A Pharmacometric Comparison of Omadacycline and Tigecycline Epithelial Lining Fluid Penetration

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ABSTRACT

Background: Omadacycline, a novel aminomethylcycline antibiotic active against Gram-positive and Gram–negative organisms, is in development for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP). Data from a Phase 1 epithelial lining fluid (ELF) study were used to develop population pharmacokinetic (PK) models to describe the time course of omadacycline and tigecycline in both plasma and ELF.

Methods: Subjects were randomized to receive either omadacycline 100 mg IV q12h x 2 doses followed by 100 mg q24h or tigecycline 100 mg IV x 1 then 50 mg q12h (42 and 21 subjects, respectively). Plasma and ELF samples were collected on Day 4 of therapy. Population PK models were fit to the collected data using NONMEN 7.2. The structural models for plasma were based on previously published population PK models [ECCMID 2016; poster P1320, AAC 2006; 50:3701–7]. Various structural models were evaluated for the characterization of ELF concentrations. Day 4 total-drug ELF and total- and free-drug plasma area under the concentration time curve (AUC) values were computed using numeric integration; these data were used to determine ELF penetration ratios. A fixed protein binding estimate (20%) was used for omadacycline while a non-linear function was used to describe tigecycline's protein binding [AAC 2010; 54:5209-13].

Results: Linear three- and two-compartment models with ELF incorporated into the first peripheral compartment best described the omadacycline and tigecycline PK data, respectively. The ELF visual predictive checks displayed in Figure 1 show that the models accurately captured the omadacycline and tigecycline ELF concentration-time profiles. Model-computed omadacycline and tigecycline total-drug ELF AUC to total-drug plasma AUC ratios were 1.54 and 1.16, respectively. Model-computed total-drug ELF AUC to free-drug plasma AUC ratios were 1.93 and 1.87, respectively.

Conclusion: Population PK models were successfully developed to characterize the disposition of both omadacycline and tigecycline in plasma and ELF. When assessed relative to free-drug plasma exposures, omadacycline and tigecycline demonstrated similar ELF penetration. Use of these data with PK-PD target attainment analyses will be useful to support omadacycline dose selection for CABP.

INTRODUCTION

- Omadacycline is a novel, first-in-class aminomethylcycline that is synthesized by chemical modification of minocycline.
  - Active against Gram-positive, Gram-negative, anaerobic, and atypical pathogens [1].
  - Overcomes efflux pump and ribosomal protection mechanisms of tetracycline resistance [1].
  - Currently in development for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP).
- A Phase 1 study evaluating omadacycline and tigecycline pharmacokinetics (PK) in the plasma and epithelial lining fluid (ELF) of healthy volunteers was previously conducted [2].

OBJECTIVES

- To develop population PK models to describe the time course of omadacycline and tigecycline in both plasma and ELF using data obtained from the above described Phase 1 study.
- To compute omadacycline and tigecycline ELF penetration ratios using the above-described population PK models and protein binding data.

METHODS

Study Design

- Healthy volunteers were randomized in a 2:1 ratio to receive either omadacycline 100 mg IV q12h x 2 doses then 100 mg q24h x 3 doses or tigecycline 100 mg IV x 1 dose then 50 mg q12h x 6 doses.
- Plasma PK samples were collected pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose on Day 4 (24 hour sample only collected for omadacycline).

METHODS

- One bronchoalveolar lavage sample was collected from each subject on Day 4. Subjects were randomized to one of the following collection times: 0.5, 1, 2, 4, 8, 12, or 24h post-dose (24 hour sample only collected for omadacycline).

Omadacycline PK Analysis

- A previously-developed omadacycline population PK model was utilized to describe omadacycline plasma PK [3].
  - The previous model was a linear three-compartment model with creatinine clearance (CLcr) as a covariate on clearance (CL).
- Several structural models were evaluated, using NONMEM v7.2, for the disposition of omadacycline in ELF. These included the following:
  - A separate biophase compartment
  - A subcompartment of peripheral compartment 1
  - Part of peripheral compartment 2
- A protein binding estimate of 20% was utilized to compute free-drug concentrations [4].

