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

AK Meagher,[1] JA Passarell,[1] K Liolios,[1] BB Cirincione,[1] SA Van Wart,[1] TH Grasela,[1] T Babinchak,[2] and EJ Ellis-Grosse[2]

[1]Cognigen Corporation, Buffalo, NY and [2]Wyeth Research, Collegeville, PA

For more information, please contact:
Julie A. Passarell
Assistant Director, Statistics
Cognigen Corporation
395 Youngs Road
Buffalo, NY 14221
(716) 633-3463, ext. 266
Julie.Passarell@cognigencorp.com

REVISED 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 (cSSSI) were evaluated.

Methods. Patients from three cSSSI studies (one Phase 2 and two Phase 3) were pooled for analysis. Patients received 100-mg loading dose and 50 mg q12h (100/50) or 50-mg loading dose and 25 mg q12h (50/25). Nausea and vomiting (classified as definitely, possibly, or 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 (AUC_{0-12}) and C_{max} 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, weight, sex, pre-existing diabetes, and region of treatment.

Results. Final dataset included 726 patients (102 with PK): 64% of patients were male; mean (SD) age and weight were 49 (16) years and 83 (23) kg; 45%, 27%, and 11% were enrolled in North America, Europe, and Latin America, respectively. Overall, nausea (vomiting) occurred in 29% (16%) of patients and 73% of first events were mild in nature. Women had more nausea and vomiting (38% and 26%) than men (23% and 9%). Nausea and vomiting were lower in Europe (14% and 4%) than in other regions. AUC_{0-12} and C_{max} were not predictive of these events. The final nausea model included age, sex, region of treatment, and dose as predictors of the first nausea occurrence ($p = 0.03$, < 0.0001, < 0.0001, and $= 0.0001$, respectively). The final vomiting model also included age, sex, region, and dose as predictors of the first vomiting occurrence ($p = 0.011$, < 0.0001, < 0.0001, and $= 0.004$, respectively).

Conclusions. Nausea and vomiting were less likely in older patients, men, Europeans, and in the 50/25 dose group. AUC_{0-12} and C_{max} were not predictors of nausea and vomiting.

BACKGROUND

- Tigecycline is a glycylcycline recently approved for the treatment of patients with serious infections, including complicated skin and skin-structure infections (cSSSI) and complicated intra-abdominal infections.
- Tigecycline has expanded activity against both gram-negative and gram-positive aerobes, anaerobes, and atypical organisms, including multiple-drug resistant strains.
- This new antimicrobial agent appears to be generally well tolerated, with nausea, vomiting, and diarrhea the most frequently reported treatment-emergent adverse events.
- The severity of nausea and vomiting reported in clinical trials has been predominantly classified as mild to moderate in nature and resulted in few discontinuations in therapy.
- From Phase 1 trials, the tolerability of tigecycline appears to be improved if the drug is administered following a meal and is also better tolerated in older subjects.
- Exposure-response analyses were performed to explore the relationship between tigecycline exposure measurements and the first occurrence of nausea and vomiting in patients with cSSSI.
- A statistical model was developed to describe the first occurrence of nausea and vomiting and to evaluate the potential impact of selected patient demographic characteristics and exposure measurements on these adverse events.

METHODS

- Data from patients enrolled in one Phase 2 and two Phase 3 studies were pooled for analysis.
- The occurrence of nausea and vomiting included any instance reported as “on treatment” and only those events classified as definitely, possibly, or probably related to tigecycline. “On treatment” was conservatively defined as those events observed from the start of the first infusion until 24 hours after the last infusion.
- PK samples were collected per protocol (4 samples per patient); of the 102 patients with PK, 43 received the 50/25 mg dose and 59 received the 100/50 dose.
- Observed C_{max} values and Bayesian exposure estimates from a tigecycline population PK model were used for individual estimates of steady-state 12-hour AUC values in the exposure-response analyses.
- The following patient covariates were evaluated as potential predictors of nausea and vomiting: dose, age, weight, sex, region of treatment, and pre-existing diabetes.
- All data processing and statistical analyses were performed using SAS® software, Version 8.2.
- An exploratory analysis of the first occurrence of nausea and vomiting versus tigecycline exposure measurements and patient demographic characteristics was conducted to determine which types of regression models were most appropriate for the exposure-safety analyses.
- Logistic regression analyses were used to determine whether exposure measures and covariates were statistically significant predictors of the first occurrence of nausea and vomiting.
- Backward elimination was utilized with a level of significance of 0.05.
- Goodness-of-fit of the logistic regression model was assessed using the Hosmer-Lemeshow goodness-of-fit test.
- Predictive ability of the model was assessed using the area under the receiver operating characteristic (ROC) curve.
- Survival analysis using the non-parametric Kaplan-Meier method was used to determine whether exposure measures and covariates were statistically significant predictors of the time to the first occurrence of nausea and vomiting.

