Efficacy of PTK796 in a Rat MRSA Infective Endocarditis (IE) Model

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ABSTRACT

Background
PTK796 is the first semi-synthetic aminomethylcycline in clinical development. It is active in vitro and in vivo against resistant pathogens, particularly MRSA and VRE. The efficacy of PTK796, tigecycline (TGC) and daptomycin (DAP) were tested in a rat infective endocarditis (IE) model with a MRSA 32 strain.

METHODS

Animals
Male Sprague-Dawley rats weighing 230–250 g were intracardioventricularly inoculated 5 days prior to infection. Rat Endocarditis Infection
Methicillin-resistant Staphylococcus aureus (MRSA) strain 32 was inoculated in Mueller Hinton broth and incubated at 37ºC with 150 rpm shaking overnight. Overnight cultures were further diluted in normal saline to obtain the target concentration. Rats were infected with 0.5 mL inoculum containing approximately 5 x 10⁶ colony-forming units (CFU) through tail vein injection.

Antibiotics Tested and Dosing Regimens
• PTK796 was synthesized at Paratek Pharmaceuticals (Boston, MA). Daptomycin (DAP) was purchased from Cubist Pharmaceuticals (Lexington, MA). Tigecycline (TGC) was purchased from Wyeth (Lexington, MA).
• PTK796 was less efficacious than tigecycline in the model, especially in the ratio of total heart sterilization (2/6 for PTK796 at 5 mg/kg vs. 5/6 for the same dose of tigecycline).

DISCUSSION

• Doses selected for this study were based on historical animal study data, not related to human doses.
• The particular MRSA strain we used in this study does not generate vegetation that is usually at least 1-2 log higher than in spleen, unless sterile. We monitored spleen bacterial counts only to show the bacteremia. Unlike in the sepsis model, endocarditis animals do not die shortly after infection unless due to heart attack.

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Figure 1. Chemical structure of PTK796.

Figure 2. Efficacy of PTK796 and its comparators against MRSA-induced IE model: (A) Rat infective endocarditis (IE) model provides a good system for evaluating antibiotics used for serious infections. (B) Efficacy of PTK796 in this MRSA-induced rat IE model indicates the potential utility of PTK796 in Gram-positive infections.