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A NOVEL APPROACH FOR EVALUATING THE MICROBIOLOGICAL EFFICACY OF TIGECYCLINE IN PATIENTS WITH COMPLICATED SKIN AND SKIN-STRUCTURE INFECTIONS

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ABSTRACT

Objectives:

Tigecycline is a glycylcycline in development for the treatment of patients with serious infections, including complicated skin and skin-structure infections (cSSSI). While cSSSI can be caused by a mixture of gram-positive and gram-negative bacteria, *Staphylococcus aureus* and streptococci are the predominant pathogens. Previous analyses by others combining all pathogens have failed to identify an exposure-response relationship. A prospective method was developed to create more homogenous patient populations for the microbiologic exposure-response analysis of tigecycline in the treatment of cSSSI.

Methods:

Patients from 3 cSSSI clinical trials (one phase 2 & two phase 3), with tigecycline pharmacokinetic data and classified as both clinically and microbiologically evaluable, were pooled for analysis. Patients received 100-mg loading dose/50mg q12h (100/50) or 50-mg loading dose/25mg q12h (50/25). At the test of cure visit, microbiologic (eradication or persistence) response was evaluated. Indeterminate responses were excluded. Non-pathogenic baseline isolates were excluded. Five patient cohorts were created based on baseline pathogens: *S. aureus* only (Cohort 1); *S. aureus* or streptococci (Cohort 2); 2 gram-positive pathogens (Cohort 3); polymicrobial (Cohort 4); other monomicrobial infections (Cohort 5). Prospective step-wise procedures for combining cohorts to increase sample size were used. Logistic regression was used to evaluate steady-state 24hr area under the concentration-time curve (AUC) to MIC ratio (AUC/MIC) to predict response.

Results:

The dataset included 58 patients with 88 observations. Cohort 1 (n=20) and Cohort 2 (n=29) could not be evaluated due to small sample size. Analysis began with pooled Cohorts 2 and 3. Continuous AUC/MIC ratio was marginally significant (p=0.1130); a patient was 5.1% more likely to have successful response for every one-unit increase in AUC/MIC. Adding Cohort 4, including pathogens with MIC values up to 16 μg/mL, decreased AUC/MIC, added cures to the lower end of the distribution, and added significant noise to the analysis. Adding Cohort 5 increased sample size and further decreased the ability to detect a relationship.

Conclusion:

Analysis of all pathogens combined could not identify an exposure-response relationship. Polymicrobial infections with gram-negative and anaerobic pathogens, associated with high MIC values, added noise to the analysis and decreased the predictive capability of the model. The prospective approach of creating homogenous populations based on two key pathogens in cSSSI, *S. aureus* and streptococci, was critical for identifying significant exposure-response relationships.

INTRODUCTION

- The detection of an exposure-response relationship in heterogeneous patient and/or pathogen populations has proven to be challenging, especially when analyzing infectious diseases that are polymicrobial in nature and those with small datasets. Analyses performed by others have been unsuccessful in identifying relationships when all pathogens are considered together.
- One of the objectives for a population PK/PD exposure-response analysis of the efficacy of tigecycline in patients with complicated skin and skin-structure infections (cSSSI) was to assess the relationship between drug exposure and microbiological response.[1] In an attempt to create more homogeneous populations for analysis, we prospectively reviewed and categorized patients based on pathogens encountered most often in cSSSI.
- Although cSSSI can be caused by a mixture of gram-positive and gram-negative aerobic and anaerobic bacteria, the predominant pathogens are gram-positive organisms, including *Staphylococcus aureus* and streptococci.[2,3]

INTRODUCTION *cont'd.*

- Prospectively categorizing patients into cohorts based on pathogens encountered most often in cSSSI (i.e., *S. aureus* and streptococci) will yield a more homogeneous patient population and may enhance the ability to establish an association between microbiological response and tigecycline exposure measures.
- Tigecycline is a new first-in-class glycylcycline antibiotic with expanded activity against both gram-negative and gram-positive aerobes and anaerobes. The spectrum of activity includes organisms frequently encountered in the treatment of cSSSI, including sensitive and multidrug-resistant *S. aureus*, streptococci, and vancomycin-resistant enterococci.

