Eravacycline Protects in B. anthracis-Infected New Zealand White Rabbits

J. Sutcliffe1, J. Selden1, A. Reddili1, K. Edwards2, K. Gillum2

Abstract

Objective: Eravacycline (ERV) is a novel broad-spectrum tetracycline being developed for the treatment of serious Gram-negative and Gram-positive aerobes and anaerobes. Bacilli infections including those by biofilm pathogens. ERV was previously shown to be efficacious in a phase 2 complicated intra-abdominal infection trial and is currently in phase 3 clinical trials. The purpose of this study was to examine the efficacy of ERV in a phase 3 clinical trial in New Zealand white (NZW) rabbits challenged with lethal doses of Bacillus anthracis to determine the efficacy of ERV in a biofilm model of treatment.

Methods: NZW rabbits were challenged with a target dose of 200 LD50 (10^5 colony forming units [CFU] per animal) of B. anthracis spores in a polyethylene chamber. There were animals from each group were treated with intravenous (i.v.) or intraperitoneal (i.p.) ERV to achieve areas under the curve (AUC) of 1000-3000 mg·h/mL at 0-24 hours post-challenge.

Results: The average aerosol challenge dose exceeded the target, delivering an average of 376 LD50 per animal. All but one animal (23/24) developed a fever by 42 hours post-challenge in the placebo treated group and 23/24 rabbits started treatment by 42 hours post-challenge. There was a significantly lower proportion of animals dying by 56 hours post-challenge in the animals treated with ERV (n = 21/24) compared to the placebo animals (n = 14/21). Of the placebo treated animals, 4/21 survived to 56 hours post-challenge, while all animals treated with ERV survived for at least 56 hours post-challenge. The proportion of animals surviving at Day 56 was 100% for animals treated with ERV compared to 19% for placebo animals.

Conclusions: ERV administered in doses that produced equivalent exposures to those used in clinical trials was 100% effective at protecting NZW rabbits from the lethal effects of pneumonia, as shown in a Phase 3 efficacy study. Further studies with ERV are warranted to confirm the efficacy seen in this study and to determine if ERV can be an important empiric therapy for the treatment of respiratory infections caused by biofilm pathogens.

Background

Bacillus anthracis, the etiologic agent of anthrax, is a Gram-positive, rod-shaped, and endospore-forming bacterium that can cause human gastrointestinal, cutaneous, or inhalation (pulmonary) routes with different clinical manifestations of disease, pulmonary being the most lethal. The inhalation route usually varies from 2 to 5 or more days depending upon the dose of infecting spores. Following an intratracheal aerosol exposure, the initial human clinical signs and symptoms are nonspecific and may include malaise, headache, fever, nausea, and vomiting. These are following a sudden onset of respiratory distress with dyspnea, stridor, cyanosis, and chest pain, leading to shock and death with close to 100% mortality. To generate the high lethality that anthrax spores using basic microbiological techniques combined with the ability of these spores to be disseminated by aerosolization combine to produce an effective biological weapon. Following the 2001 civilian attacks, efforts to develop and license the use of medical countermeasures for therapeutic and post-exposure prophylaxis were increased. This study was designed to determine the efficacy of a novel antibiotic eravacycline for the treatment of inhalational anthrax in the NZW rabbit model.

Materials and Methods

Experimental test system. New Zealand white rabbits (Oryctolagus cuniculus) surgically implanted with two vertical ports for access (heparinized) and collecting blood samples (paw venipuncture) were inoculated by intratracheal aerosol delivery of 200 LD50 of B. anthracis spores in a polyethylene chamber. There were 24 animals per group with 6 animals randomised to receive saline at 24 and 48 hours following the first lethal challenge dose (LTD1) or control (saline) compared to 24 animals randomised to receive 100 mg/kg of eravacycline at 24 and 48 hours following the first lethal challenge dose (LTD1) or control (saline).

Experimental outcomes. Rabbits were observed for death or evidence of disease including blood and tissue samples collected for culture. Tissue samples were collected at sacrifice or autopsy. Physician Review of the Medical Record (MedRec) was performed on all rabbits.

Results

The animals receiving eravacycline had a lower proportion of animals dying by 56 hours post-challenge in the placebo treated group and 23/24 rabbits started treatment by 42 hours post-challenge. There was a significantly lower proportion of animals dying by 56 hours post-challenge in the animals treated with eravacycline (n = 21/24) compared to the placebo animals (n = 14/21). Of the placebo treated animals, 4/21 survived to 56 hours post-challenge, while all animals treated with eravacycline survived for at least 56 hours post-challenge. The proportion of animals surviving at Day 56 was 100% for animals treated with eravacycline compared to 19% for placebo animals.

Conclusions

ERV administered in doses that produced equivalent exposures to those used in clinical trials was 100% effective at protecting NZW rabbits from the lethal effects of pneumonia, as shown in a Phase 3 efficacy study. Further studies with ERV are warranted to confirm the efficacy seen in this study and to determine if ERV can be an important empiric therapy for the treatment of respiratory infections caused by biofilm pathogens.

Contact: Jennifer Sutcliffe, j.sutcliffe@tetraphase.com

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