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Noncompartmental Pharmacokinetics of Tigecycline in Phase 3 Studies of Patients with Complicated Skin and Skin-Structure and Intra-Abdominal Infections

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ABSTRACT

Purpose. Tigecycline is the first glycylcycline to reach Phase 3 clinical trials and is active against multidrug-resistant organisms. Four Phase 3 studies have examined tigecycline for the treatment of complicated skin and skin-structure (cSSSI) and intra-abdominal infections (cIAI). Pharmacokinetics (PK) of multiple-dose tigecycline in subsets of patients with cSSSI and cIAI from three of these studies have been examined and compared.

Methods. cSSSI and cIAI were studied separately. Patients received a loading dose infusion of tigecycline (100 mg) followed by 50 mg every 12 hr for up to 14 days. Infusion durations were 0.5 hr (cIAI) or 1 hr (cSSSI). Four blood samples for PK analysis were obtained on the day of or the day before discharge from the hospital. Samples were collected before start of infusion, at the end of infusion, and 3 and 6 hr after start of infusion. Serum was analyzed by LC/MS/MS. $C_{ss,max}$, $C_{ss,min}$, AUC_{ss}, and clearance (CL) were calculated using noncompartmental methods.

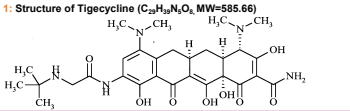
Results. A total of 122 patients were included in the PK analysis of the three studies (107 cIAI and 15 cSSSI patients). All patients received at least six doses of tigecycline before PK sampling (steady-state). The mean AUC_{0-12} values from all studies correlated to a daily AUC greater than the target, 6 μg·hr/mL, determined from previous studies. Mean (± SD) values for $C_{ss,max}$, $C_{ss,min}$, AUC_{ss} and CL in one of the cIAI studies (n = 83) were 794 ng/mL (± 479), 152 ng/mL (± 72), 3.16 μg·hr/mL (± 1.46) and 18.3 L/hr (± 6.9), respectively. Mean AUC_{ss} and CL values in the cIAI and cSSSI patients were similar to those observed in healthy subjects and previously studied patients with cIAI and cSSSI. $C_{ss,max}$ values were similar to those observed in previous studies with comparable infusion durations. AUC_{ss} and CL values between Phase 3 cSSSI and cIAI patients were in the same range.

Conclusions. These studies demonstrate no substantial differences in steady-state PK parameters of tigecycline between healthy subjects and patients with cSSSI and cIAI, suggesting similar exposures to tigecycline among all groups studied.

BACKGROUND

- Tigecycline (Tygacil™) is a first-in-class glycylcycline that exhibits a broad spectrum of activity against many aerobic and anaerobic gram-positive and gram-negative organisms, as well as atypical pathogens, including many multiple-drug resistant organisms.

Figure 1: Structure of Tigecycline ($C_{29}H_{39}N_5O_8$, MW=585.66)



- Pharmacokinetic/pharmacodynamic analyses in experimental animal models of infection have indicated that AUC:MIC ratio is the index that is most likely to correlate with the efficacy of tigecycline
- The efficacy of tigecycline against pathogens responsible for skin and skin-structure infections and intra-abdominal infections has been demonstrated in Phase 2 and 3 trials. Tigecycline has been approved for use against cSSSI and cIAI.
- Tigecycline has a mean half-life following intravenous (IV) infusion of between 30-60 hr. The volume of distribution at steady-state is approximately 700-1300 L, indicating extensive distribution into tissues.
- This study presents the Phase 3 noncompartmental analysis for tigecycline in patients with either cSSSI or cIAI as portions of studies comparing tigecycline treatment to vancomycin/aztreonam (cSSSI) or imipenem/cilastatin (cIAI) treatment.

OBJECTIVE

To evaluate the noncompartmental PK parameters of tigecycline in serum from a subset of patients with either cSSSI or cIAI participating in one of three Phase 3 trials.

METHODS

Subjects

- Patients enrolled in Studies 3074A1-301-WW and 3074A1-306-WW consisted of hospitalized patients with cIAI.
- Patients enrolled in Study 3074A1-305-WW had clinical signs and symptoms of cSSSI.
- Patients were randomly assigned (in a 1:1 ratio) to receive either:
  - IV tigecycline with placebo or imipenem/cilastatin for up to two weeks (for patients with cIAI) or
  - IV tigecycline or vancomycin/aztreonam treatment (for patients with cSSSI).
- Patients remained hospitalized until the end of test article administration.
- The subsets of patients receiving IV tigecycline are included in this presentation.

