Comparative efficacy of omadacycline (PTK796) in lethal Streptococcus pneumoniae and Staphylococcus aureus pneumonia models

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ABSTRACT

Objective: Omadacycline is a novel aminomethylcycline with excellent activity against pulmonary pathogens and overcomes tetracycline resistance. The objective of these studies was to evaluate omadacycline as a clinical candidate to treat Gram-positive pneumonias.

Methods: Neutrophic (cyclophosphamide treated) male CD-1 mice were infected intranasally with S. pneumoniae (USA300) at a dose of 10^6 CFU. Animals were treated with omadacycline, comparator, or saline at 2 hours post-infection and survival determined out to 7 days post infection.

RESULTS (continued)

Figure 1. Nonlinear regression survival curves for the S. pneumoniae non-neutropenic respiratory tract infection model at 72 hours pi

Table 1. Efficacy of omadacycline versus clinical comparators in a non-neutropenic lethal Streptococcus pneumoniae pneumonia model

Figure 2. Nonlinear regression survival curves for the S. pneumoniae non-neutropenic respiratory tract infection model at 72 hours pi

Table 2. Efficacy of omadacycline versus clinical comparators in a non-neutropenic lethal Streptococcus pneumoniae pneumonia model

Figure 3. Comparative efficacy of omadacycline in lethal Streptococcus pneumoniae and Staphylococcus aureus pneumonia models

Table 3. Efficacy of omadacycline versus clinical comparators in a neumococcal lethal streptococcal pneumonia model.

CONCLUSIONS

In the neutropeephnic S. pneumoniae pulmonary infection model, omadacycline, tigecycline, and ceftriaxone performed well although the log-bacffic activity for all drugs was reduced.

Omadacycline and the comparator agents all benefitted substantially from the presence of an intact immune system. All exhibited substantially reduced dose requirements for efficacy and benefit was observed for long-term survival.

In vitro activity and the pharmacodynamic requirements for efficacy were not achieved by a single intravenous dose in either neutrophilic or normal mice. Vancomycin was ineffective in the neutropeephnic pneumonia model but benefitted substantially from an intact immune system.

Omadacycline and tigecycline were superior to dosypbicacycline and vancomycin in the S. aureus pulmonary model in neutrophilic mice. The inability of the S. aureus model to cause a lethal pulmonary infection in non-neutrophilic animals prevented the evaluation of the contribution of the immune system in the treatment of this infection.

These results support the development of omadacycline in bacterial pneumonia caused by pneumococci and staphylococci in patients with normal immune function. The role of the immune system on the response to therapy should be carefully considered in the determination of the pharmacodynamic relationship of drug, pathogen, and host.