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EXPOSURE-RESPONSE ANALYSIS OF THE EFFICACY OF TIGECYCLINE IN PATIENTS WITH COMPLICATED SKIN AND SKIN-STRUCTURE INFECTIONS

AK Meagher[1], JA Passarell[1], BB Cirincione[1], SA Van Wart[1], K Liolios[1], T Babinchak[2], EJ Ellis-Grosse[2], PG Ambrose[3]

[1]Cognigen Corporation, Buffalo, NY • [2]Wyeth Research, Collegeville, PA • [3]ICPD/Ordway Institute, Albany, NY

ABSTRACT

Objectives:

Tigecycline, the first glycylcycline to reach clinical trials, is in development for the treatment of patients with serious infections, including complicated skin and skin-structure infections (cSSSI). Pharmacokinetic/pharmacodynamic (PK/PD) relationships, including patient covariates, for microbiological and clinical efficacy of tigecycline were evaluated in patients with cSSSI.

Methods:

Patients from 3 cSSSI clinical trials (one phase 2 and two phase 3), with PK data and classified as both clinically and microbiologically evaluable, were pooled for analysis. A prospective approach for categorizing patients into cohorts was used and patients with infections due to *Staphylococcus aureus* and/or streptococci, the predominant pathogens in cSSSI, were the focus of this evaluation. Patients received 100-mg loading dose and 50 mg q12h (100/50) or 50-mg loading dose and 25 mg q12h (50/25). At the test of cure visit, microbiological (eradication or persistence) and clinical (cure or failure) outcomes were assessed. Indeterminate responses were excluded. Steady-state 24-hour area under the concentration-time curve (AUC) and AUC/MIC ratio were evaluated as predictors of response. Patient covariates included: age, weight, country, baseline *Pseudomonas aeruginosa* or anaerobes, and comorbidities (diabetes, peripheral vascular disease). Classification and regression tree (CART) analyses determined AUC/MIC breakpoints. Logistic regression (one observation/patient) was performed to determine predictors of efficacy.

Results:

The dataset included 35 patients with 40 *S. aureus* and/or streptococcal baseline pathogens. MIC values ranged from 0.06 to 0.5 μg/mL. Clinical cure was achieved in 30 (85.7%) patients and 35 (87.5%) pathogens were successfully eradicated. The median AUC/MIC ratio was 13.5 and 29 for the 50/25 and 100/50 mg dose groups, respectively. Covariates were not significant predictors of efficacy. CART identified a significant AUC/MIC breakpoint of 12.5 (p=0.0177 for microbiological and 0.0341 for clinical response). The continuous AUC/MIC ratio was marginally significant based on sample size (p=0.0563 for microbiological and 0.1960 for clinical response) and was deemed the most informative model. For each unit increase in AUC/MIC, within the observed range, patients were 3.7% more likely to have a successful clinical response and 17.1% more likely to have a successful microbiological response.

Conclusion:

Patients with AUC/MIC ratios ≥ 12.5 were 13 times more likely to have successful microbiological response. At the median AUC/MIC ratio of 13.5 and 29 for the 50/25 and 100/50 dose groups, the model-predicted probability of clinical success was 0.6597 and 0.9570, respectively. Tigecycline is likely to be an important treatment option for cSSSI.

BACKGROUND

- Tigecycline, a novel glycylcycline, has demonstrated an expanded spectrum of *in vitro* activity against gram-positive and gram-negative aerobic and anaerobic bacteria, including sensitive and multiple-drug resistant strains of methicillin-resistant *Staphylococcus aureus* (MRSA), streptococci, and vancomycin-resistant enterococcal species (VRE).
- Tigecycline has a time-dependent pattern of bactericidal activity against many gram-positive and gram-negative organisms, including streptococci, *Haemophilus influenzae*, and *Neisseria gonorrhoeae* in *in vitro* studies.[1]
- *In vivo* studies have demonstrated that tigecycline has a prolonged post-antibiotic effect (PAE) against *S. pneumoniae* and *E. coli* (8.9 and 4.9 hours, respectively).[2]
- The prolonged PAE, in combination with the relatively long half-life of tigecycline in humans (~40 hours), would suggest that the AUC/MIC ratio is likely to be the pharmacokinetic/pharmacodynamic (PK/PD) index predictive of therapeutic efficacy.[2,3]
- The goals of these analyses were:
  - To utilize a novel approach to evaluate the PK/PD relationships associated with the microbiological and clinical efficacy of tigecycline in the treatment of patients with complicated skin and skin-structure infections (cSSSI) due to *S. aureus* and/or streptococci, the predominant pathogens in cSSSI.[4]
  - To evaluate various patient demographic factors and covariates on clinical and microbiological outcomes.