RESULTS

- 726 patients were included in the PK/PD exposure-response analyses of nausea and vomiting.
- 89% 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.
  - The mean age was 49 years and ranged from 18 to 90 years.
  - The mean weight was 83 kg, with a range of 40 to 227 kg.
  - Approximately 26% of patients had diabetes.
- Tigecycline exposure measures were available in 102 (14%) patients.
  - Mean (SD) AUC_{0-12} was 2604 (795) ng·hr/mL and ranged from 1403 to 4681 ng·hr/mL for the 100/50 mg dose group.
  - Mean (SD) observed C_{max} was 493 (235) ng/mL (range 189 to 1326 ng/mL).
  - Within the 100/50 mg dose group, patients enrolled in European trials appeared to have higher median AUC_{0-12} values as compared to patients enrolled in trials in North America.
    - Median AUC for EU patients was approximately 2-fold higher (3250 ng·hr/mL) compared to US patients (1800 ng·hr/mL).
    - This was most likely the result of lower body weights observed in Europe, resulting in lower clearance and higher AUC values.

Nausea

- 29% of patients (208/726 patients) had at least one occurrence of nausea in the Phase 2/3 population.
- Approximately 14% of patients administered the 50/25 mg dose regimen and 30% of patients administered the 100/50 mg dose regimen had at least one nausea occurrence.
- The majority of first nausea events occurred within three days of the start of tigecycline treatment.
- The majority (68%) of patients who had nausea had only one occurrence.
- Female patients (38%) had a higher occurrence of nausea compared to male patients (23%).
- A lower incidence of first nausea occurrences was observed in Europe (14%) compared to all other regions: North America (33%), Latin America (38%), and other regions (33%).
- The Kaplan-Meier plot of estimated probability of first nausea occurrence versus study day stratified by dose is provided in **Figure 1**.
- Approximately 73% of first nausea occurrences were mild in nature and 24% were moderate. Similar percentages of severity of first nausea occurrences were observed across study day.
- The first occurrence of nausea did not appear to be related to AUC_{0-12} (**Figure 2**), although the incidence of first nausea was higher in patients who received the 100/50 mg dose regimen versus the 50/25 mg dose regimen.
- Univariate logistic regression models assessing the impact of tigecycline exposure and demographic covariates on the probability of the first occurrence of nausea were evaluated.
  - AUC_{0-12} and C_{max} were not statistically significant predictors of the probability of first nausea occurrence ($p = 0.6082$ and 0.4203, respectively) and were eliminated from multivariable modeling.
  - Dose, sex, and region of treatment (grouped as Europe versus all other regions) were statistically significant predictors of the probability of first nausea occurrence ($p = 0.0030$, < 0.0001, and < 0.0001, respectively).
- After multivariable modeling, the final logistic regression model included age, sex, region, and dose as significant predictors of the probability of first nausea occurrence (**Table 2**).
  - As age increased, the model-predicted probability of first nausea occurrence decreased [odds ratio (OR) 0.988].
    - As age increases by 10 years, the model-predicted probability of nausea decreases by approximately 12%.
    - At the 50 mg dose level, for a 49 year old non-European male, the model-predicted probability of nausea was 0.2535; this probability would decrease to 0.2189 for a 65 year old male.
  - Female patients tended to have a higher probability of first nausea occurrence than male patients (OR 2.405).
  - Patients enrolled in European trials had a lower probability of first nausea occurrence than patients from all other regions of the world (OR 0.256).
  - Patients administered the 100/50 mg dose regimen had a higher probability of first nausea occurrence than patients administered the 50/25 mg dose regimen (OR 3.813).
- The Hosmer-Lemeshow goodness-of-fit statistic was 8.65 with 8 degrees of freedom ($p = 0.3726$).
- The area under the ROC curve was 0.70, indicating an adequate fitting and predictive model.
  - For a male patient at the median age of 49 years who was administered the 100/50 mg dose regimen, the model-predicted probability of first nausea occurrence was 0.147 and 0.254 for Europe and all other regions, respectively.
  - For a female patient, at the same age and dose, the model-predicted probability of first nausea occurrence was 0.211 and 0.345 for Europe and all other regions, respectively.

Vomiting

- 16% of patients (113/726) had at least one occurrence of vomiting.
- Approximately 6% of patients administered the 50/25 mg dose regimen and 17% of patients administered the 100/50 mg dose regimen had at least one occurrence of vomiting.
- The majority of patients who had vomiting had only one occurrence (approximately 67%).
- Approximately 26% of females and 9% of males had at least one occurrence of vomiting.
- A lower incidence of vomiting was observed in Europe (4%) compared to all other regions: North America (17%), Latin America (22%), and other regions (26%).
- As with nausea, the majority of first vomiting events occurred within three days of the start of tigecycline treatment.
- Approximately 73% of first vomiting occurrences were mild and 27% were moderate in nature. Only one vomiting occurrence was considered serious.
- The Kaplan-Meier plot of estimated probability of vomiting versus study day stratified by dose is provided in **Figure 3**.