Dosage

- Studies 3074A1-301-WW and 3074A1-306-WW
  - Patients received a 100-mg IV infusion of tigecycline followed 12 hr later by 50-mg tigecycline infusions twice a day (approximately every 12 hr). Additionally, patients received placebo (100 mL normal saline) IV doses every 12 hr starting 6 hr after the first tigecycline dose.
  - All infusions of tigecycline were 0.5 hr in duration.
- Study 3074A1-305-WW
  - Patients received a 100-mg IV infusion of tigecycline followed 12 hr later by 50-mg tigecycline infusions twice a day (approximately every 12 hr).
  - All infusions of tigecycline were 1 hr in duration.

Sampling

- Blood samples for tigecycline PK analysis were drawn from patients on the day of or the day prior to discharge from the hospital.
- 5-mL samples were drawn at the following times: immediately before the start of infusion, immediately at the end of infusion (0.5 or 1.0 hr), 3 hr from the start of infusion, and 6 hr from the start of infusion.

Drug Analysis

- Serum tigecycline concentrations were quantified using a validated LC/MS/MS methodology with a lower limit of quantitation of 10 ng/mL.
- The overall precision and accuracy for standards and QC samples were in the range of 0.9% to 12% and 93% to 110%, respectively.

Noncompartmental Analysis

- PK parameters were calculated using WinNonlin® Professional Version 4.0.
- The pre-dose serum concentration (the trough steady-state concentration) was assigned to the time of the start of infusion (zero time).
- Additionally, this zero hr concentration-time point was assigned to the 12-hr time point.
- AUC_{ss} was determined by the log-linear trapezoidal rule (Method 3 in WinNonlin) from time zero to the 12-hr assigned concentration.
  - Linear trapezoidal rule used between two increasing concentration-time points
  - Log trapezoidal rule between two decreasing concentration-time points
- $C_{ss,max}$ and $C_{ss,min}$ were obtained directly from the observed concentration data.
- Systemic CL for tigecycline was calculated by WinNonlin using **Equations 1 and 2**.

$$CL = (Dose/AUC_{ss}) \quad \textbf{(1)}$$

$$CL = (Dose/AUC_{ss})/BWT \quad \textbf{(2)}$$

Where, BWT = patient body weight.

- Patients were excluded from PK analysis if one or more of the four concentration-time points for AUC calculation were missing or below the limit of quantitation or if the actual $C_{ss,max}$ was not at the end of infusion point (0.5- or 1-hr sample).

RESULTS

- 24 patients from Study 3074A1-301-WW (72.2 ± 16.9 kg, mean ± SD), 83 patients from Study 3074A1-306-WW (74.8 ± 13.8 kg), and 15 patients from Study 3074A1-305-WW (83.7 ± 33.7 kg) were included in the PK analysis.
- For the purposes of summarizing the data, mean PK parameters were calculated independent of the number of previous doses that the patient had received. All patients in this analysis received at least six doses prior to the PK sampling dose. Previous analyses have shown that steady-state conditions have been achieved by the sixth dose.
- Tigecycline serum concentration versus time profiles are presented in **Figures 2, 3, and 4** (mean profiles) and **Figures 5, 6, and 7** (individual profiles). Mean $C_{ss,max}$, $C_{ss,min}$, AUC_{ss}, and CL values from these Phase 3 studies are compared to results from Phase 1 and Phase 2 studies in **Tables 1 and 2**.

Figure 2: Mean (SD) Steady-State Tigecycline Serum Concentration-Time Profile After a 100-mg Loading Dose Followed 12 hr Later by 50 mg bid (n = 24) in Patients with cIAI (Study 3074A1-301-WW)

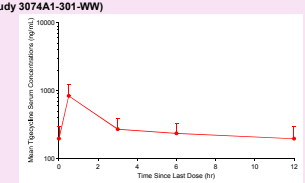


Figure 3: Mean (SD) Steady-State Tigecycline Serum Concentration-Time Profile After a 100-mg Loading Dose Followed 12 hr Later by 50 mg bid (n = 83) in Patients with cIAI (Study 3074A1-306-WW)

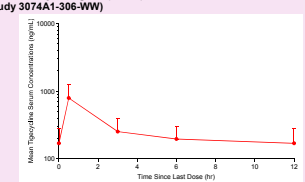


Figure 4: Mean (SD) Steady-State Tigecycline Serum Concentration-Time Profile After a 100-mg Loading Dose Followed 12 hr Later by 50 mg bid (n = 15) in Patients with cSSSI (Study 3074A1-305-WW)