Tigecycline PK Analysis

- A linear two-compartment model was utilized to characterize the disposition of tigecycline in plasma [5, 6].
- Several structural models were evaluated using NONEM v7.2 for the disposition of tigecycline in ELF. These included the following:
  - A separate biophase compartment
  - A subcompartment of peripheral compartment 1
- A previously-developed protein binding function was utilized to compute free-drug concentrations [7]:

$$\%\text{Free Drug} = 9.0896 + 15.339 / Cp - 0.999 / Cp^2 + 0.0232 / Cp^3$$

CP = Total-Drug Plasma Concentration

Simulations

- Monte Carlo simulations were conducted using the developed population PK models and protein binding estimates for omadacycline and tigecycline, respectively.
- The following regimens were administered to simulated subjects:
  - Omadacycline 100 mg IV q12h x 2 doses then 100 mg q24h x 3 doses
  - Tigecycline 100 mg IV x 1 dose then 50 mg q12h x 6 doses
- Day 4 free-drug plasma and total-drug ELF area under the concentration time curve (AUC) values were computed through numeric integration of the simulated concentration-time profiles.

RESULTS

Analysis Dataset

- Data utilized for population PK model development are described in **Table 1**.

Table 1. Number of plasma and ELF PK samples utilized for population PK model development by agent

Exposure Matrix	Omadacycline (n)	Tigecycline (n)
Plasma	446[a]	169
ELF	41	16[b]

a. After exclusion of 3 below the lower limit of quantitation samples, 2 outliers.
b. After exclusion of 1 outlier.

RESULTS

Population PK Models

- Omadacycline plasma and ELF data were well described by a linear 3-compartment model which included an ELF subcompartment of peripheral compartment 1.
- Tigecycline plasma and ELF data were well described by a linear 2-compartment which includes an ELF subcompartment of peripheral compartment 1.
- Both models utilized a proportionality term, intended to scale the amount of drug in the ELF to a true concentration ("Frac").
- Plasma and ELF PK profiles were well-described by the final models, as displayed by the high r^2 values and lack of biases in **Figure 1**.
- Final model parameter estimates for both the omadacycline and tigecycline models are displayed in **Table 2**.
- **Figure 2** displays the results of ELF visual predictive checks for both omadacycline and tigecycline. For both agents, the median predicted ELF profile captured the central tendency of the observed data well. In addition, variability in the ELF observations was well captured, indicting reliability of the model in simulation exercises.

Figure 1. Goodness-of-fit plots for individual – and model-predicted omadacycline and tigecycline free-drug plasma (A and B, respectively) and total-drug ELF (C and D, respectively) concentrations

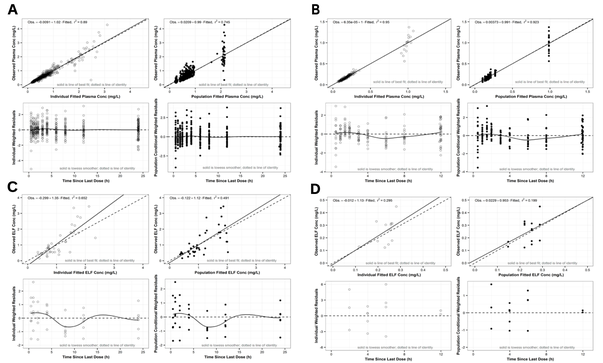
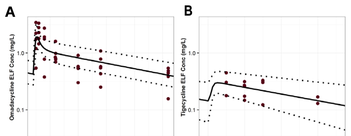


Figure 2. Evaluation of omadacycline (A) and tigecycline (B) population PK models using ELF visual predictive checks



