Efficacy of Fluorocycline TP-434 in the Neutropenic Thigh Infection Model is Predicted by AUC/MIC

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Abstract

Background: TP-434 is a novel broad-spectrum antibiotic being developed by Tetraphase Pharmaceuticals for a wide range of infections. The current study was performed to determine the pharmacodynamics parameters (PDs) that best predict efficacy of TP-434 in a thigh infection model.

Methods: Female C3H/HeN mice were treated with a single dose of TP-434 (6.0 mg/kg) or amoxicillin-clavulanate (3.0 mg/kg) intravenously immediately post-infection. After 24 hours, thighs were removed and processed for CFU counts. TP-434 was administered SC from 1 to 90 mg/kg to determine PK parameters (C max, AUC, T>MIC) in neutropenic, thigh-infected animals. The correlation coefficients of the PD parameters to efficacy in the thigh model were determined for AUC/MIC, %T>MIC and %T24>MIC, respectively.

Results: Correlations of R²=0.994 and 0.964 were observed for AUC and C max values of 0.3 – 4 hrs.

Conclusion: The AUC/MIC ratio of 1.39 and 13.34 ± 1.34 µg/mL for concentrations from 0.1 to 10 µg/mL can predict efficacy of TP-434 in neutropenic thigh infections. It is recommended that clinical studies with TP-434 be administered intravenously to predict clinical efficacy in neutropenic thigh infections.

Introduction

TP-434 is designed as a broad-spectrum antibiotic with the potential for superior efficacy against Gram-positive and Gram-negative pathogens (see F1-2163). In vitro studies with TP-434 have demonstrated greater potency in comparison to currently marketed antibiotics. Pharmacokinetic and pharmacodynamic studies have shown that TP-434 exhibits the desired pharmacokinetic properties necessary for infection treatment. Pharmacokinetic studies with TP-434 have demonstrated excellent activity against a broad range of pathogens, including drug-resistant strains. These data support the development of TP-434 for a wide range of bacterial infections, including those caused by highly resistant strains.

Methods and Materials

Mice: Female C3H/HeN mice aged 6-8 weeks were used. Neutropenic C3H/HeN mice were rendered neutropenic by IP injection of Cytoxan (150/100 mg/kg) 1 day pre-infection. TP-434 was administered SC from 1 to 90 mg/kg at days -4/-1 pre-infection.

Thigh Infecion: Methicillin-resistant and -sensitive Staphylococcus aureus (MRSA and MSSA) were used as infection strains. Identical doses were used for each of the dose fractionations.

PK: The PK parameters (C max, AUC, T>MIC) were determined by compartmental analyses. The concentration-time profiles were analyzed over 24 hours.

PD: Correlations were determined by testing the ability of the PD parameters to predict the efficacy of TP-434 in the thigh model. The AUC/MIC, %T>MIC and %T24>MIC were found to be the best predictive parameters for efficacy in the thigh model.

Summary and Conclusions

TP-434 is a novel broad-spectrum antibiotic being developed by Tetraphase Pharmaceuticals for a wide range of infections. The current study was performed to determine the PD parameters that best predict efficacy of TP-434 in a thigh infection model. The AUC/MIC ratio of 1.39 and 13.34 ± 1.34 µg/mL for concentrations from 0.1 to 10 µg/mL can predict efficacy of TP-434 in neutropenic thigh infections. It is recommended that clinical studies with TP-434 be administered intravenously to predict clinical efficacy in neutropenic thigh infections.

References


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