Pharmacokinetic/Pharmacodynamic Model for the Safety of Tigecycline in Patients with Complicated Skin and Skin-Structure Infections

AK Meagher,1 JA Passarelli,2 K Liolios,3 BB Cinccinno,1 SA Van Wart,1 TH Grasela,1 T Babinchak,2 and EJ Ellis-Grosse2

1Cognigen Corporation, Buffalo, NY, and 2Weyer Research, Collegeville, PA

REVIEWED ABSTRACT

Purpose. Tigecycline is a first-in-class glycylcycline for the treatment of serious bacterial infections. Reported adverse events from clinical trials include nausea and vomiting. Exposure-response relationships and patient covariates predictive of the first occurrence of nausea and vomiting in patients with complicated skin and skin-structure infections (cSSIs) were evaluated.

Methods. Patients from three cSSIs studies (one Phase 2 and two Phase 3) were pooled for analysis. Patients received 10 mg/kg loading dose and 50 mg/oral (100 mg) or 20 mg/kg loading dose and 20 mg/oral (50 mg). Nausea and vomiting (classified as defined, possibly, probably related) reported from the start of infusion until 24 hours after the last dose were included. Bayesian estimates of steady state 12-hour AUC (AUC12) and Cmax were derived using a population PK model. Logistic regression was used to evaluate predictors of the first occurrence of nausea and vomiting. Covariates included exposure, age, sex, pre-existing diabetes, and region of treatment.

RESULTS

• 739 patients were included in the PK/PD exposure-response analyses of nausea and vomiting.
• 88% of patients received the FDA-approved 100/50 mg tigecycline dosage regimen.
• Table 1 provides summary statistics of the demographic characteristics of the Phase 2 and 3 patients.

METHODS

• Tenosynovial fluid samples from one Phase 2 and two Phase 3 studies were pooled for analysis.
• Nausea and vomiting were classified as defined, possibly, probably related to tigecycline.
• Age, sex, weight, and region of treatment were centrally adjudicated as defined, possibly, probably related to tigecycline.

CONCLUSIONS

• Nausea and vomiting were less likely in older patients, men, Europeans, and in the 50/25 mg dose group. AUC12 and Cmax were not predictors of nausea and vomiting.

REVIEWED ABSTRACT

Purpose. Tigecycline is a first-in-class glycylcycline for the treatment of serious bacterial infections. Reported adverse events from clinical trials include nausea and vomiting. Exposure-response relationships and patient covariates predictive of the first occurrence of nausea and vomiting in patients with complicated skin and skin-structure infections (cSSIs) were evaluated.

Methods. Patients from three cSSIs studies (one Phase 2 and two Phase 3) were pooled for analysis. Patients received 10 mg/kg loading dose and 50 mg/oral (100 mg) or 20 mg/kg loading dose and 20 mg/oral (50 mg). Nausea and vomiting (classified as defined, possibly, probably related) reported from the start of infusion until 24 hours after the last dose were included. Bayesian estimates of steady state 12-hour AUC (AUC12) and Cmax were derived using a population PK model. Logistic regression was used to evaluate predictors of the first occurrence of nausea and vomiting. Covariates included exposure, age, sex, pre-existing diabetes, and region of treatment.

RESULTS

• 739 patients were included in the PK/PD exposure-response analyses of nausea and vomiting.
• 88% of patients received the FDA-approved 100/50 mg tigecycline dosage regimen.
• Table 1 provides summary statistics of the demographic characteristics of the Phase 2 and 3 patients.

METHODS

• Tenosynovial fluid samples from one Phase 2 and two Phase 3 studies were pooled for analysis.
• Nausea and vomiting were classified as defined, possibly, probably related to tigecycline.
• Age, sex, weight, and region of treatment were centrally adjudicated as defined, possibly, probably related to tigecycline.

CONCLUSIONS

• Nausea and vomiting were less likely in older patients, men, Europeans, and in the 50/25 mg dose group. AUC12 and Cmax were not predictors of nausea and vomiting.