Vomiting (Continued)

- The first occurrence of vomiting did not appear to be related to AUC_{0-12}, although the incidence of first vomiting was higher in patients administered the higher 100/50 mg dosing regimen (**Figure 4**).
- Using univariate logistic regression, neither AUC_{0-12} nor C_{max} were statistically significant predictors of the probability of first vomiting occurrence ($p = 0.5476$ and 0.2422, respectively).
- Dose, race (Caucasian versus all others), weight, sex, and region (four level categorical covariate) were statistically significant predictors of the probability of first vomiting occurrence ($p = 0.0219$, 0.0027, 0.0067, < 0.0001, and < 0.0001, respectively).
- As shown in **Table 2**, the final logistic regression model included age, sex, region, and dose as significant predictors of the probability of first vomiting occurrence.
  - Younger patients, females (OR 4.41), non-European patients (OR 7.38 for North America), and those in the 100/50 mg dose group (OR 4.25) had a higher model-predicted probability of first vomiting occurrence.
- The Hosmer-Lemeshow goodness-of-fit statistic was 12.85 with 8 degrees of freedom ($p = 0.1170$).
- The area under the ROC curve was 0.77, indicating an adequate fitting and predictive model.
  - At a median age of 49 years, a male patient administered the 100/50 mg dose regimen had a model-predicted probability of first vomiting occurrence of 0.156, 0.069, 0.066, and 0.009 for Europe, North America, Latin America, and other regions, respectively.
  - For a 49-year-old female patient administered the 100/50 mg dose regimen, the model-predicted probability of first vomiting occurrence was 0.279, 0.134, 0.129, and 0.018 for Europe, North America, Latin America, and other regions, respectively.

Antiemetic Data

- Information on antiemetic utilization (as either prophylaxis or treatment) was collected for the Phase 3 studies.
- Of the 566 patients in Phase 3 with and without adverse events, 167 reported using at least one antiemetic at some time during the study.
- Only 6% of patients received antiemetics for the entire treatment interval.
  - 57% of patients who reported antiemetic usage, received these medications for up to half of their recorded treatment duration.
- As shown in **Figure 5**, 58% used prokinetic agents (such as metoclopramide) and 24% received antihistaminic agents (such as dimenhydrinate).

Table 1. Patient Demographics

Demographic Characteristics	Summary Statistics
Age (years) [mean (SD)]	49 (16)
Weight (kg) [mean (SD)]	83 (23)
Sex, n (%)	
Male	465 (64)
Female	261 (36)
Ethnicity, n (%)	
White	464 (64)
Black	79 (11)
Hispanic	94 (13)
Other	89 (12)
Region of Treatment, n (%)	
Europe	196 (27)
North America	326 (45)
Latin America	82 (11)
Other	122 (17)

Table 2. Final Logistic Regression Model for the First Occurrence of Nausea and Vomiting

	p-value	
Parameter	Nausea	Vomiting
Age (years)	0.0299	0.0110
Sex[a]	< 0.0001	< 0.0001
Region of Treatment[b]	< 0.0001	< 0.0001
Dose (mg)[c]	0.0001	0.0038

Reference categories:
[a] Male patients
[b] Patients from countries other than Europe
[c] Patients in the 50/25 mg dose group

Figure 1. Kaplan-Meier Probability of Nausea

Figure 3. Kaplan-Meier Probability of Vomiting

Figure 2. First Occurrence of Nausea

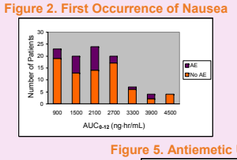


Figure 4. First Occurrence of Vomiting

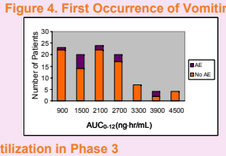
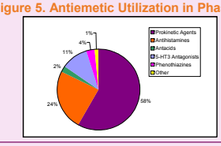


Figure 5. Antiemetic Utilization in Phase 3



CONCLUSIONS

- Nausea and vomiting were less likely to occur in older patients, men, European patients, and those in the 50/25 mg dose group.
- AUC_{0-12} and C_{max} were not significant predictors of nausea and vomiting in the Phase 2 and 3 patient population.
- A previous analysis using Phase 1 data, with doses ranging from 12.5 to 300 mg, identified AUC and C_{max} as significant predictors of the probability of the first occurrence of nausea and vomiting (< 0.0001) (J Passarell, et al. (P894) ECCMID 2004). The range of AUC values from the 50/25 mg and 100/50 mg dose arms in the Phase 2 and 3 trials, in combination with the small sample size, may not have provided enough power to detect a significant relationship.