The Efficacy of PTK 0796 (BAY 73-6944) in Murine Models of *Streptococcus pneumoniae* Infections

*D. McKenney, J.M. Quinn, C.L. Jackson, J.L. Guilmet, J.A. Landry, S.K. Tanaka, and E.P. Cannon*

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**The Efficacy of PTK 0796 in Murine Models of Streptococcus pneumoniae Infections**

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**ABSTRACT**

Respiratory pathogens (e.g. Streptococcus pneumoniae) are a major cause of community-acquired pneumonia, in significant rates of hospitalization and mortality, and in a lowering treatment-resistant to antibiotics. PTK 0796, a novel 2-amino methylcycline is a novel non-ribosomal peptide containing efflux-inhibitor that has broad and enhanced activity against Streptococcus and multi-drug-resistant gram-positive bacteria. PTK 0796 was tested in four in vitro infection models to evaluate its potential as a therapeutic agent.

**Methods**

PTK 0796 was tested in four in vitro infection models: a respiratory mucin model, following infection, increasing single dose treatments of PTK 0796 or comparator drugs were then administered IV. For post-infection survival, survival rates were monitored for 7d and PD50 is calculated.

**RESULTS**

For the in vivo model, mice per group were infected with 10^8 CFU/ml of tetracycline resistant S. pneumoniae 6R in the left thigh and treated OIU of resistant S. pneumoniae in the right thigh. Mice were then treated IV with increasing doses of PTK 0796 and comparator drugs post infection. Bacterial burdens of the thighs were then obtained by 24h post-infection. PTK 0796 showed greater efficacy in both the systemic IP challenge model, and the chronic lung model. In vivo mouse per group received intraperitoneal (IP) PTK 0796 or Comparator at a dose range of 0.06 to 0.075 of the minimum effective dose. All four comparators were tested in this range of efficacies. PTK 0796 showed greater efficacy in the tetracycline susceptible and resistant thigh wound model in immunocompromised mice than all comparators other than Vancomycin tested in this study.

**Conclusions**

PTK 0796 is a novel 2-amino methylcycline, with broad and enhanced activity against susceptible and multi-drug-resistant gram-positive bacteria. PTK 0796 showed greater efficacy in the tetracycline susceptible and resistant lower respiratory tract infection models than all comparators other than Vancomycin tested in this study.

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**REFERENCES**

1. Experimental models: Male CD-1 mice (18-25g) were used. Female ICR (20–30g) mice were used for the systemic IP challenge model, 5 mice per group were infected with 10^12 CFU/ml of a tetracycline susceptible or resistant pneumococcal strain. A range of increasing single doses of PTK 0796 or comparator drugs were then administered IV. For post-infection survival, survival rates were monitored for 7d and PD50 is calculated.

2. In vivo model: PTK 0796 was administered orally in three different models: the respiratory mucin model, following infection, increasing single dose treatments of PTK 0796 or comparator drugs were then administered IV. For post-infection survival, survival rates were monitored for 7d and PD50 is calculated.

3. Quantitative chemotherapy: for the thigh wound model, mice per group were infected with 10^8 CFU/ml of tetracycline resistant S. pneumoniae 6R in the left thigh and treated with increasing doses of PTK 0796 or comparator drugs. For post-infection efficacy, bacterial burdens of the thighs were then obtained by 24h post-infection. PTK 0796 showed greater efficacy in both the systemic IP challenge model, and the chronic lung model. In vivo mouse per group received intraperitoneal (IP) PTK 0796 or Comparator at a dose range of 0.06 to 0.075 of the minimum effective dose. All four comparators were tested in this range of efficacies. PTK 0796 showed greater efficacy in the tetracycline susceptible and resistant thigh wound model in immunocompromised mice than all comparators other than Vancomycin tested in this study.

4. **RESULTS**

PTK 0796 showed greater efficacy in the tetracycline susceptible and resistant thigh wound model than all comparators tested.

5. **Conclusions**

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**METHODS**

**Abstract**

Respiratory pathogens (e.g. S. pneumoniae) are a major cause of community-acquired pneumonia, in significant rates of hospitalization and mortality, and in lowering treatment-resistant to antibiotics. PTK 0796, a novel 2-amino methylcycline is a novel non-ribosomal peptide containing efflux-inhibitor that has broad and enhanced activity against Streptococcus and multi-drug-resistant gram-positive bacteria. PTK 0796 was tested in four in vitro infection models to evaluate its potential as a therapeutic agent.

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