METHODS

Patients

- Data from patients diagnosed with cSSSI enrolled in three completed clinical trials (one phase 2 and two phase 3 trials) were pooled for analysis.
  - Prior to analysis, patients were clinically evaluated and protocols were reviewed for differences in study design and inclusion and exclusion criteria to determine if the patient populations were homogeneous.

METHODS *cont'd.*

  - Patients in the phase 2 study received either tigecycline 50-mg loading dose followed by 25 mg twice daily (50/25) or 100-mg loading dose followed by 50 mg twice daily (100/50) for up to 14 days.
  - Patients in the phase 3 studies received the tigecycline 100/50 dosing regimen for up to 14 days.
  - The test-of-cure (TOC) visit occurred ≥ 14 days after the end of therapy.
- Patient- and disease-related descriptors were collected during the screening visit and evaluated as potential predictors of efficacy. It was assumed that baseline values remained constant for the duration of the trial.
  - Demographics: age, weight, gender, and region of treatment.
  - Baseline anaerobe and/or *P. aeruginosa*.
  - Monomicrobial or polymicrobial infection status.
  - Co-morbidities: pre-existing diabetes and peripheral vascular disease (PVD).

Pharmacokinetics

- Exposure estimates were generated using a previously developed population PK model for tigecycline.[5]
  - Individual Bayesian PK parameter estimates were used to predict steady-state tigecycline concentrations and calculate a 24-hour steady-state AUC.

Clinical and Microbiological Response

- Clinical efficacy was classified as cure (improvement or resolution of signs and symptoms), failure (persistence of presenting signs and symptoms or additional antibiotic required), or indeterminate.
- Microbiological efficacy was evaluated at both the pathogen and patient level.
  - At the pathogen level, a microbiological response of documented or presumed eradication, persistence, or indeterminate (death, lost to follow-up, or no baseline pathogen) was assigned.
  - The patient level microbiological response was categorized as eradication, persistence, superinfection, or indeterminate.
  - Patient-level microbiological responses classified as superinfections were evaluated:
    - If a patient had a pathogen-level microbiological response of eradication for all baseline pathogens, the patient-level microbiological response was categorized as a patient-level microbiological success.
    - If there was a mix of outcomes (both eradication and persistence) for baseline pathogens, the patient was categorized as a patient-level microbiological failure.
- Indeterminate clinical and microbiological responses were excluded.

Cohorts

- The methodology for the prospective cohort classification system and results from an all-pathogen analysis have been presented elsewhere.[4]
- Patients with infections due to *S. aureus* and/or streptococci, the predominant pathogens in cSSSI, were the focus of this evaluation.
- Baseline pathogens were identified for all evaluable patients and each patient was classified into one of five predefined cohorts (**Table 1**).
  - Minimum inhibitory concentrations (MIC) were identified for each baseline pathogen and an AUC/MIC ratio was calculated.
  - *S. epidermidis*, coagulase-negative staphylococci, and *Corynebacterium* were not considered pathogenic organisms in this analysis.

Table 1. Prospective Cohort Classification System

	Baseline Pathogens	MIC Range (μg/mL)	Number of Patients (Pathogens)	Pathogen Eradication (%)	Clinical Cure (%)
Cohort 1	Monomicrobial *S. aureus*	0.12 – 0.5	20 (20)	75%	85%
Cohort 2	Monomicrobial *S. aureus* or Streptococcus spp.	0.06 – 0.5	29 (29)	93%	93%
Cohort 3	Polymicrobial (2) gram-positive pathogens	0.06 – 0.5	7 (12)	92%	86%
Cohort 4	Polymicrobial (>2) gram-positive and/or gram-negative pathogens	0.06 – 16	14 (39)	79%	71%
Cohort 5	Other: monomicrobial anaerobes or gram-negative pathogens	0.25 – 1	8 (8)	100%	100%

Statistical Analyses

- Prior to conducting the statistical analyses, the sample size within each cohort was evaluated to determine whether exploratory or statistical analyses could be performed or if cohorts should be combined to increase sample size.
- All data processing, data clean-up, database creation, and statistical analyses were performed using SAS® software, version 8.2, unless otherwise specified. Analyses were performed using S-Plus, version 6.2.

METHODS *cont'd.*

- Using S-Plus, version 6.2, classification and regression tree (CART) analyses were performed separately for each cohort to determine breakpoints in exposure measures stratified by response.
- Logistic regression analyses were used to determine whether exposure measures and patient covariates were statistically significant predictors of response.
  - In the case of multiple observations (pathogens) per patient, logistic regression using Generalized Estimating Equations (GEE) was used.
- Univariate analyses were followed by multivariable modeling utilizing a backward elimination procedure with a level of significance defined by sample size to identify predictor variables with a statistically significant influence on microbiological or clinical response.
- 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.

