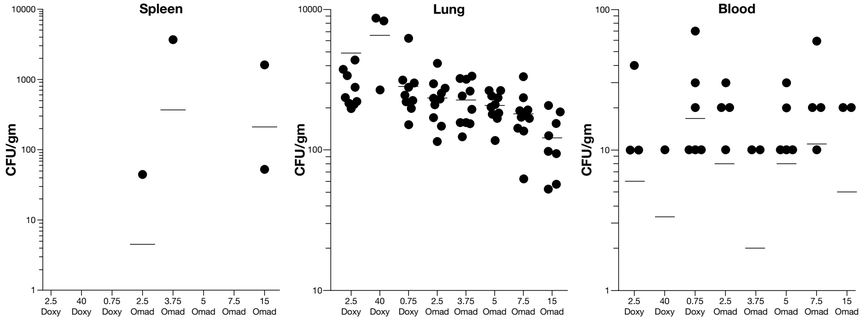
Figure 1. Kaplan-Meier survival data: Omadacycline efficacy vs inhalational anthrax caused by ciprofloxacin-resistant *B. anthracis*



All doses were administered q12h. Survival rates for omadacycline 2.5 mg/kg, 3.75 mg/kg, 5 mg/kg, 7.5 mg/kg and doxycycline 2.5 mg/kg were slightly offset from 100 to distinguish between treatment groups.

Figure 2. *B. anthracis* bacterial loads, due to ungerminated spores, in the spleen, lung and blood of mice surviving at day 28



All doses were administered q12h.

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