METHODS

- The analysis included patients with cSSSI from one phase 2 and two phase 3 clinical trials.
  - Clinical trials were assessed for the appropriateness of pooling data.
  - Protocols were reviewed for trial design and inclusion and exclusion criteria to determine if the patients represented in these trials were homogenous in nature.
- Patients received tigecycline as either a 50-mg loading dose followed by 25 mg every 12 hours (50/25; phase 2 only) or a 100-mg loading dose followed by 50 mg every 12 hours (100/50, phases 2 and 3).
- Patients classified as both clinically and microbiologically evaluable at the test-of-cure visit (≥ 14 days after end of therapy) and those having tigecycline exposure measurements (PK) were included.
- Microbiological efficacy was evaluated at the pathogen and patient level.
  - Microbiological responses at the pathogen level were categorized as eradication (documented or presumed), persistence (documented or presumed), or indeterminate.
  - Patient-level microbiological responses were categorized as eradication (documented or presumed), persistence (documented or presumed), superinfection, or indeterminate.
  - If the TOC patient-level microbiological outcome was classified as a superinfection, it was treated in one of two ways for this analysis:
    - Patients with pathogen-level microbiological responses of eradication for all baseline pathogens at the end of therapy were categorized as a patient-level microbiological success.
    - Patients with multiple baseline pathogens and a mix of outcomes (both eradication and persistence), were classified as a patient-level microbiological failure.
- Clinical responses were categorized as cure (resolution of the skin infection), failure (additional surgical and/or additional antimicrobial therapy required, or death), or indeterminate.
- Indeterminate clinical and microbiological responses were not considered in this analysis.
- Prior to conducting the analysis, baseline pathogens were evaluated and pathogenic and non-pathogenic species were identified.
  - *S. epidermidis*, coagulase-negative staphylococci, and *Corynebacterium* were not considered pathogenic organisms.
- Each patient was then classified into one of five cohorts, depending upon the specific pathogens present at baseline (**Table 1**).
- Prior to conducting the statistical analysis, the sample size within each cohort was evaluated to determine whether exploratory or statistical analyses could be performed or if cohorts needed to be combined to increase sample size.
- A prospective procedure for combining cohorts to increase sample size via evaluation of the distribution of cures and failures within cohorts was employed.
- An additional analysis of all pathogens combined was performed to justify the use of the cohort classification system.

METHODS *cont'd.*

- Bayesian parameter estimates from a previous tigecycline population PK model were utilized to generate individual estimates of tigecycline exposure (AUC and AUC/MIC ratio)
- Exploratory analysis of microbiological response was conducted to identify relationships between outcome and exposure measurements.
- Logistic regression analyses were used to determine whether exposure measures were statistically significant predictors of microbiological response.
- In the case of multiple observations per patient (multiple pathogens), logistic regression using Generalized Estimating Equations (GEE) was used.
- 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.

Table 1. Baseline Pathogen Classification System

Cohort	Baseline Pathogen(s)	MIC Range (μg/mL)	Number of Patients
1	Patients with monomicrobial *S. aureus infections*	0.12 – 0.5	20
2	Patients with monomicrobial *S. aureus* **or** *Streptococcus* spp. infections (includes Cohort 1)	0.06 – 0.5	29
3	Patients with polymicrobial infections with *S. aureus* **plus** *Streptococcus* spp. **or** patients with two *Streptococcus* spp.	0.06 – 0.5	7
4	Patients with other polymicrobial gram-negative +/- gram-positive infections	0.06 – 16	14
5	Patients with gram-negative or anaerobic monomicrobial infections	0.25 – 1	8

RESULTS

- For the 50/25 mg dose group, the median (range) AUC and AUC/MIC values were 2.33 (1.49 – 4.98) μg·hr/mL and 9.5 (0.1 – 54), respectively.
- For the 100/50 mg dose group, the median (range) AUC and AUC/MIC values were 5.16 (2.81 – 9.36) μg·hr/mL) and 29 (0.2 – 102).
- The final analysis dataset included 58 patients with 88 pathogens (**Table 1**).
- The frequency distribution of AUC and AUC/MIC ratios for combined Cohorts 2, 3, and 4 are displayed in **Figures 1. and 2.**, respectively.

Figure 1. Frequency Distribution of Baseline MIC Values for Patients Included in Cohorts 2, 3, and 4

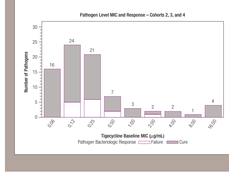
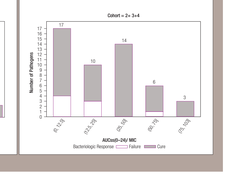


Figure 2. Frequency Distribution of AUC/MIC Values for Patients Included in Cohorts 2, 3, and 4



RESULTS *cont'd.*

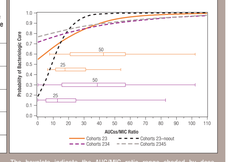
- Cohort 1 had only 20 patients with monomicrobial *S. aureus* infections and Cohort 2, which included patients in Cohort 1, had only 29 patients with monomicrobial gram-positive infections. Formal statistical analyses could not be performed due to small sample size.
- Analysis began with combined Cohorts 2 and 3 (36 patients and 41 pathogens) and since the majority of patients had monomicrobial infections, standard logistic regression analysis (one observation per patient defined by patient-level response) was used.
- This analysis was performed both with and without a potential medical outlier.
  - This patient had a history of hernia repair with prolene mesh (unremoved) and recurrent *S. aureus* abscess formation at the surgical site. The baseline pathogen was documented as *S. aureus* (MIC 0.12 μg/mL) and the AUC/MIC ratio was approximately 65.
- **Table 2** provides a summary of microbiological response for combined cohorts and the model-predicted probability of microbiological response is represented in **Figure 3**.