RESULTS

Patients

- There were 61 patients (**Table 2**) with 91 pathogens who were clinically, microbiologically, and pharmacokinetically evaluable.
  - Approximately 57% and 43% of patients were administered the 100/50 and 50/25 mg dosage regimens.
  - Approximately 10% of patients had PVD and 26% had diabetes.
  - 56% of patients had monomicrobial infections at baseline, 31% had two baseline pathogens, and 13% had three or more baseline pathogens.
  - Five (8%) patients had an anaerobe at baseline.
  - Four (7%) patients had *P. aeruginosa* (MIC range 8 to 16 μg/mL) at baseline.
- One patient with recurrent foreign body infections may have been inappropriately enrolled in one of the phase 3 cSSSI trials and was deemed a potential medical outlier. This patient had recurring *S. aureus* abscesses at the site of a hernia repair where prolene mesh had been surgically inserted and had not been removed.

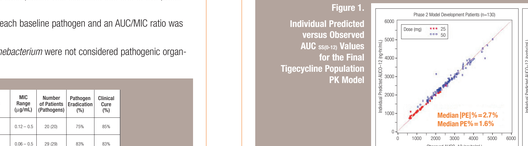
Table 2. Summary Statistics of Patient Demographic Characteristics (n=61)

Demographic Characteristic	Summary Statistics
Age (years) [mean (SD)]	45.8 (15.3)
Weight (kg) [mean (SD)]	81.2 (21.7)
Height (cm) [mean (SD)]	172 (7.45)
Gender, n (%) Male Female	44 (72) 17 (28)
Ethnicity, n (%) Caucasian Black Hispanic Other	38 (62.3) 7 (11.5) 13 (21.3) 3 (4.92)
Region of Treatment, n (%) Europe USA	17 (28) 44 (72)
Study Phase, n (%) Phase 2 Phase 3	42 (69) 19 (31)

Pharmacokinetics

- The final population PK model for tigecycline was a two-compartment model with zero-order input and first-order elimination. **Figure 1** shows the goodness-of-fit plots for the population PK model.

Figure 1. Individual Predicted versus Observed AUC 0(0-12) Values for the Final Tigecycline Population PK Model



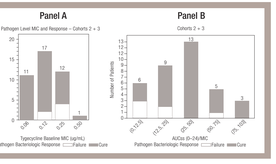
- Patient demographics and observed tigecycline concentration data were similar between phase 2 and phase 3 patients (data not shown).
- The phase 2 model provided a relatively unbiased fit to the phase 3 cSSSI patient data without model refinement.

Statistical analyses

- Based on an adequate distribution of cures and failures and sufficient sample size, the final dataset included 36 patients (combined Cohorts 2 and 3) with 41 *S. aureus* and/or streptococcal baseline pathogens (**Figure 2, panel A**).
- The analysis was performed both with and without (n=35) the potential medical outlier (recurrent *S. aureus* foreign body infections).

RESULTS *cont'd.*

Figure 2. Frequency Distribution of MIC and AUC/MIC Values for Patients in Cohorts 2 and 3 (n=36)



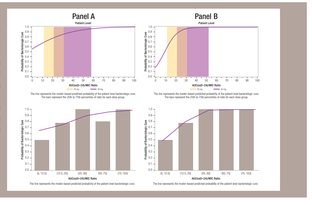
- For all patients administered the 50/25 regimen, the mean (SD) AUC and AUC/MIC values were 2.67 (0.99) μg·hr/mL (range 1.49 to 4.98 μg·hr/mL) and 13.3 (13.5) (range 0.09 to 54.1), respectively.
- The mean (SD) AUC and AUC/MIC values for the 50/100 regimen were 5.46 (1.62) μg·hr/mL (range 2.81 to 9.36 μg·hr/mL) and 33.4 (24.3) (range 0.21 to 102), respectively.
- Similar ranges of AUC values were observed across each cohort.
- **Figure 2, panel B** displays the distribution of AUC/MIC values for patients in combined Cohorts 2 and 3.

- CART analysis identified AUC/MIC breakpoints at 12.5 and 16.4.
  - The AUC/MIC breakpoint at 12.5 occurred more frequently and had a better distribution of cures and failures around the breakpoint: 7 (32%) and 3 (8%) microbiological failures occurred below and above the breakpoint, respectively (p = 0.0324).
  - At the CART-identified breakpoint of 16.4, 8 (30%) and 2 (6%) microbiological failures occurred below and above the breakpoint respectively (p = 0.0340).
- Standard logistic regression (one observation per patient) was used since the majority of data included monomicrobial infections.