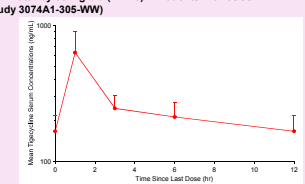


Figure 5: Individual and Mean (solid line) Steady-State Serum Concentrations of Tigecycline within a Dosage Interval After a 100-mg Loading Dose Followed 12 hr Later by 50 mg bid (n = 24) in Patients with cIAI (Study 3074A1-301-WW)

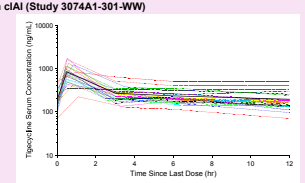


Figure 6: Individual and Mean (solid line) Steady-State Serum Concentrations of Tigecycline within a Dosage Interval After a 100-mg Loading Dose Followed 12 hr Later by 50 mg bid (n = 83) in Patients with cIAI (Study 3074A1-306-WW)

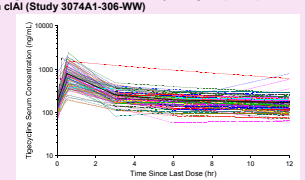


Figure 7: Individual and Mean (solid line) Steady-State Serum Concentrations of Tigecycline within a Dosage Interval After a 100-mg Loading Dose Followed 12 hr Later by 50 mg bid (n = 15) in Patients with cSSSI (Study 3074A1-305-WW)

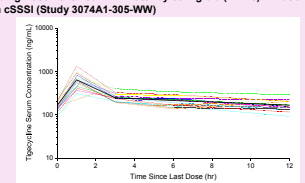


Table 1: Comparison of Mean PK Parameters at Steady-State of Tigecycline in Healthy Subjects and in Patients with cIAI

PK Parameters	Healthy Subjects[a]	Patients with cIAI		
	3074A1-101-US (n = 5)	3074A1-202-US[b] (n = 65)	3074A1-306-WW[c] (n = 83)	3074A1-301-WW[c] (n = 24)
$C_{ss,max}$ (μg/mL)	—[d]	—[d]	0.794 (60)	0.837 (47)
$C_{ss,min}$ (μg/mL)	0.145 (16)	0.179 (38)	0.152 (47)	0.192 (51)
AUC_{ss} (μg·hr/mL)	3.07 (12)	2.88 (31)	3.16 (46)	3.52 (37)
CL (L/hr)	16.5 (12)	19.1 (34)	18.3 (37)	15.9 (36)

Data are presented as Mean (%CV)

[a] In the Phase 1 Study (3074A1-101-US), subjects received 50 mg tigecycline bid with PK sampling on Day 9 or Day 10 (1-hr infusions).
[b] In the Phase 2 Study (3074A1-202-US), patients received 50 mg tigecycline bid 12 hr after a 100-mg loading dose (1-hr infusions).
[c] In the Phase 3 Studies (3074A1-306-WW and 3074A1-301-WW), patients received 50 mg tigecycline bid 12 hr after a 100-mg loading dose (0.5-hr infusions).
[d] Value not included, comparison to Studies 3074A1-301-WW and 3074A1-306-WW are inappropriate due to differing infusion times.

Table 2: Comparison of Mean PK Parameters at Steady-State of Tigecycline in Healthy Subjects and Patients with cSSSI

PK Parameters	Healthy Subjects[a]	Patients with cSSSI[b]	
	3074A1-101-US (n = 5)	3074A1-200-US (n = 43)	3074A1-305-WW (n = 15)
$C_{ss,max}$ (μg/mL)	0.621 (15)	0.403 (45)	0.633 (22)
$C_{ss,min}$ (μg/mL)	0.145 (16)	0.140 (52)	0.162 (31)
AUC_{ss} (μg·hr/mL)	3.07 (12)	2.24 (40)	3.04 (27)
CL (L/hr/kg)	0.204 (9)	0.313 (40)	0.221 (28)

Data are presented as Mean (%CV)

[a] In the Phase 1 study (3074A1-101-US), subjects received 50 mg tigecycline bid with PK sampling on Day 9 or Day 10 (1-hr infusions).
[b] In the Phase 2 (3074A1-200-US) and Phase 3 (3074A1-305-WW) studies, patients received 50 mg tigecycline bid 12 hr after a 100-mg loading dose (1-hr infusions).

CONCLUSIONS

- The mean AUC_{0-12} for patients in Phase 3 studies with either cSSSI or cIAI was greater than 3.0 μg·hr/mL. This would correlate to a daily AUC of greater than 6 μg·hr/mL which is consistent with previous target AUC values from both animal and clinical studies.
- These studies demonstrate no substantial differences in steady-state PK parameters ($C_{ss,max}$, $C_{ss,min}$, AUC_{ss}, and CL) of tigecycline between healthy subjects and patients with cSSSI and cIAI, suggesting similar exposures to tigecycline among all groups studied.