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 fluorocycline being developed by Tetraphase Pharmaceuticals for a wide range of infections. The current study was performed to determine the pharmacodynamic parameter (PD) that best predicts efficacy of TP-434.

Methods: Female CD-1 mice were rendered neutropenic by IP injection of Cyclophosphamide (150/100 mg/kg at days 0/-1 pre-infection). Infection was induced by IP injection of 10^8 CFU of MRSA USA300 (240 µg/mL) in the right thigh. Dose fractionation studies (q24h, q12h, q6h) were done with 1.00 mg SC for MRSA. All thighs were removed after ca. 96 h post-infection and processed for CFU counts. TP-434 was administered SC from 1 to 60 mg/kg to determine PK parameters (Cmax, AUC, T1/2) in neutropenic, thigh-injected animals. The dose vs change in CFUs relationship vs untreated controls was determined for each organism and related to the PK parameters at each dose. Protein binding was determined by equilibrium dialysis and size exclusion chromatography.

Results: The static dose for MRSA was 1.31 mg/kg. The correlation coefficients of the PD parameters to efficacy in the thigh were r = 0.85 for AUC, r = 0.83 for Cmax and r = 0.62 for MIC. The 24 hr total AUC/MIC ratio necessary to achieve a static effect and 1 log reduction in CFU were 38.4 and 40.5, respectively. The Cmax/MIC ratio was 58.5% for MRSA.

Conclusion: The efficacy of TP-434 in the neutropenic thigh model for a representative MSSA strain, USA300 correlated best with the AUC/MIC, which is similar to other published tetracycline molecules.

Introduction

TP-434 is a novel broad-spectrum fluoroquinolone with the potential for superior efficacy against Gram-negative, Gram-positive, and anaerobic pathogens (see F1-2107-2109). In vitro studies with TP-434 have demonstrated greater potency in comparison to currently marketed antimicrobials. Preliminary data have shown that TP-434 also has the potential to be developed as an oral therapy (see F1-2104). TP-434 has successfully completed Phase 1 clinical studies (see A1-029-2009) and is poised to enter Phase 2 in 2010. The current study was performed to determine the pharmacokinetic/pharmacodynamic parameter that best predicts the efficacy of TP-434 in bacterial infections.

Methods and Materials

Mice: Female 5–6 week old CD-1 mice (18-22 g).

Neutropenia: Female CD-1 mice were rendered neutropenic by IP injection of Cyclophosphamide (150 mg/kg day 0 and 100 mg/kg day -1 pre-infection).

Thigh Infection: A fresh overnight culture of a Staphylococcus aureus (MRSA) strain was diluted to approx. 2 x 10^7 CFU/mL, and 0.1 mL injected (10/50 final dil. mL) into the thighs of the pre-treated mice.

MICs: MICs (mg/L) were determined by the microdilution method with CLSI guidelines.

PK: TP-434 was administered SC at 5 selected doses (1 – 60 mg/kg, with 9 time points and 3 mice in order to determine pharmacokentic parameters for each dose). Pharmacokinetics were performed in neutropenic, thigh-infected animals to best predict potential local ex vivo efficacy relationships at several dosing intervals in the efficacy study described below. Dose fractionation studies were done to reach the target PK parameters in the efficacy study described above.

Dose Ranging Study: An initial dose-ranging study (single dose at 1.5 hrs post-infection) was performed with a wide range of doses (2.5 – 60 mg/kg) in thigh-infected animals in order to determine the defined range that will be used in the dose fractionation studies.

Dose Fractionation: TP-434 was administered by the same route used for the PK and dose ranging study at up to 8 different daily doses (selected from the dose ranging studies and covering a dose range ranging from maximal to the no-effect level). Each total dose was given at 3 different regimens (q24h, q12h, q6h). Efficacy in the thigh infection model was compared to calculated PK parameters at each of the dose fractionations.

General References

1. W. J. WEISS, M. PULSE, P. RENICK, J. SUTCLIFFE.
2. Poster 183: Efficacy of Fluorocycline TP-434 in the Neutropenic Thigh Infection Model is Predicted by AUC/MIC.

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