Microbiological Response for Combined Cohorts 2 and 3

- The pathogen-level microbiological responses (% eradication) are displayed in **Table 1**.
- Due to small sample size, the presence of a baseline anaerobe or *P. aeruginosa* and monomicrobial infection status as covariates could not be evaluated.
- Pre-existing diabetes and PVD could not be evaluated as categorical covariates due to the distribution of outcomes.
- Univariate logistic regression models indicated that the CART-identified AUC/MIC breakpoints at 12.5 and 16.4 were statistically significant predictors of microbiological response (p = 0.0309 and 0.0118, respectively).
  - An odds ratio of 9 and 13 were identified for the AUC/MIC breakpoints of 12.5 and 16.4, respectively.
  - The AUC/MIC ratio (as a continuous covariate) was on the verge of statistical significance (p = 0.1130) and provided the most informative model for these data (**Figure 3, Panel A**).

Figure 3. Final Logistic Regression Models of Microbiological Response versus AUC/MIC Ratio for Cohorts 2 & 3 with and without a Potential Medical Outlier by Dose Group and Overlaid on Observed MIC Data



- The Hosmer-Lemeshow goodness-of-fit statistic was 11.45 with 7 degrees of freedom (p = 0.1201) and the area under the ROC curve was 0.78, indicating an adequate and predictive model.
- At the median exposure values of AUC/MIC ratio of 13.5 and 29 for the 50/25 and 100/50 mg dose groups, the model-predicted probability of microbiological success was 0.7024 and 0.8352, respectively.
- None of the other exposure measures (AUC) or patient covariates were significant predictors of microbiological success.

RESULTS *cont'd.*

Microbiological Response for Cohorts 2 and 3 Excluding Medical Outlier

- The potential medical outlier enrolled with an infection due to *S. aureus* (MIC = 0.12 μg/mL) had an AUC and AUC/MIC value of 7.8 μg·hr/mL and 65, respectively, and was considered a microbiological failure.
- Excluding this outlier (**Figure 3, Panel B**), the univariate logistic regression model identified AUC/MIC ratio (as a continuous covariate) as a predictor of microbiological success (p = 0.0563) and the significance of this relationship was increased as compared to the model including this outlier (p = 0.1130).
  - The Hosmer-Lemeshow goodness-of-fit statistic was 5.25 with 6 degrees of freedom (p = 0.5121) and the area under the ROC curve was 0.89, indicating a highly predictive model.
- The CART-identified AUC/MIC breakpoints at 12.5 and 16.4 were also statistically significant predictors of microbiological success (p = 0.0177 and 0.0086, respectively).
  - The odds ratios for the AUC/MIC breakpoints of 12.5 and 16.4 increased to 13.5 and 25.9, respectively.
- In addition, AUC became a borderline statistically significant predictor (p = 0.0595), whereas, with this patient included, it was not significant (p = 0.2951).
- At the median AUC/MIC values of 13.5 and 29 for the 50/25 and 100/50 mg dose groups, the model-predicted probability of microbiological success was 0.6597 and 0.9570, respectively.

Clinical Response for Combined Cohorts 2 and 3 With and Without Outlier

- 30/36 (83%) patients in combined Cohorts 2 and 3 were clinically cured.
- Univariate logistic regression models identified AUC/MIC ratio (as a continuous covariate) to be on the verge of statistical significance (p = 0.1723)
- The CART-identified AUC/MIC breakpoint of 12.5 was a statistically significant predictor of clinical response (p = 0.0309) and AUC was also a marginally statistically significant predictor of clinical response (p = 0.0650).
- Excluding the potential medical outlier had little effect on the clinical response models since the patient was classified as a clinical cure.

CONCLUSIONS

- Using an approach to categorize cSSSI patients treated with tigecycline into cohorts based on pathogens encountered most often in this infectious disease, *S. aureus* and/or streptococci, resulted in the identification of an exposure-response relationship for microbiological outcome. The strength of this relationship was dramatically increased with the exclusion of a patient with recurrent foreign body infections.
- The CART-identified AUC/MIC breakpoint of 12.5 was a remarkably consistent across both clinical and microbiological outcomes as a significant predictor of success, regardless of inclusion or exclusion of the single patient identified as a medical outlier.
- A trend towards an exposure-response relationship using AUC/MIC ratio as a continuous variable was identified for predicting microbiological and clinical success. The significance of the relationship for microbiological outcome was greatly increased with the exclusion of the outlier. This patient was considered clinically cured, however, and a strengthened relationship for clinical response was not observed.
- Given these positive results, tigecycline is likely to be an important antimicrobial agent for the treatment of complicated skin and skin-structure infections.

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