RESULTS

Table 2. Parameter estimates for the final structural population PK models

	Parameter	Omadacycline Final estimate	Omadacycline %SEM	Tigecycline Final estimate	Tigecycline %SEM
Plasma	CL (L/h)	-	-	22.0	4.64
	CL_{NR} (L/hr)	6.46	17.7	-	-
	CL_R (L/hr) coefficient at CLcr of 109 mL/min/1.73 m^2	2.90	44.6	-	-
	Vc (L)	10.8	52.1	21.7	8.88
	CLd1 (L/h)	90.9	26.2	86.7	4.96
	Vp1 (L)	37.2	30.6	246	5.1
	CLd2 (L/h)	59.1	13.4	-	-
	Vp2 (L)	129	13.7	-	-
	ω^2 for CL	0.0606 (24.6% CV)	45.6	0.0183 (13.5% CV)[a]	43.1
	ω^2 for Vc	0.544 (73.3% CV)	125	-	-
	ω^2 for CLd1	0.000525 (2.29% CV)	1440	-	-
	ω^2 for Vp1	0.385 (62.1% CV)	44.7	-	-
	ω^2 for Vp2	0.086 (29.3% CV)	40.3	-	-
	Covariance(CL,Vc)	0.145 (r^2 = 0.637)	85.6	-	-
	Covariance(CL,Vp2)	0.0625 (r^2 = 0.119)	44.5	-	-
	Covariance(Vc,Vp2)	0.107 (r^2 =0.246)	137	-	-
	$\sigma^2_{Additive}$	0.000000647 (0.000804 SD)	7960	-	-
	σ^2_{CCV}	0.0287 (16.7% CV)	6.84	0.0141 (11.9% CV)	14.3
ELF	Frac	1.54	7.53	1.16	16.6
	$\sigma^2_{Additive}$	0.00000148 (0.00122 SD)	7870	0.00839 (0.0916 SD)	168
	σ^2_{CCV}	0.169 (41.1% CV)	40.7	0.0192 (13.8% CV)	1530
Minimum Value of the Objective Function		-1420		-1093	

a. ω^2 value of 0.131 (36.2%CV) was utilized for simulations.

Simulations

- Model-computed total-drug ELF AUC to free-drug plasma AUC ratios were 1.93 and 1.87 for omadacycline and tigecycline, respectively (**Table 3**).

Table 3. Free-drug plasma and total-drug ELF concentrations and penetration ratios for omadacycline and tigecycline

Antibacterial Agent	Exposure matrix	Exposure measure	Median	Interquartile range
Omadacycline	Plasma	Free-drug $AUC_{72\text{-}96}$ (mg·h/L)	9.61	8.07 – 11.3
	ELF	Total-drug $AUC_{72\text{-}96}$ (mg·h/L)	18.5	15.5 - 21.8
	ELF	Penetration Ratio[a]	1.93	---
Tigecycline	Plasma	Free-drug $AUC_{72\text{-}84}$ (mg·h/L)	1.38	1.14 – 1.59
	ELF	Total-drug $AUC_{72\text{-}84}$ (mg·h/L)	2.59	1.97 – 3.33
	ELF	Penetration Ratio[b]	1.87	----

a. Represents the ratio of total-drug ELF $AUC_{72\text{-}96}$ to free-drug plasma $AUC_{72\text{-}96}$.
b. Represents the ratio of total-drug ELF $AUC_{72\text{-}84}$ to free-drug plasma $AUC_{72\text{-}84}$.

CONCLUSIONS

- Population PK models were successfully developed to characterize the disposition of both omadacycline and tigecycline in plasma and ELF.
- When assessed relative to free-drug plasma exposures, omadacycline and tigecycline exposures in ELF, which were higher than those in plasma, demonstrated a similar magnitude of penetration into ELF.
- Results of the data described herein, together with PK-PD target attainment analyses, will be useful to support omadacycline dose selection for CABP.

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