Table 2. Microbiological Response Rates Stratified by Combined Cohorts

Cohorts (Patients/ Pathogens)	Pathogen-Level Microbiological Response		Odds Ratio for AUC/MIC	Area under the ROC[a] Curve
	Eradication n (%)	Persistence n (%)		
2 + 3 excluding outlier (35/40)	35 (88%)	5 (12%)	1.171	0.890
2 + 3 including outlier (36/41)	35 (85%)	6 (15%)	1.051	0.767
2 + 3 + 4 (50/80)	66 (83%)	14 (17%)	1.025	0.611
2 + 3 + 4 + 5 (58/88)	74 (84%)	14 (16%)	1.023	0.604

[a] Receiver Operator Characteristic

Figure 3. Probability of Microbiological Eradication versus AUC/MIC Ratio



The boxplots indicate the AUC/MIC ratio range shaded by dose. The grey dashed line represents Cohorts 2, 3, 4, and 5 combined; the purple dashed line represents Cohorts 2,3, and 4 combined; the orange solid line represents Cohorts 2 and 3 combined; and the black dashed line represents Cohorts 2 and 3 combined excluding a potential medical outlier.

- For combined Cohorts 2 and 3, the AUC/MIC ratio (as a continuous covariate) was marginally statistically significant and provided the most informative model for these data.
  - As the AUC/MIC ratio increased, the model-predicted probability of microbiological success increased.
  - The odds ratio of 1.051 indicated that for a one-unit increase in AUC/MIC, a patient was 5.1% more likely to have a successful microbiological response.
- Excluding the potential medical outlier from the combined Cohorts 2 and 3, the ER relationship was strengthened.
  - The significance of the AUC/MIC ratio as a continuous covariate increased dramatically and the odds ratio increased to 1.171.
  - Removal of the potential medical outlier improved the model fit and resulted in an increased ROC value of 0.89, indicating a highly predictive model.
- An additional step was taken to evaluate the impact of adding polymicrobial infections (Cohort 4).
  - Combined Cohorts 2, 3, and 4 included 50 patients with 80 pathogens.

RESULTS *cont'd.*

- Since 58% of these patients had polymicrobial infections, longitudinal logistic regression analyses defined by multiple pathogens using Generalized Estimating Equations (GEE) were required.
- The AUC/MIC ratio (as a continuous covariate) was on the verge of statistical significance and the odds ratio was 1.025 indicating a smaller magnitude of effect as compared to the two previous models.
- The area under the ROC curve was 0.61 indicating a less predictive model as compared to the two previous models.
- Finally, Cohorts 2, 3, 4, and 5 were combined to evaluate the effect of combining all pathogens in an exposure-response analysis.
  - 58 patients with 88 pathogens were included in the all-pathogen analysis.
  - The AUC/MIC ratio (as a continuous covariate) was not statistically significant.
- Although combining cohorts increased the sample size and potentially the ability to detect an exposure-response relationship, the magnitude of the effect decreased due to increased heterogeneity in the patient population.

DISCUSSION and CONCLUSIONS

- Heterogeneous patient and/or pathogen populations can hinder the detection of exposure-response relationships. Such heterogeneity can be especially problematic when analyzing small datasets.
- We hypothesized that our ability to detect exposure-response relationships would increase with patient and infecting pathogen population homogeneity and prospectively created pathogen cohorts to test this hypothesis.
- We demonstrated that sensitivity and specificity, as measured by the ROC value, increase as population homogeneity increased. The strongest exposure-response relationship, as measured by the AUC/MIC ratio, was associated with the most homogeneous patient and pathogen population.
- These findings may suggest that the AUC/MIC ratio predictive of response is likely different for those pathogens in Cohort 2 and 3 (staphylococci and streptococci) versus those in Cohorts 4 and 5 (gram-negative bacilli and anaerobes).
- Grouping patients into cohorts based on pathogens encountered most often in the treatment of complicated skin and skin-structure infections (i.e.; gram-positive organisms) and evaluating them in a prospective iterative fashion proved to be a valuable approach in detecting an exposure-response relationship.

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